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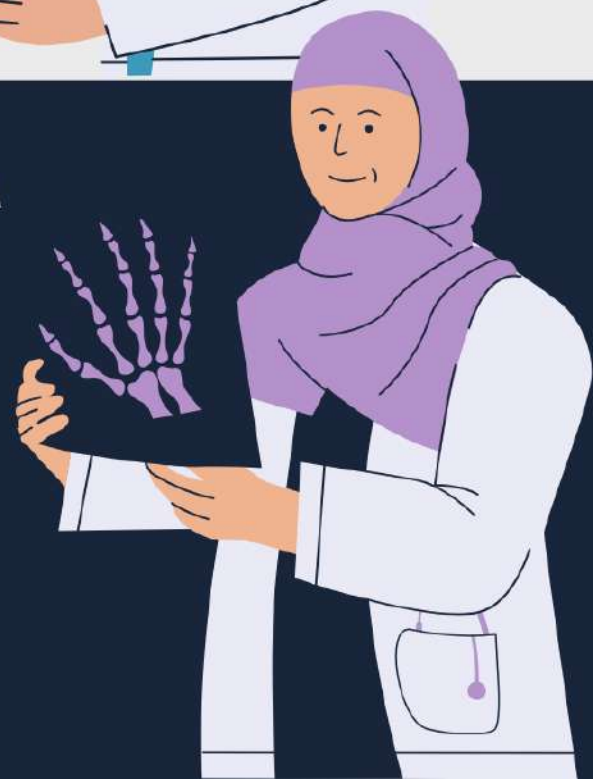
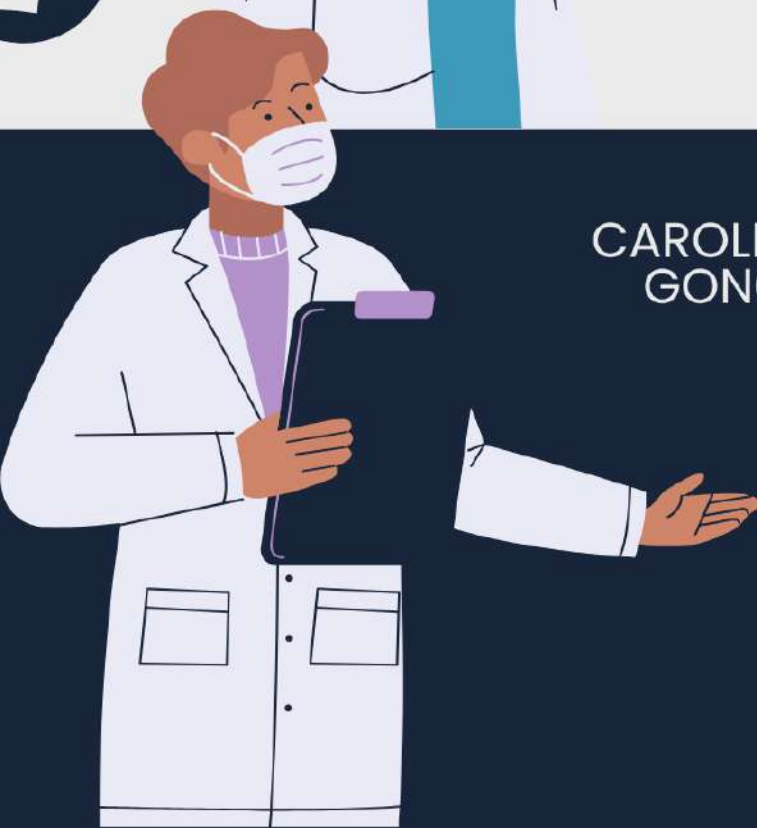
Pathways to Health:

**INNOVATIONS AND APPROACHES
IN HEALTH SCIENCES**



2ND EDITION

**CAROLINNE SILVA
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Thaissa Akemy Eda de Souza
Thakimare da Conceição das Neves Garcez
Thales Soares Tavares
Thalia Candido Araujo
Thalita Fontana Manocchi
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Theodoro Ribeiro Andrade
Thiago Alves Diques
Thiago Carvalho Barros de Oliveira
Thiago Pereira Cruz
Thiago Vales de Mesquita
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PRESENTATION

Health is a field of knowledge in which different disciplines intertwine to form a greater whole. **Pathways to Health: Innovations and Approaches in Health Sciences – 2 ed** is a work that expands this interconnection, bringing together 72 articles on various topics, written by experts from different areas of knowledge.

Developed by **Seven Publications**, this book presents a broad overview of the challenges, discoveries and advances in fields such as alzheimer's disease, maxillary sinus lift, use of point-of-care ultrasound and much more.

SUMMARY

COMBINED THERAPY WITH DONEPEZIL AND MEMANTINE IN THE TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE

Isabela Cerchiari, Clícia Ferreira Gardenal, Taynara Maria Gomes dos Santos, Beatriz Oliveira Rocha, Alana Alves Ibanhes Valejo, Nicole Oliveira Jordão, Milene Márcia de Faria Rodrigues, Luiza Antonello Pedrazzi, Maria Auxiliadora Bezerra Fecine, Michell Ícaro Lima Oliveira, Augusto Rafael Barsella, Leandra dos Passos e Silva, Maria Fernanda Landivar de Moraes, Millena Beatriz Alves Fernandes Medeiros, Maria Eduarda Bianchi Bitar de Moraes, Thais da Silva Martha Kradichi, Saulo Lacerda César, Mariáh França Guimarães Meirelles de Paula, Lucas Oliveira Moraes, Amanda Lobo de Siqueira, Iza Pereira Bezerra, Valéria Paula Sassoli Fazan, André Sanazar Borklian.

  <https://doi.org/10.56238/sevened2026.020-001>

24-32

ASSOCIATION BETWEEN GLP-1 ANALOGUES AND PANCREATITIS: AN INTEGRATIVE REVIEW OF CURRENT EVIDENCE

Alexandre Alves Neves Pereira, Júlia Mateus Soares, Rafaela Cristina Bandeira Maia, Júlio César Gomes Bezerra, Heitor Bernardo Freitas, Nathalia Santos Gonçalves, Charles Albani Dadam Junior, Leonardo dos Santos Döbele, Roberto de Moraes Ferreira dos Santos Neto, Luiz Henrique Menezes Oliveira, Yuri Papacosta Siqueira, Marcella de Fátima Lomeu Marinho, Giovanna Arjona Lamussi Silva, Romário Gomes da Silva, Lisandra Díaz Talones Souza, Vinicius Silveira Amaral, Bárbara Bicalho Dias, Valéria Goulart Viana, José Eduardo Matias da Silva, Felipe Veiga Kezam Gabriel, Caio Sussuarana de Castro, Vanessa Neglisoli, Ester de França Ruby, Ana Sombrio Tenfen, Carlos Alberto Barbieri.

  <https://doi.org/10.56238/sevened2026.020-002>

33-42

MAXILLARY SINUS LIFT: COMPARISON BETWEEN THE LATERAL WINDOW TECHNIQUE AND THE TRANSCRESTAL TECHNIQUE

Roberto Machado Cruz, Marcelo Vitale, Patrícia de Hollanda Cavalcanti Aragão Costa, Micaell da Silva Souza, Cristiane Elisa Ribas Batista, Caio Uriel Vinhote do Nascimento, Julia de Araújo Koplowitz Bento, Matheus Rodrigues Serafim Silva, Priscila Pereira Batista, Douglas José de Araújo Ferreira, Giovanni Daleffe, Theodoro Ribeiro Andrade, Jefferson José de Oliveira, Ulo Roberto Steinberg da Cruz de Almei, Mariana Silva Cestari, Caroline Weinert Marçal, Robson José Mendonça Dias, Fernanda Karla Duailibe Fontes, Ivan Silva Andrade, Vilmar Santos de Almeida, Brunno Pereira Silva, Arnoldo Brasil Muniz Júnior, Renato Mendes Almeida, Ronald Rojas Concepción, Claudiony Henrique Dantas de Sousa Azevedo.

  <https://doi.org/10.56238/sevened2026.020-003>

43-53

ACUTE MYOCARDIAL INFARCTION WITH CORONARY OCCLUSION WITHOUT ST-SEGMENT ELEVATION: A SYSTEMATIC LITERATURE REVIEW

Élton Martins Vieira, João Vitor Souza Rodrigues, Kaila Sâmý Oliveira Soares Peréa Garcia, Kevin Santos Oliveira, Luiz Henrique Gasparelo.

  <https://doi.org/10.56238/sevened2026.020-004>

54-69

USE OF THE ALLIUM CEPA BIOASSAY AS AN INDICATOR OF CYTOTOXICITY OF PESTICIDES IN VITICULTURE

Renata Sano Lini, Eduardo Daniel Righi Dornelles, Camilla Yumi Endo, Débora Hayane Vidal Pereira, Larissa Tiemi Akamine Motomura, Mariana Yumi Date, Thalita Fontana Manocchi, Priscilla de Laet Santana, Tânia Cristina Alexandrino Becker, Edilson Nobuyoshi Kaneshima, Simone Aparecida Galerani Mossini, Alice Maria de Souza Kaneshima.

  <https://doi.org/10.56238/sevened2026.020-005>

70-85

CLINICAL AND EPIDEMIOLOGICAL CHARACTERIZATION, ANESTHETIC-SURGICAL PROCEDURE, AND INTRAOPERATIVE PHARMACOLOGICAL MANAGEMENT: ELECTIVE CRANIOPLASTY

Lucas Dalla Maria, Jamerson Fiorentin, Victor Luiz Ferreira Kauer, Marcelo Augusto Landim Arteiro de Oliveira, Eugenio Pagnussatt Neto, Shana Ginar da Silva, Ivana Loraine Lindemann.

  <https://doi.org/10.56238/sevened2026.020-006>

86-105

PHYSIOLOGICAL CHANGES DURING AGING

Danilo Campos Talhari, Livia de Sousa Torres, Kayky Oliveira Moraes, Thakimare da Conceição das Neves Garcez, Sebastião Venicius Tavares da Silva, Brenda Carvalho Silva, Gisele Milhomem da Silva Campos, Rick Mendes Matias Cardoso, Bianca Pâmela Santana Costa, Marcos Antonio do Nascimento.

  <https://doi.org/10.56238/sevened2026.020-007>

106-119

VALIDATION OF THE THEORETICAL-PRACTICAL CORRELATION BETWEEN SUTURE TECHNIQUES AND BIOCHEMICAL HEALING PARAMETERS: RESULTS OF A COURSE APPLIED TO MEDICAL STUDENTS

Rian Rodrigues Bragança, Aline Dos Santos Atherly Pedraça, Patrick Torres Nascimento, João Vitor Silva dos Santos, Hermin Dário Ayala Reyes.

  <https://doi.org/10.56238/sevened2026.020-008>

120-136

ASSESSMENT OF THE RISK OF DEVELOPING TYPE 2 DIABETES MELLITUS AMONG MEDICAL STUDENTS AT UNIDA-PARAGUAY USING THE FINDRISC SCORE

Andreza Thátila Assunção e Medeiros, Aline Dos Santos Atherly Pedraça, Darcy Maria Da Conceição Laura dos Santos, Patrick Torres Nascimento, Hermin Dário Ayala Reyes.

  <https://doi.org/10.56238/sevened2026.020-009>

137-149

SURVEILLANCE OF EMERGING AND RE-EMERGING DISEASES: CHALLENGES FOR GLOBAL HEALTH AND MULTIPROFESSIONAL ACTION

Vânia Cristina Ribeiro Brilhante, Dayvison Santos de Oliveira, Rita de Cássia Maia Rebelo, Mariana Elizabeth Lopes de Sales, Jeane da Silva Facioni, Tchescolly Dias Araujo, Micheline Santos da Fonseca, Valdemar Mendes de Moraes Filho, Juliana Botelho Araújo, Michelle Barbosa Silva, Débora Teruko Kajitani Cruz, Arilana de Jesus Carretilha, Jander Marcus Cirino Lopes, Aline de Moraes Gomes, Amanda Emanuele dos Santos Correa, Deivid Junio Guilherme de Lanes, Rafaela Baliot de Souza, Jhennifer Stefany Teles Gonçalves Meira, Anna Monise Rigon Von Heimburg, Jean-Claude Martins de Andrade, Tassiane Martins Bezerra, Sirlene de Miranda Julião, Júlia Roberta Silva Garcia, Eduardo Silva Rodrigues, Brayan Almeida Ferreira, Neide Garcia Ribeiro.

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150-165

USE OF POINT-OF-CARE ULTRASOUND (POCUS) IN THE ASSESSMENT OF FLUID RESPONSIVENESS: PRACTICAL APPLICATIONS AND METHODS

Luan Caimar Fuchs, Bruna Turra Aimi, Felipe Romão Hatisuka, José Henrique Gorgone Zampieri, Jaime Javier Garcia Caro, Kelen Marques de Souza, Lucas Braun Gonçalves, João Marcello Fernandes Zanata, Júnior Girardi, Maria Eduarda Faraldo Calore, Filippo Fabi Bez, Adriano Pereira Rocha, Bráulio Queiros de Andrade, Luís Otávio Garcia de Oliveira, Lucas Marcos Balduino, Débora Vieira de Melo Agra Duarte Nunes, Lara Cristine Quaresma Oliveira, João Vicente Soares Martins, Emily Carboni Silveira Neto, Rafael de Cristo, Giulia Regina Frangiotti, Gabriela Zanardo Sousa.

  <https://doi.org/10.56238/sevened2026.020-011>

166-176

USE OF NITROUS OXIDE IN ELDERLY PATIENTS WITH COMORBIDITIES: AN INTEGRATIVE REVIEW

Ana Beatriz Nunes Santos e Silva Barroso, Joyce Costa Moreira.

 <https://doi.org/10.56238/sevened2026.020-012>

.....177-184

USE OF DUAL AND TRIPLE INCRETIN AGONISTS (TIRZEPATIDE AND RETATRUTIDE) IN THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS

Felipe Veiga Kezam Gabriel, Marilda Lopes Cruz, Tamires Soster, Antonio Matheus Melo Soares, Vanessa Neglisoli, Otávio de Meireles Delfino, Marcella de Fátima Lomeu Marinho, Laura Lappe Bombardelli, Gabriele Longo Cruz, Valéria Goulart Viana, Diegomaier Nunes Neri, Mateus Souza Dezan, Giovanna Yumi Asanome Galli, Giovanna Lima Scherolt da Costa, Juliana Peterle Barbosa, Isabela Braga do Valle Guimarães, Carolina Figueiredo Gomes de Rezende, Larissa Rodrigues Cardoso Santos, Moniki Rocha da Costa, Lucas Lopes Barbosa, Alyne Santana Rosa, Larissa Caixeta Sampaio.

 <https://doi.org/10.56238/sevened2026.020-013>

.....185-194

INCIDENCE OF CERVICAL CANCER IN THE STATE OF PARAÍBA IN 2023 AND ITS CORRELATION WITH CYTOPATHOLOGICAL EXAMINATION

Amanda Santos Fernandes Costa, Claudiane Macedo Fernandes de Aguiar, Eduardo Sérgio Soares Sousa, Sibebe Vieira Pereira, Hartt Hindenburg Medeiros Cordeiro, Davi Pereira Maurício de Barros, Clara Cristina Marques Teodoro de Figueiredo Gadelha.

 <https://doi.org/10.56238/sevened2026.020-014>

.....195-217

ASSOCIATION BETWEEN THE DIETARY INFLAMMATORY INDEX AND PLASMA CYTOKINES IN RECREATIONAL ROAD RUNNERS AND SEDENTARY INDIVIDUALS

Priscila da Trindade Flores, Joane Severo Ribeiro, Bruna Moraes Isidoro, Alessandra Peres.

 <https://doi.org/10.56238/sevened2026.020-015>

.....218-234

WHEN TERRITORY DETERMINES CARE: THE UNEQUAL DISTRIBUTION OF HEALTH PROFESSIONALS AND ITS DIRECT IMPACTS ON LIFE AND DEATH IN REMOTE REGIONS

João Carlos Tavares da Costa, Everaldo dos Santos Mendes, Nelzo Moda Neto Lourenço.

 <https://doi.org/10.56238/sevened2026.020-016>

.....235-251

BLOOD PRESSURE PROFILE IN UNIVERSITY STUDENTS WHO PRACTICE SPORTS VERSUS SEDENTARY INDIVIDUALS

Beatriz Rato Conceição, António Filipe Pinto Rodrigues, Patrícia Margarida dos Santos Carvalheiro Coelho.

 <https://doi.org/10.56238/sevened2026.020-017>

.....252-266

GENETIC LITERACY IN ADOLESCENTS WITH GENETIC DISORDERS: A BIOPSYCHOSOCIAL AND CLINICAL APPROACH

Ramón Miguel Vargas-Vera, Piedad Gisela Mejía-Gavilánez, Martha Placencia-Ibadango, Saúl Alexander Alencastro-Placencia, Jorge Luis Gunsha-Aguilar, Andrea Jimena Tipán-Hidalgo, Melanie Nicole Lino-Mejía, Karen Soraya Vargas Silva.

 <https://doi.org/10.56238/sevened2026.020-018>

.....267-290

INTRAPARTUM ASPHYXIA AND NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: PATHOPHYSIOLOGICAL BASES, DIAGNOSIS, AND CLINICAL MANAGEMENT

Ramón Miguel Vargas-Vera, Martha Placencia-Ibadango, Jocelyn Maribel Alencastro-Placencia, Ana María Flores-Luna, César William Luciano Salazar, Lito Danny Campos-Carbo, Norma Matilde Erazo-Flores, Kathiuska Stefany Vargas-Silva, Allison Deyalit Mero-Sánchez, Paul Vilchez Castro.

  <https://doi.org/10.56238/sevened2026.020-019>

.....291-309

HUMAN TERATOGENESIS: GENE-ENVIRONMENT INTERACTION AND FOUNDATIONS FOR PREVENTION

Ramón Miguel Vargas-Vera, Martha Placencia-Ibadango, Ana María Flores-Luna, Saúl Alexander Alencastro-Placencia, Jorge Luis Gunsha-Aguilar, Lito Danny Campos-Carbo, Kalid Stefano Vargas-Silva, María del Socorro Palacios-Távora.

  <https://doi.org/10.56238/sevened2026.020-020>

.....310-345

ANTICANCER ACTIVITY OF AMINOCHALCONES. SCIENTIFIC And TECHNOLOGICAL PROSPECTING

Hercília Maria Lins Rolim, Hécio Silva dos Santos, Stanley Juan Chavez Gutierrez, Railson Pereira Souza, José Ailton Freire de Souza.

  <https://doi.org/10.56238/sevened2026.020-021>

.....346-356

PRESENCE OF LACTOSE IN MEDICATIONS FOR THE TREATMENT OF HYPERTENSION

Alexandra Pimenta de Almeida Dias, Lucca Kayan Silva Peixoto, Leandra de Almeida Ribeiro Oliveira, Letícia Cristina Alves de Sousa, Pamela Cristina de Sousa Guardiano Reis Oliveira, Pedro Alexandre Sampaio Oliveira, Idari Francisco de Oliveira Netto, Daniela Borges Marquez Barbosa.

  <https://doi.org/10.56238/sevened2026.020-022>

.....357-366

WORLD EPIDEMIOLOGY OF LEISHMANIASIS: A NARRATIVE REVIEW

Anna Cláudia Ferreira Nunes, Anna Luiza de Araújo Ribeiro, Tales Alexandre Aversi-Ferreira, Maria Tereza Mendes Aversi.

  <https://doi.org/10.56238/sevened2026.020-023>

.....367-383

PHYSICAL VARIABLES OF LEISHMANIASIS TRANSMISSION

Luca Casale Guerreschi, Maria Amália Garcia da Silveira Araújo, Tales Alexandre Aversi-Ferreira, Maria Tereza Mendes Aversi.

  <https://doi.org/10.56238/sevened2026.020-024>

.....384-399

USE OF ANABOLIC HORMONE THERAPIES IN SARCOPENIA IN OLDER ADULTS: CURRENT EVIDENCE AND PROGNOSIS

Celsilvana Teixeira Gomes, Leonardo dos Santos Döbele, Eduardo Duarte Guimarães, Matheus Alvino Liutti de Oliveira Salvadego, Leandro Dias Costa, Luiza Slaviero, Giovanna Maria Oliveira Rocha, Marcela Torquato Rocha Correia, Nildo da Silva Prado Júnior, Vanessa Neglisoli, Otávio de Meireles Delfino, Ana Claudia Medeiros Vilela, Hannah Shmulerg Chou, Karlla Gabrielle Holanda Corilaço Cordeiro, Valéria Goulart Viana, Julia Moya Resende, Mateus Nunes Vieira, Vinícius Gomes e Martins, Aliandro Willy Duarte Magalhães, Guilherme Esteves Najjar Valle, Gardênia Santos Pereira, Marianna Medeiros Barros da Cunha.

  <https://doi.org/10.56238/sevened2026.020-025>

.....400-409

DIGITAL TRANSFORMATION AND MULTIPROFESSIONAL INTEGRATION: NEW PATHWAYS TO PATIENT SAFETY AND SUSTAINABILITY OF HEALTH SYSTEMS

Dayvison Santos de Oliveira, Mariana Elizabeth Lopes de Sales, Lauriene Karina Ramos da Costa Ferreira, Kárita Roberta da Silva Melo, Kátia Lamara de Araújo Santos, Juliana Botelho Araújo, Monize Lopes de Araújo Gomes, Alynne Cristina Ferreira Coutinho, Arilana de Jesus Carretilha, Jander Marcus Cirino Lopes, Vânia Cristina Ribeiro Brilhante, Amanda Emanuele dos Santos Correa, Tamyres Cristine Mafra Gomes, Jailson Otávio Ribeiro Lopes, Rita de Cássia Maia Rebelo, Thais Castro de Oliveira, Rosilene Abrahão de Freitas de Souza, Valdemar Mendes de Moraes Filho, Thiago Pereira Cruz, Laura Silva Monteiro, Maiara Ivone Bastos de Oliveira, Eloisa Elena Macedo de Souza, Debora Vita da Silva Martins, Jamile Almeida Sarrazin, Suzana Helena Campelo Nogueira Lima, Dione Marília Albuquerque Cunha.

  <https://doi.org/10.56238/sevened2026.020-026>

.....410-424

RATIONAL USE OF OPHTHALMIC MEDICATIONS IN PRIMARY CARE: AN APPROACH FOR GENERAL PRACTITIONERS ON PHARMACOKINETICS, IATROGENESIS, AND PRESCRIPTIVE SAFETY

Otávio Paino Paim.

  <https://doi.org/10.56238/sevened2026.020-027>

.....425-450

THE INFLUENCE OF THE THERAPEUTIC ALLIANCE ON ADHERENCE TO PSYCHOLOGICAL TREATMENT: A LITERATURE REVIEW

Andréia Oliveira da Mata, Hareli Fernanda Garcia Cecchin.

  <https://doi.org/10.56238/sevened2026.020-028>

.....451-462

NURSING CARE FOR HYPERTENSION CONTROL IN PRIMARY HEALTH CARE: EFFECTIVENESS AND STRATEGIES

Gleiziane dos Santos Taciano, Millena Santini Mendes, Denilson Welliton dos Anjos Sousa, Getúlio José do Carmo Neves Netto, Alda Lima Lemos, Glauciney Pereira Gomes, Guilherme Augusto Barros Conde, Valney Mara Gomes Conde.

  <https://doi.org/10.56238/sevened2026.020-029>

.....463-481

INSERTION OF INTRAUTERINE DEVICE (IUD) BY FAMILY AND COMMUNITY PHYSICIANS IN PRIMARY HEALTH CARE IN SANTA MARIA, RIO GRANDE DO SUL, BRAZIL

Luiz Felipe Dias Carli, Nathieli Bianchin Bottari, Cristine Kolling Konopka, Luciane Flores Jacobi.

  <https://doi.org/10.56238/sevened2026.020-030>

.....482-511

PHARMACOTHERAPY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (2015-2025)

Bernardo Tolentino Costa, Ana Laura Almeida Rodovalho, Fabio Kendy Nishino, Bruno Santos De Oliveira, Rafael da Silva, Cauã Cabral Magno da Fonseca, Paulo Ricardo Rocha de Araujo, Lis Melo de Lima, Luiz Gustavo Barbosa Fantin, Amanda Souza dos Santos, André Mateus Marques, Erick Silva Cardoso, Giovanna Menezes Lima.

  <https://doi.org/10.56238/sevened2026.020-031>

.....512-534

EFFICACY AND SAFETY OF INJECTABLE INCRETIN THERAPIES IN THE MANAGEMENT OF OBESITY: A SYSTEMATIC REVIEW

Fernanda Rodrigues Lopes, Travis Ricardo Johnson, Fabrício Soares Ferreira, Arthur Alberth Lopes, Marcos Antônio de Amorim, Theo Gabriel de Matos Nery Lima, Giovana Abadia Braga Martins, Nicolas Ferreira Melo, Quintiliano Duarte Araujo, Maria Beatriz Almeida Dario, Fernando Daniel Pereira Barbosa, Hygor Henrique Silva Sales.

  <https://doi.org/10.56238/sevened2026.020-032>

.....535-553

THE IMPACT OF WORKLOAD OVERLOAD IN NURSING AND ITS CONSEQUENCES FOR PATIENT CARE

Camila Alves Samartino, Maria Antonia Queiroz Miranda, Clarissa Albuquerque Vaz Nunes, Livia Moreira da Silva, Bruna Marçal Guidoti Eleutério, Fabricio Sidnei da Silva, Amanda Oliva Spaziani, Rauer Ferreira Franco.

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.....554-566

DIAGNOSIS AND MANAGEMENT OF NEONATAL ESOPHAGEAL ATRESIA: A SYSTEMATIC REVIEW OF CURRENT EVIDENCE

Raquel Oliveira Santos, Beatrice de Lucena Ramos, Camila Coutrin Coutinho, Helloá Victoria Sales Pereira, Marcelly do Nascimento Miranda, Pedro Henrique de Oliveira e Oliveira, Rania dos Reis de Melo, Thaissa Akemy Eda de Souza.

  <https://doi.org/10.56238/sevened2026.020-034>

.....567-579

REPORT ON THE EXPERIENCE OF IMPLEMENTING RADIOGRAPHIC DOWSING IN THE INTEGRATIVE MEDICINE OUTPATIENT CLINIC - INTEGRATIVE AND COMPLEMENTARY PRACTICES AT A HOSPITAL IN THE CITY OF SÃO PAULO

Joseli Beatriz Suzin, Juliane Cristina Burgatti Coelho, Alice Hiroko Otani, Eduardo Campos Costa Neto.

  <https://doi.org/10.56238/sevened2026.020-035>

.....580-587

CHALLENGES AND PERSPECTIVES OF HEALTH EDUCATION IN THE TRANSITION FROM A HOSPITAL-CENTRIC MODEL TO HEALTH PROMOTION

Sara Gabriela Josiane Mazi, Maria Rita Alves dos Santos, Jéssica da Silva Francelino, Adriana Garcia Costa, Isléia Nonis da Silva, Flávia Cristina Custódio, Fabricio Sidnei da Silva, Rauer Ferreira Franco.

  <https://doi.org/10.56238/sevened2026.020-036>

.....588-600

EFFECT OF TIRZEPATIDE ON THE REDUCTION OF CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Pedro Henrique Souza e Silva, Francielly Ramos Araújo, Wesley Wagner dos Santos, Maria Fernanda Souza Freitas, Anderson Alves da Costa, Gustavo Oliveira Queiroz, Marjorie de Castro Machado, Géssica Gomes Pereira Modesto, Juan de Menezes Goes, Daniel Gonçalves Feltrin, Ruben Enrique Flores Mamani, Augusto Rafael Barsella, Júlia Cristina Caverçan Gomes, Suellen Carvalho de Mendonça Gusmão, Marco Antonio Fidelis Vieira, João Paulo Moraes Gomes, Matheus Alvino Liutti de Oliveira Salvadego, Lucas Victor Araújo de Almeida, Laura Rezende Marques, Rúbia Sousa de Araújo, Kamylla Pessoa Figueira, Marcella de Fátima Lomeu Marinho, Allan Jacques Garcia, João Victor Faleiros Cardoso Faion, Alice Rodrigues Vanini.

  <https://doi.org/10.56238/sevened2026.020-037>

.....601-614

LUDWIG'S ANGINA: EARLY DIAGNOSIS AND AIRWAY MANAGEMENT IN DEEP CERVICAL INFECTIONS

José Laurentino Ferreira Filho, Ana Paula Granja Scarabel Nogueira Bella, Renata Helena Ferreira Caraméz, Aline Farias, Vivian Rabelo Cunha, Carolina Dieguez Rabelo Ferreira, Larissa Priscilla dos Santos Nascimento, Wilton Costa Neto, Claudiony Henrique Dantas de Sousa Azevedo, Cristiano Veloso, Marcelo Magalhães Dias, Gabrielle Oliveira de Sousa, Marcelo Ferraro Bezerra, Dárcio Rodrigues Freire, Reginaldo Conceição Vieira Junior, Chrislei Resende Costa, Thaís Karoline Moura Dias, Julia de Araújo Koplowitz Bento, Marcelo Vitale, Andressa Alana Locatti Sian, Thiago Alves Dignes, Valeska Camargo Lacerda, Gabriell Mafuz Penteado, Laura Mônaco.

  <https://doi.org/10.56238/sevened2026.020-038>

.....615-626

CARDIAC PATHOLOGIES: HEMODYNAMIC ASSESSMENT AND COMPLICATIONS

Taciara Bohn, Vítor Antunes de Oliveira, Pauline Brendler Goettems Fiorin, Matias Nunes Frizzo.

  <https://doi.org/10.56238/sevened2026.020-039>

.....627-656

WOMEN'S PERCEPTIONS OF THE SIGNS AND SYMPTOMS OF CLIMACTERIC ASSOCIATED WITH SEXUAL ACTIVITY

Camila Vitória Viana Silva, Layana Santos do Nascimento, Arlete Rodrigues Chagas da Costa, Ingridy Fátima Alves Rodrigues, Solange de Paiva Pinto, Ageu Procópio Almeida de Albuquerque, Domitília Bonfim de Macêdo Mihaliuc, Leila Barbosa Rezende Teixeira.

  <https://doi.org/10.56238/sevened2026.020-040>

.....657-677

TOBACCO-ALCOHOL TOXIC-NUTRITIONAL OPTIC NEUROPATHY: A CASE REPORT

Anderson Gustavo Teixeira Pinto, Letícia Fernandes Barroso, Bruna Cordeiro Benvenutti Castro, Carla Duhau Boni, Gabriela Furlan Ribeiro Barbosa Netto, Gabriela Ponte Gutierrez, Giulia Longoni Manfro, Sara Oliveira Reis.

  <https://doi.org/10.56238/sevened2026.020-041>

.....678-682

CLINICAL AND LABORATORY PARAMETERS AS PREDICTORS OF CHANGES IN ARTERIAL PATENCY AFTER PERCUTANEOUS INTERVENTION IN HEMODYNAMIC SERVICES

Taciara Bohn, Vítor Antunes de Oliveira, Pauline Brendler Goettems Fiorin, Matias Nunes Frizzo.

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.....683-728

USE OF DAPAGLIFLOZIN (FORXIGA) IN THE TREATMENT OF HEART FAILURE: CURRENT EVIDENCE AND CLINICAL EFFICACY

Júlia Chermont Crema, Alessandra Matsuoka Borges da Silva, Ana Paula Schonarth, Kelen Marques de Souza, Fernanda Dominique de Souza Gonçalves, Felipe Veiga Kezam Gabriel, Suzielly Ramos Barbosa Lima Xavier, Luigi Mestrinelli Santiago, Gardênia Santos Pereira, Felipe Romão Hatisuka, Vitor de Castro Ramos, Áureo Nios de Oliveira Sousa, Renato Saraiva da Silva, Larisse Bernardi Simplicio, Leôncio Pinheiro Pereira, Michell Ícaro Lima Oliveira, Linaldo Serafim, Ygor Torres Pinto, Daniella Rodrigues Alves, Isabela Godoy Santos, Rosane Cristina de Araújo Portes Paiva, Pedro Henrique Souza e Silva.

  <https://doi.org/10.56238/sevened2026.020-043>

.....729-739

AUTISM SPECTRUM DISORDER IN THE CONTEXT OF PUBLIC SCHOOLS: CONTRIBUTIONS OF PHYSICAL EDUCATION TO THE DEVELOPMENT OF LANGUAGE: MEDIATION, BODY AND EMBODIED COGNITION

Valéria de Nazaré de Paula Bessa, Éder do Vale Palheta, Biratan dos Santos Palmeira, Luciano Barros da Silva, Mauricio Martins Cabral, Márcia de Araujo da Costa, Marco Antônio Barros dos Santos, Danilo da Costa Souza.

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.....740-756

TYPE 2 DIABETES MELLITUS AND SYSTEMIC ARTERIAL HYPERTENSION: ETIOLOGICAL, PATHOGENIC, AND PATHOPHYSIOLOGICAL ASPECTS

Daniele Fernanda Wille, Fernanda D'Avila da Silva, Caroline Brandão Quines, Matias Nunes Frizzo.

  <https://doi.org/10.56238/sevened2026.020-045>

.....757-783

CLINICAL AND LABORATORY PARAMETERS AS PROGNOSTIC AND MONITORING BIOMARKERS IN PATIENTS WITH CARDIOVASCULAR AND METABOLIC DISEASES

Daniele Fernanda Wille, Fernanda D'Avila da Silva, Caroline Brandão Quines, Matias Nunes Frizzo.

 <https://doi.org/10.56238/sevened2026.020-046>

.....874-816

USE OF CANNABIDIOL IN THE PREVENTION OF POSTOPERATIVE COMPLICATIONS AFTER THIRD MOLAR EXTRACTIONS

Natalia Rosa Teixeira, Reginaldo Conceição Vieira Junior, Franciely Ferrari, Marcelo Magalhães Dias, Gabrielle Oliveira de Sousa, Cristiano Veloso, Lizandra Cristina Oriel de Sousa, Adriana do Paço Soares, Karina Imaculada Rosa Teixeira, Raquel Helena Rodrigues Rapozo, Wilker de Castro Magalhães, Eduardo J. M. Martins, Monique Xavier de Sousa, Cecília de Oliveira Costa Amorim, Wilton Costa Neto.

 <https://doi.org/10.56238/sevened2026.020-047>

.....817-826

IMPACT OF POLYPHARMACY ON THE HEALTH OF THE ELDERLY PERSON: NURSING STRATEGIES

Beatriz Ornelas Mascarenhas, Isadora Souza Honorato, Millena Gomes Fonseca, Daniele Pereira Ramos, Luiz Sinésio Silva Neto, Kaiê Wolney Santana Silva, Vanessa Gomes Matos dos Santos, Genilcilene Brito da Conceição Souza.

 <https://doi.org/10.56238/sevened2026.020-048>

.....827-838

HYDROLOGICAL DISASTERS AND HUMAN HEALTH: SCOPING REVIEW

Gregório Neto Batista de Sousa, Emerson Machado de Carvalho, Grasiely Faccin Borges, Renan Borges de Jesus Junior, Adriano Frederico Donatti.

 <https://doi.org/10.56238/sevened2026.020-049>

.....839-852

THERAPEUTIC ALTERNATIVES IN HYPERTENSIVE PATIENTS INTOLERANT TO ACE INHIBITORS/ARBs: A LITERATURE REVIEW

Laura Carbonel Michelutti, Isabela Neves Onives Dias, Clara Tomaz Silva, Camila Martins Dias Rondelli, Isabella Caetano Romão, Ana Luiza Hooper Romeiro Acevedo, Lucas Rocha Cronemberger, Pedro Henrique Simões de Lima Assis, Gabriel Gonçalves de Oliveira Junqueira, Ana Luiza Dantas Portocarrero.

 <https://doi.org/10.56238/sevened2026.020-050>

.....853-867

CHILD FOOD EDUCATION: ASSESSMENT OF DIETARY PROFILE AND PLAYFUL STRATEGIES FOR THE PROMOTION OF HEALTHY HABITS WITH CHILDREN FROM COMMUNITIES IN RECIFE

Euclides José Leão do Nascimento Filho, Ingrid Maria Durval de Alencar, Aline Gabriela Alves da Silva, Emily Vitória Ferreira Alves, Rebeca Suênia Medeiros de Macedo Olímpio, Marcony Edson da Silva Júnior.

 <https://doi.org/10.56238/sevened2026.020-051>

.....868-895

TUBERCULOSIS/HIV/AIDS CO-INFECTION IN PARAÍBA: ANALYSIS OF THE DECADE 2014–2024

Maurício dos Anjos Alves, Carlos Ernandes dos Anjos Alves, Evellyn do Nascimento de Alexandria, Lorena Evelyn Pereira, Mariza Mayume da Silva, Maria Aparecida de Souza Oliveira, Kaellyda Marques Lopes, Basílio Felizardo Lima Neto, Vinicius Longo Ribeiro Vilela, Thais Ferreira Feitosa.

 <https://doi.org/10.56238/sevened2026.020-052>

.....896-902

OPERATIONAL PERFORMANCE INDEXES IN HOSPITALS: CONTROL TOOL FOR AUDITING

Jordana Cargnelutti Ceretta, Rosane Maria Seibert, Clea Beatriz Macagnan.

  <https://doi.org/10.56238/sevened2026.020-053>

.....903-928

IMPACT OF SCHOOL LIFESTYLE ON SPINAL HEALTH IN CHILDREN AND ADOLESCENTS

Laís Hubert Kroger Barbosa de Souza, Paloma da Silva Muniz, Pâmela Rinaldi Aroz D'Almeida Santana, Isabella Andrade Ferreira, Karen Vitória Casilli Paiva, Pedro Henrique de Oliveira Paes.

  <https://doi.org/10.56238/sevened2026.020-054>

.....929-942

TIRZEPATIDE AND THE RISKS OF USE WITHOUT MEDICAL PRESCRIPTION

Bruna Eduarda da Silva, Natalia Dame Alves, Jéssica da Silva Francelino, Amanda Oliva Spaziani, Bruna Marçal Guidoti Eleutério, Fabricio Sidnei da Silva, Dirce Maria Ignácio dos Santos Gonzaga, Rauer Ferreira Franco.

  <https://doi.org/10.56238/sevened2026.020-055>

.....943-956

OMEGA-3 IN REDUCING CARDIOMETABOLIC RISK IN PATIENTS WITH DYSLIPIDEMIA AND METABOLIC SYNDROME: CURRENT CLINICAL EVIDENCE

Valéria Goulart, Livia Lotfi de Moura, Eduardo Duarte Guimarães, Paula Vanuza Rohden Thome, Amanda de Alencar Mariano Lopes, Ana Elisa Rocha Caldeira, Marina Moura, Breno Pigola Garcia, Adriana Cristina Bessa Vaccari Ruiz, Carlos Henrique Aires Magalhães Seixas, Leonardo dos Santos Döbele, Rassyre de Jesus Santos Ulhôa, Lucas de Souza Nunes, Leôncio Pinheiro Pereira, Jéssica Mayara Franciscon, Carla Lorena Moraes de Sousa Carneiro, Vitória Magalhães Gonzaga, Fellipe Augusto Anchieta Freitas, Anderson Alves da Costa, Quezia Juliana Andrade Fiorido, Wesley Wagner dos Santos, Renato Saraiva da Silva, José Francisco Almeida Vieira Filho, Giullyan Nóbrega Primo, Samuel Marques Gomes.

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.....957-967

DIABETES MELLITUS AND MENTAL HEALTH: DEVELOPMENT OF EDUCATIONAL MATERIALS FOR INTEGRATED CARE

Thalia Candido Araujo, Talita Kellen dos Anjos Soares, Felipe Caboi Avelino da Cruz, Júlia Peghini Vilela Borges, Tiago Henrique Faccio Segato, Fabricia Viana Fonseca, Sharon Schilling Landgraf.

  <https://doi.org/10.56238/sevened2026.020-057>

.....968-984

SEX AND ASA CLASSIFICATION, NOT FASTING TIME, ARE ASSOCIATED WITH THE LIKELIHOOD OF COMPLICATIONS IN THE POSTOPERATIVE PERIOD

Adeline Mariano Silva Resende, José Luis Braga de Aquino, Vania Aparecida Leandro-Merhi.

  <https://doi.org/10.56238/sevened2026.020-058>

.....985-1004

FAST, ACCURATE, AND COST-EFFECTIVE: E-FAST'S BREAKTHROUGH IN OPTIMIZING THORACIC TRAUMA MANAGEMENT

Gustavo Pellegrini Magaldi, Vitor Favali Kruger, Hércules Henrique Fachiolli Magaldi, Elcio Shiyoití Hirano, Vania Aparecida Leandro-Merhi, José Luis Braga de Aquino.

  <https://doi.org/10.56238/sevened2026.020-059>

.....1005-1021

DOES ULTRASOUND DETECT JOINT AND INTESTINAL CHANGES IN PSORIATIC ARTHRITIS AND ULCERATIVE COLITIS AFTER IMMUNOBIOLOGICAL TREATMENT: A CASE REPORT

José Alexandre Mendonça, José Luís Braga de Aquino.

 <https://doi.org/10.56238/sevened2026.020-060>

.....1022-1034

COVID-19 VACCINATION AND INFODEMIC: CHALLENGES FOR NURSING IN PROMOTING HEALTH LITERACY

João Pedro Correia Fernandes, Liliana Rodrigues, Gregório Magno Freitas.

 <https://doi.org/10.56238/sevened2026.020-061>

.....1035-1054

ANTINEOPLASTIC POTENTIAL OF PSEUDOBOMBAX MILLEI: PHYTOCHEMICAL, GENOMIC AND MOLECULAR INTEGRATION IN UTERINE LEIOMYOMAS

Ramón Miguel Vargas Vera, Martha Placencia-Ibadango, Cruz Marisol Zerna Bravo, Viviana Katherine Idrovo Chiriboga, Moisés Esteven Zambrano-Burbano, Kalid Stefano Vargas-Silva, Adriana Catalina Demera Marcalupo.

 <https://doi.org/10.56238/sevened2026.020-063>

.....1055-1076

INTEGRATIVE APPROACH IN THE REHABILITATION OF FLACCID TETRAPARESIS AFTER CERVICAL HERNIA: A CASE REPORT

Adriana Maioli Lovatti, Rebeka Ferro Tosta Kalil.

 <https://doi.org/10.56238/sevened2026.020-064>

.....1077-1098

EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON OBSTRUCTIVE SLEEP APNOEA IN PATIENTS WITH OBESITY

Luan Caimar Fuchs, Sebastião Carlos Dias Muniz, Tiago Junqueira Pedras Zuppardo, Carlos Alberto Ilha dos Santos, Eduarda Seixas Frizon, Breno Pigola Garcia, Luísa Nucci Sevá Pereira, Eliana Dorabiallo Bark, Eberson da Silva Rodrigues do Nascimento, Lívia Maria da Silva, Allan Jacques Garcia, André Barreto Damasceno, Milena Costa Rodrigues, Ernandes Felipe da Silva Oliveira, Marcella de Fátima Lomeu Marinho, Leonardo André Perles, Thales Soares Tavares, Emily Miranda D'Assis Leonardo, Joice Patricia Coutinho Nunes, Geovanni Félix Stivanin, Elisabeth Dotti Consolo, Chrystianne Ferreira da Silva Braz Cunha, Carolina Yunes Lima, Thiago Vales de Mesquita.

 <https://doi.org/10.56238/sevened2026.020-065>

.....1099-1109

ARTIFICIAL INTELLIGENCE AND PREVENTIVE PHYSIOTHERAPY: TECHNOLOGICAL STRATEGIES FOR QUALITY OF LIFE AND HEALTH PROMOTION

Marcos Riccelli Costa Mendes, Danusa Costa Mendes, Carlos Riedel Porto Carreiro, Geraldo Flamarion da Ponte Liberato Filho, Francisco José Lopes Cajado, Rickardo Léo Ramos Gomes.

 <https://doi.org/10.56238/sevened2026.020-066>

.....1110-1126

TRAINING IN THE PUBLIC SECTOR: TOWARDS JOB SATISFACTION AND WELL-BEING

Neli Maria Pimentel Fontes, Amanda Raquel de França Filgueiras D'Amorim, Luciane Albuquerque Sá de Souza, Elídio Vanzella.

 <https://doi.org/10.56238/sevened2026.020-067>

.....1127-1144

INVESTIGATION OF ACCESS TO OPHTHALMIC CARE IN CEARÁ: WHAT ARE THE MAIN BARRIERS AND HOW TO INTERVENE?

Paulo Marcelo Ferreira da Rocha Filho, Nicolle Melo Leite Queiroz de Souza, Isadora Mara Cunha Bezerra, Thiago Carvalho Barros de Oliveira.

  <https://doi.org/10.56238/sevened2026.020-068>

.....1145-1155

NEW GUIDELINES FOR PULP TREATMENT WITH BIODENTINE

Isabela de Oliveira Camargo, Evelin Fernandes Lourenço, Letícia Aliceda Rossi, Tawana Pascon, Edgard Bergamaschi Junior, Matheus Bento Medeiros Moscatel, Luis Anselmo Mariotto, Fabiane Lopes Toledo.

  <https://doi.org/10.56238/sevened2026.020-069>

.....1156-1177

THE CONNECTION BETWEEN ALZHEIMER'S DISEASE AND PERIODONTITIS: A RELATIONSHIP THAT GOES BEYOND THE ORAL CAVITY

Jessica Salazar Matute, Bruno Conte Andre.

  <https://doi.org/10.56238/sevened2026.020-070>

.....1178-1185

PROSTHODONTIC REHABILITATION IN PATIENTS WITH BRUXISM: CLINICAL CHALLENGES AND THERAPEUTIC STRATEGIES

Diane Guerra Pereira, Claudiony Henrique Dantas de Sousa Azevedo, Adriana do Paço Soares, Lucas Vinicius da Silva Milani, Carla Cristine Vieira Araújo Machado, Waliston Moreira dos Santos, Felipe Gomes Russo, Ariane Caroline Castro Alves, Gabrielli Souza da Silva, Elcimar Bicego Vilas Bôas, Fabiano de Paiva Sales, Ryan Luiz Guimarães Santos, Marcelo Basílio da Motta Gabriel, Bianca Thuany Maciel, Suzana Vitória de Fátima Konopka, Ana Carolina Valente Figueirôa, Gabriell Mafuz Penteado, Janaína Gomes Maciel, Dayanne Meyrelle Alves da Silva Lima, Paulo Antônio Melo Resende, Ana Carolina Dias da Silva, Matheus Alencar da Silva Vasconcelos, Eduarda de Souza Ricardo, Sthefany Bento e Silva, Leandro Campos Silva.

  <https://doi.org/10.56238/sevened2026.020-071>

.....1186-1200

RETATRUTIDE USE IN THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND OBESITY: AN INTEGRATIVE REVIEW

Gabriela Vitória dos Santos, Ebersson da Silva Rodrigues do Nascimento, Rafaela Oliveira Vidal Carvalho, Miguel Siqueira Teixeira, Paulo Tiago Moura Bezerra, Luís Henrique Santiago Vieira, Iza Pereira Bezerra, Matheus Alvino Liutti de Oliveira Salvadego, Bruna Gabriela Frizzo Alexandre, Silas Basílio do Nascimento, Saile Lucyanne de Oliveira Ruy Nascimento, Marina Moura, Flávio de Oliveira Bastos, Amanda Lobo de Siqueira, Felipe Mendes Machado, Igor Paolinelli e Silva, Amanda Carolina Galvão de Oliveira, Carlos Arthur Marinho da Silva Beltrão, Hélio Bordoli Amestoy, Renata Karam de Almeida, Vitória Gabriela Grando, Tâmilis de Azevedo Neves, Diegomaier Nunes Neri, Tatiane da Silva Oliveira Reis.

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.....1201-1212

THE RELATIONSHIP BETWEEN ORAL CAVITY BACTERIA AND CANCER DEVELOPMENT: MICROBIOLOGICAL EVIDENCE, PATHOGENIC MECHANISMS AND CLINICAL IMPLICATIONS

Gleidson Carlos da Silva Gonçalves, Gabriel Araújo Gonçalves, Matheus da Cruz Rocha, Ana Carolina Magalhães de Oliveira, Áquila Helionay Nascimento dos Santos, Carlos Eduardo Canuto Carvalho, Aracelio Viana Colares, José Walber Gonçalves Castro.

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.....1213-1233

COMBINED THERAPY WITH DONEPEZIL AND MEMANTINE IN THE TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE

TERAPIA COMBINADA COM DONEPEZILA E MEMANTINA NO TRATAMENTO DA DOENÇA DE ALZHEIMER MODERADA A GRAVE

TERAPIA COMBINADA CON DONEPEZILO Y MEMANTINA EN EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER DE MODERADA A GRAVE



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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive, behavioral, and functional decline, particularly in moderate to severe stages. In this context, combination therapy with donepezil, an acetylcholinesterase inhibitor, and memantine, an NMDA receptor antagonist, has been proposed as a therapeutic strategy to enhance clinical outcomes. This study aims to analyze the efficacy and safety of this combination in the treatment of moderate to severe Alzheimer's disease. This is an integrative literature review with a qualitative and descriptive approach, based on studies retrieved from PubMed, SciELO, LILACS, covering publications from 2016 to 2026. The findings indicate that combination therapy provides superior benefits compared to monotherapy in terms of cognition, daily functioning, and behavioral symptoms, although clinical gains are generally modest. A favorable safety profile and potential cost-effectiveness were also observed, particularly in public healthcare settings. It is concluded that the association of donepezil and memantine is a valid therapeutic option, and its use should be individualized according to patient clinical characteristics.

Keywords: Alzheimer's Disease. Donepezil. Memantine. Combination Therapy. Dementia.

RESUMO

A Doença de Alzheimer é uma enfermidade neurodegenerativa progressiva que compromete funções cognitivas, comportamentais e funcionais, especialmente em estágios moderados a graves. Nesse contexto, a terapia combinada com donepezila, um inibidor da acetilcolinesterase, e memantina, um antagonista dos receptores NMDA, tem sido proposta como estratégia terapêutica para potencializar os efeitos clínicos. O presente estudo tem como objetivo analisar a eficácia e segurança dessa associação no tratamento da Doença de Alzheimer moderada a grave. Trata-se de uma revisão integrativa da literatura, de abordagem qualitativa e descritiva, com busca realizada nas bases PubMed, SciELO, LILACS, contemplando publicações entre 2016 e 2026. Os resultados indicam que a terapia combinada apresenta benefícios superiores à monoterapia em relação à cognição, funcionalidade e sintomas comportamentais, embora os ganhos clínicos sejam, em geral, modestos. Observou-se ainda perfil de segurança favorável e potencial custo-efetividade, especialmente em contextos de saúde pública. Conclui-se que a associação entre donepezila e memantina constitui uma alternativa terapêutica válida, devendo ser utilizada de forma individualizada conforme as características clínicas do paciente.

Palavras-chave: Doença de Alzheimer. Donepezila. Memantina. Terapia Combinada. Demência.

RESUMEN

La enfermedad de Alzheimer es una enfermedad neurodegenerativa progresiva que deteriora las capacidades cognitivas, conductuales y funcionales, especialmente en las etapas moderadas a graves. En este contexto, se ha propuesto la terapia combinada con donepezilo, un inhibidor de la acetilcolinesterasa, y memantina, un antagonista del receptor NMDA, como estrategia terapéutica para potenciar los efectos clínicos. Este estudio tiene como objetivo analizar la eficacia y seguridad de esta combinación en el tratamiento de la enfermedad de Alzheimer de moderada a grave. Se trata de una revisión bibliográfica integradora, con un enfoque cualitativo y descriptivo, con búsquedas realizadas en las bases de datos PubMed, SciELO y LILACS, incluyendo publicaciones entre 2016 y 2026. Los resultados indican que la terapia combinada presenta beneficios superiores a la monoterapia en relación con la cognición, la funcionalidad y los síntomas conductuales, aunque las mejoras clínicas son generalmente modestas. También se observó un perfil de seguridad favorable y una posible relación coste-eficacia, especialmente en contextos de

salud pública. Se concluye que la combinación de donepezilo y memantina constituye una alternativa terapéutica válida y debe utilizarse de forma individualizada según las características clínicas de cada paciente.

Palabras clave: Enfermedad de Alzheimer. Donepezilo. Memantina. Terapia Combinada. Demencia.

1 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia in the elderly population, being a progressive neurodegenerative disease characterized by cognitive decline, functional impairment and behavioral changes that significantly impact the quality of life of patients and their caregivers. In this context, it is a relevant global public health problem, especially in view of the aging population and the significant increase in its prevalence. Its pathophysiology is complex and multifactorial, involving the accumulation of beta-amyloid plaques, the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, and important neurochemical alterations, such as cholinergic deficit and glutamatergic excitotoxicity, processes that directly contribute to synaptic dysfunction and progressive neuronal loss, configuring the main mechanisms underlying the clinical evolution of the disease (Costa et al., 2024; Rosado, 2021).

In the therapeutic field, the available pharmacological approaches are predominantly symptomatic, especially acetylcholinesterase inhibitors, such as donepezil, and NMDA receptor antagonists, such as memantine. These drugs act on pathways distinct from the pathophysiology of AD, with donepezil being responsible for increasing the availability of acetylcholine in synapses, while memantine reduces the effects of glutamate-mediated excitotoxicity, promoting modulation of neurotransmission (Neto et al., 2025; Lemos et al., 2024).

In the moderate to severe stages of the disease, greater functional impairment is observed, with significant loss of autonomy and intensification of cognitive and behavioral symptoms, which limits the effectiveness of isolated interventions. In this context, the combination therapy between donepezil and memantine has been proposed as a potentially more effective strategy, based on synergistic action on different neurotransmitter systems involved in the pathophysiology of the disease (Feitoza et al., 2024; Oliveira et al., 2026).

In addition to clinical outcomes, recent literature has emphasized the importance of economic evaluation of these interventions. Evidence indicates that the use of memantine, alone or in association with donepezil, can have a positive impact on the cost-effectiveness ratio, especially in public health systems such as the Unified Health System (SUS), by contributing to the slowing of disease progression, reduction of institutionalization, and reduction of the care burden (De Azevedo Filho et al., 2025).

However, despite the potential clinical and economic benefits, there are still controversies in the literature regarding the magnitude of the effects of combination therapy and its superiority over monotherapy. Studies present heterogeneous results, especially with regard to functionality, behavioral symptoms, and quality of life, reinforcing the need for

critical, up-to-date, and methodologically robust analyses on the subject (Caramelli et al., 2022; Silveira Sales and Silva et al., 2024).

In view of this scenario, the present study aims to critically analyze the efficacy, safety, and applicability of the combination therapy with donepezil and memantine in the treatment of Alzheimer's disease in moderate to severe stages, based on the available scientific evidence.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a qualitative approach, conducted according to the methodological proposal of Whittemore and Knafl (2005), with the objective of analyzing the efficacy, safety and applicability of the combined therapy with donepezil and memantine in the treatment of Alzheimer's Disease in moderate to severe stages. The integrative review was chosen because it allows the comprehensive synthesis of different methodological designs, enabling the integration of evidence from clinical and observational studies and systematic reviews.

The bibliographic search was carried out in the PubMed/MEDLINE, SciELO and LILACS databases, recognized for their relevance in the indexing of scientific literature in the health area. As a complementary strategy, a manual search was performed in the reference lists of the selected studies.

Controlled and uncontrolled descriptors in Portuguese and English were used, combined by Boolean operators, including: ("Alzheimer Disease" OR "Alzheimer's Disease") AND "Donepezil" AND "Memantine" AND "Combination Therapy". The searches included publications in the period from 2016 to 2026.

The inclusion criteria included original articles, clinical trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines that directly addressed the use of donepezil and memantine combination therapy in patients with moderate to severe Alzheimer's disease, available in full. Duplicate studies, case reports, incomplete articles, and those that were not directly related to the proposed objective were excluded.

The study selection process was carried out in stages, by reading the titles and abstracts to identify potentially relevant studies, followed by the analysis of the full texts of the eligible articles, according to the previously established criteria.

Data analysis was carried out using a descriptive and analytical approach, with the organization of findings into thematic categories related to clinical outcomes, safety, cost-effectiveness, and applicability of the combined therapy, allowing a critical synthesis of the available evidence.

3 RESULTS

The analysis of the selected studies showed that the combination therapy with donepezil and memantine has a positive impact on different clinical outcomes in patients with moderate to severe Alzheimer's disease. In general, it was observed that the drug association is related to the improvement or deceleration of cognitive decline when compared to monotherapy, especially in more advanced stages of the disease, although with variations in the magnitude of the effects between the studies analyzed (FEITOZA et al., 2024; LEMOS et al., 2024; BIRKS; HARVEY, 2018).

In addition to cognitive outcomes, it was evidenced that combined therapy contributes to better performance in activities of daily living, with longer maintenance of patients' functional autonomy. Additionally, positive effects on behavioral and psychological symptoms of dementia were observed, including agitation, aggressiveness, and mood swings, aspects that directly impact the quality of life and burden of caregivers (OLIVEIRA et al., 2019; LEMOS et al., 2024; SILVEIRA SALES E SILVA et al., 2024).

Regarding safety, studies have indicated that combination therapy has a profile similar to that of monotherapies, and is considered well tolerated. The most frequently reported adverse events included gastrointestinal symptoms, dizziness, and headache, with no significant increase in serious events, which reinforces its applicability in clinical practice (LEMOS et al., 2024; KUMAR; GUPTA; SHARMA, 2023).

From an economic point of view, evidence suggests that the association between donepezil and memantine may be cost-effective, especially in public health systems, by contributing to the slowdown of disease progression and reduction of the need for intensive care. However, some studies indicate that, although statistically significant, clinical benefits tend to be modest and variable among patients, depending on factors such as disease stage and individual characteristics, which may influence the interpretation of the results (DE AZEVEDO FILHO et al., 2025; OLIVEIRA et al., 2019; CARAMELLI et al., 2022).

In general, the findings indicate that combination therapy is an effective and safe therapeutic strategy, with a positive impact on multiple clinical domains, although the magnitude of its effects varies among the included studies.

4 DISCUSSION

The findings of this review suggest that donepezil and memantine combination therapy outperforms monotherapy in patients with moderate to severe Alzheimer's disease, particularly on outcomes related to cognition, functionality, and behavioral symptoms. This benefit can be explained by the complementary action on the cholinergic and glutamatergic

systems, promoting a broader modulation of the neurochemical mechanisms involved in the progression of the disease (Feitoza et al., 2024; Lemos et al., 2024).

From the pathophysiological perspective, the pharmacological combination is based on the hypothesis of therapeutic synergism, since acetylcholinesterase inhibitors increase the availability of acetylcholine in synapses, while memantine acts in the modulation of excitotoxicity mediated by NMDA receptors. This interaction can contribute to the preservation of neuronal function and slow clinical progression, especially in more advanced stages of the disease (Neto, 2025).

However, the magnitude of these benefits remains controversial. Evidence indicates that, although combination therapy has statistically significant superiority over monotherapy, clinical gains tend to be modest, especially in functional and behavioral outcomes, which suggests that statistical significance does not always translate into relevant clinical benefit in care practice (Oliveira et al., 2019; Caramelli et al., 2022).

In addition, the methodological heterogeneity of the included studies, with a predominance of observational designs and variations in clinical assessment instruments, may influence the consistency of the results. The lack of standardization in the outcomes analyzed and the limited follow-up time in some studies also represent important limitations, which may overestimate or underestimate the effects of combined therapy.

From an economic point of view, the literature suggests that the association between donepezil and memantine can be cost-effective, especially in public health systems, by slowing the progression of the disease and reducing the need for institutional care. However, these benefits depend directly on factors such as treatment adherence, time of use, and access to medications, which can significantly impact the observed outcomes (De Azevedo Filho et al., 2025; Oliveira et al., 2019).

Another relevant aspect refers to interindividual heterogeneity in the therapeutic response, possibly related to genetic factors, stage of the disease, and associated comorbidities, reinforcing the need for individualized therapeutic strategies centered on the clinical profile of each patient (Silveira Sales and Silva et al., 2024).

Finally, although combination therapy has a safety profile similar to that of monotherapies, continuous monitoring is essential to ensure the maintenance of clinical benefit and the early identification of adverse effects, especially in elderly patients and those with multiple comorbidities (Lemos et al., 2024).

Thus, despite the favorable evidence, important gaps persist in the literature, especially related to the magnitude of the clinical benefit, the standardization of outcomes, and the scarcity of long-term randomized clinical trials, reinforcing the need for more robust

studies, with a rigorous methodological design and prolonged follow-up, to better define the real clinical impact of combination therapy in care practice.

5 CONCLUSION

Combined therapy with donepezil and memantine is a relevant therapeutic strategy in the management of moderate to severe Alzheimer's disease, as it acts in a complementary way on different pathophysiological mechanisms of the disease. Evidence indicates superiority over monotherapy, although the clinical benefits observed are generally modest and heterogeneous among patients.

In this context, the effectiveness of the therapy is directly related to the individualization of the conduct, considering factors such as the stage of the disease, clinical profile and adherence to treatment. In addition, the favorable safety profile and cost-effective potential reinforce its applicability, especially in public health systems.

However, uncertainties persist regarding the magnitude of the clinical benefit and its relevance in care practice, highlighting the need for more robust studies, with a rigorous methodological design and long-term follow-up.

Thus, combination therapy should be understood as a valid therapeutic option, but not universal, whose indication should be based on individualized clinical criteria and on the critical evaluation of the available evidence.

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ASSOCIATION BETWEEN GLP-1 ANALOGUES AND PANCREATITIS: AN INTEGRATIVE REVIEW OF CURRENT EVIDENCE

ASSOCIAÇÃO ENTRE ANÁLOGOS DE GLP-1 E PANCREATITE: REVISÃO INTEGRATIVA DAS EVIDÊNCIAS ATUAIS

ASOCIACIÓN ENTRE ANÁLOGOS DE GLP-1 Y PANCREATITIS: UNA REVISIÓN INTEGRAL DE LA EVIDENCIA ACTUAL



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ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists have been widely used in the treatment of Type 2 Diabetes Mellitus and obesity due to their effectiveness in glycemic control and weight reduction. However, concerns regarding their pancreatic safety, particularly the risk of acute pancreatitis, have been raised in the scientific literature. This study aimed to analyze the association between the use of GLP-1 analogues and the occurrence of pancreatitis through an integrative literature review. The search was conducted in PubMed/MEDLINE, SciELO, and LILACS, including studies published between 2016 and 2026. Original articles, observational studies, systematic reviews, meta-analyses, and clinical guidelines available in full text were included. The results demonstrated that GLP-1 analogues have a well-established efficacy profile; however, findings regarding pancreatitis risk are heterogeneous. Observational studies suggest a possible association, whereas systematic reviews do not demonstrate a statistically significant increase in risk, indicating a low absolute risk and no definitive causal relationship. It is concluded that, although a direct causal association cannot be established, caution is recommended when prescribing these drugs, especially in patients with risk factors, and further studies are needed to better clarify this potential relationship.

Keywords: GLP-1. Acute Pancreatitis. Type 2 Diabetes Mellitus. Obesity. Drug Safety.

RESUMO

Os análogos do GLP-1 têm sido amplamente utilizados no tratamento do Diabetes Mellitus tipo 2 e da obesidade, em virtude de sua eficácia no controle glicêmico e na redução do peso corporal. Entretanto, questionamentos acerca de sua segurança pancreática, especialmente quanto ao risco de pancreatite aguda, têm sido levantados na literatura científica. O presente estudo teve como objetivo analisar a associação entre o uso de análogos do GLP-1 e a ocorrência de pancreatite, por meio de uma revisão integrativa da literatura. A busca foi realizada nas bases de dados PubMed/MEDLINE, SciELO e LILACS, incluindo estudos publicados entre 2016 e 2026. Foram incluídos artigos originais, estudos observacionais, revisões sistemáticas, metanálises e diretrizes clínicas disponíveis na íntegra. Os resultados evidenciaram que os análogos do GLP-1 apresentam perfil de eficácia consolidado; contudo, os achados referentes ao risco de pancreatite mostram-se heterogêneos. Estudos observacionais sugerem possível associação, enquanto revisões sistemáticas não demonstram aumento estatisticamente significativo do risco, indicando baixo risco absoluto e ausência de relação causal definida. Conclui-se que, embora não seja possível estabelecer associação causal direta, recomenda-se cautela na prescrição, especialmente em pacientes com fatores de risco, sendo necessários estudos adicionais para melhor elucidação dessa possível relação.

Palavras-chave: GLP-1. Pancreatite Aguda. Diabetes Mellitus Tipo 2. Obesidade. Segurança Medicamentosa.

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RESUMEN

Los análogos del GLP-1 se han utilizado ampliamente en el tratamiento de la diabetes mellitus tipo 2 y la obesidad debido a su eficacia en el control glucémico y la reducción del peso corporal. Sin embargo, en la literatura científica se han planteado dudas sobre su seguridad pancreática, especialmente en lo que respecta al riesgo de pancreatitis aguda. Este estudio tuvo como objetivo analizar la asociación entre el uso de análogos del GLP-1 y la aparición de pancreatitis mediante una revisión integradora de la literatura. La búsqueda se realizó en las bases de datos PubMed/MEDLINE, SciELO y LILACS, incluyendo estudios publicados entre 2016 y 2026. Se incluyeron artículos originales, estudios observacionales, revisiones sistemáticas, metaanálisis y guías clínicas disponibles en su totalidad. Los resultados mostraron que los análogos del GLP-1 tienen un perfil de eficacia consolidado; sin embargo, los hallazgos sobre el riesgo de pancreatitis son heterogéneos. Los estudios observacionales sugieren una posible asociación, mientras que las revisiones sistemáticas no demuestran un aumento estadísticamente significativo del riesgo, lo que indica un riesgo absoluto bajo y la ausencia de una relación causal definida. Se concluye que, si bien no es posible establecer una relación causal directa, se recomienda precaución en la prescripción, especialmente en pacientes con factores de riesgo, y se necesitan más estudios para dilucidar mejor esta posible relación.

Palabras clave: GLP-1. Pancreatitis Aguda. Diabetes Mellitus Tipo 2. Obesidad. Seguridad Farmacológica.

1 INTRODUCTION

Type 2 diabetes mellitus (DM2) and obesity are important global public health problems, associated with high morbidity and mortality and substantial socioeconomic impacts. These conditions share complex pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, and systemic metabolic dysfunctions, which reinforces the need for more effective, integrated, and multi-axis therapeutic approaches (VOGT et al., 2025; CHRIST et al., 2025).

In this scenario, recent advances in metabolic pharmacotherapy have boosted the use of drugs based on glucagon-like peptide type 1 (GLP-1), especially its receptor agonists (GLP-1RA), which demonstrate high efficacy in glycemic control and body weight reduction (STAICO et al., 2023; PACHECO et al., 2025). These agents act by modulating the incretin axis, promoting glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, and increased satiety, contributing significantly to the management of T2DM and obesity (BARROS et al., 2021; LIMA MACIEL et al., 2026). In addition, evidence from clinical studies and cardiovascular outcome analyses indicate additional benefits, especially in reducing major cardiovascular events, increasing its therapeutic relevance (VOGT et al., 2025).

However, the rapid expansion of the clinical use of GLP-1 receptor agonists, including molecules such as semaglutide and liraglutide, has been accompanied by growing questions about their safety profile, particularly with regard to pancreatic adverse events (MAGALHÃES et al., 2025). Acute pancreatitis, an inflammatory condition of the pancreas with variable clinical presentation, can progress from mild and self-limiting forms to severe conditions, associated with organ dysfunction and increased mortality (MATOS et al., 2025).

From the pathophysiological point of view, it has been hypothesized that GLP-1 agonists may influence pancreatic dynamics through stimulation of ductal and acinar cells, in addition to possible effects on cell proliferation and the inflammatory microenvironment, although such mechanisms remain controversial and not fully elucidated in the current literature. At the same time, classical etiological factors, such as gallstones, alcoholism, and metabolic disorders, continue to be the main determinants of pancreatitis, which complicates the causal attribution to drug use.

In this context, the possible association between GLP-1 receptor agonists and pancreatitis has been extensively investigated through observational studies, pharmacovigilance databases, and systematic reviews. However, the findings remain inconsistent, reflecting methodological heterogeneity, the presence of confounding biases, and limitations inherent to the designs used (SILVA et al., 2024; FONSECA et al., 2024).

Although some studies suggest increased risk, more robust analyses indicate that the absolute risk of pancreatitis associated with these agents is low, and it is not possible to establish a definitive causal relationship to date (FONSECA et al., 2024).

In addition, it should be considered that individuals with DM2 and obesity have an increased baseline risk for pancreatic diseases, which represents an important confounding factor and makes it difficult to interpret the available findings (INDIANI et al., 2025). Such a scenario highlights the need for critical analysis of the evidence, with attention to methodological limitations and the clinical applicability of the results.

Given this scenario, there is a gap in the consolidation of the available evidence, especially with regard to the magnitude of the risk, the consistency of the findings, and the pathophysiological mechanisms potentially involved. Thus, the present study aims to analyze, through an integrative review of the literature, the association between the use of GLP-1 receptor agonists and the occurrence of pancreatitis, seeking to critically synthesize the most recent evidence and contribute to a more robust evaluation of the safety of these drugs in clinical practice.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a qualitative and descriptive approach, conducted according to the steps proposed by Whittemore and Knafl (2005), which include: identification of the problem, search in the literature, evaluation of data, analysis and synthesis of results.

The search was carried out in the PubMed/MEDLINE, SciELO and LILACS databases, including studies published in the period from 2016 to 2026. Controlled and uncontrolled descriptors in English and Portuguese were used, based on the terms MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors), including: "GLP-1 receptor agonists", "GLP-1 analogs", "pancreatitis", "acute pancreatitis", "diabetes mellitus type 2" and "obesity", as well as their counterparts in Portuguese.

The search strategy was structured using Boolean operators (AND and OR), according to the following model: ("GLP-1 receptor agonists" OR "GLP-1 analogs") AND ("pancreatitis" OR "acute pancreatitis") AND ("diabetes mellitus type 2" OR "obesity"), adapted according to the specificities of each database.

The following inclusion criteria were established: original articles, randomized clinical trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines that directly addressed the association between GLP-1 analogues and pancreatitis; studies published in the delimited period; and articles available in full. Duplicate studies, isolated

case reports, studies with low methodological rigor, and those that did not have a direct relationship with the research objective were excluded.

The selection of studies was carried out in stages, including reading of titles, abstracts and, subsequently, full texts, according to the previously defined eligibility criteria. After this stage, the selected studies were read in full to extract the relevant data.

The data were organized and analyzed in a descriptive manner, and were later grouped into thematic categories, according to the convergence of the findings, including: metabolic efficacy, weight reduction, safety profile, and association with pancreatitis. This process allowed the comparison between the studies and the identification of patterns, divergences, and gaps in the literature.

Finally, the synthesis of the data was carried out in a critical and integrative manner, enabling the construction of a comprehensive analysis of the available evidence, with emphasis on the safety and risk of pancreatitis associated with the use of GLP-1 receptor agonists, contributing to evidence-based clinical practice.

3 RESULTS

The search in the databases resulted in the identification of relevant studies on the association between GLP-1 receptor agonists and the occurrence of acute pancreatitis. After applying the eligibility criteria, publications were included between 2016 and 2026, covering different methodological designs, including observational studies, systematic reviews, and pharmacovigilance analyses.

In general, studies have shown that GLP-1 receptor agonists are associated with improved glycemic control in individuals with type 2 diabetes mellitus, with a consistent reduction in glycated hemoglobin levels, a finding observed recurrently in different study designs (VOGT et al., 2025).

In the context of body weight, evidence indicated an association between the use of GLP-1 analogues and weight reduction in overweight and obese individuals. Studies have attributed this effect to appetite modulation and delayed gastric emptying, resulting in increased satiety and reduced caloric intake (LIMA MACIEL et al., 2026). Additionally, sustained weight loss over time has been described, as well as improvement in metabolic parameters, including insulin resistance and lipid profile (RAMOS et al., 2024; SANT'ANA, 2023). Among the most frequently reported drugs, semaglutide and liraglutide stood out, consistently associated with the metabolic outcomes described (STAICO et al., 2023).

Regarding the safety profile, studies have reported that the adverse effects most frequently associated with the use of GLP-1 receptor agonists are gastrointestinal in nature,

including nausea, vomiting, and abdominal discomfort, especially in the early stages of treatment (LACERDA LEOPOLDINO et al., 2025). In addition, comparative studies have described favorable effects on cardiovascular outcomes in patients with associated comorbidities (MAGALHÃES et al., 2025).

Regarding the occurrence of pancreatitis, observational studies and pharmacovigilance analyses have reported cases in patients using GLP-1 receptor agonists, particularly among individuals with previous risk factors, such as obesity and metabolic disorders (SILVA et al., 2024). Reviews involving specific drugs, such as semaglutide, have also described the occurrence of pancreatitis, without establishing a direct causal relationship (LEITE et al., 2024).

On the other hand, systematic reviews indicated the absence of a statistically significant increase in the risk of pancreatitis associated with the use of these drugs, with a description of low absolute risk in the studies analyzed (FONSECA et al., 2024). Similar findings have been reported in other investigations, which have highlighted the inconsistency of the results and the methodological heterogeneity among the available studies (MATOS et al., 2025).

Additionally, it has been described that individuals with type 2 diabetes mellitus and obesity have an increased baseline risk for pancreatic diseases, and this factor is pointed out as a potential confounding variable in the analysis of the association between the use of GLP-1 receptor agonists and the occurrence of pancreatitis (INDIANI et al., 2025). Finally, studies have highlighted the need for clinical monitoring during the use of these drugs, especially in the face of the occurrence of rare adverse events (CHRIST et al., 2025).

4 DISCUSSION

The analysis of the included studies shows that GLP-1 receptor agonists have consistent efficacy in the management of type 2 diabetes mellitus and obesity, with a significant impact on the reduction of glycemic levels and body weight. These findings were observed recurrently across different methodological designs, including observational studies and clinical trials, which reinforces the robustness of the available evidence (VOGT et al., 2025; LIMA MACIEL et al., 2026). Similarly, Ramos et al. (2024) and Sant'Ana (2023) describe sustained weight reduction, while Magalhães et al. (2025) report additional benefits in cardiovascular outcomes, expanding the spectrum of clinical applicability of these drugs.

Despite the well-established metabolic benefits, the pancreatic safety of GLP-1 receptor agonists remains a point of debate in the literature. Observational studies and data from pharmacovigilance, such as those presented by Silva et al. (2024), suggest a possible

association between the use of these drugs and the increased incidence of acute pancreatitis, especially in individuals with previous risk factors. Convergently, Leite et al. (2024) report cases of pancreatitis associated with the use of semaglutide, indicating the need for clinical monitoring.

On the other hand, evidence from systematic reviews and analyses with greater methodological rigor do not consistently corroborate this association. Fonseca et al. (2024) demonstrate the absence of a statistically significant increase in the risk of pancreatitis among users of GLP-1 analogues, while Matos et al. (2025) highlight that the current evidence is insufficient to establish a direct causal relationship. This contrast between the findings suggests the influence of methodological factors, including heterogeneity among studies, selection bias, and possible confounding *by indication phenomena*, in which the clinical condition that indicates the use of the drug may be associated with the outcome investigated.

In addition, individuals with type 2 diabetes mellitus and obesity have an increased baseline risk for pancreatic diseases, which can act as an important confounding variable and make it difficult to interpret the results (INDIANI et al., 2025). This aspect reinforces the need for caution in attributing causality, especially in observational studies.

From the pathophysiological point of view, it has been proposed that GLP-1 receptor agonists may influence pancreatic function through modulation of acinar and ductal cells, in addition to potential effects on the pancreatic inflammatory microenvironment. However, such mechanisms remain controversial and have not yet been fully elucidated, which limits the interpretation of the available clinical findings.

Regarding the global safety profile, Lacerda Leopoldino et al. (2025) highlight that the most frequent adverse effects are gastrointestinal in nature, while pancreatic events are considered rare. In consonance, Christ et al. (2025) point out that, in the general context, these drugs have a favorable safety profile, particularly when considering their metabolic benefits.

Another relevant aspect refers to the growing incorporation of these drugs in clinical practice. Staico et al. (2023) and Pacheco et al. (2025) highlight the wide use of agents such as semaglutide and liraglutide, which may contribute to greater detection of rare adverse events in post-marketing studies, influencing the perception of risk associated with these drugs.

Thus, it is observed that the literature presents conflicting results regarding the association between GLP-1 receptor agonists and pancreatitis. While some studies suggest a possible increase in risk, more robust evidence does not consistently confirm this

relationship. In this context, the available findings indicate that the risk of pancreatitis associated with these drugs remains low, although it cannot be completely ruled out.

Thus, the interpretation of the data should consider the methodological limitations of the studies, as well as the clinical characteristics of the populations evaluated. Overall, current evidence suggests that the benefit-risk profile of GLP-1 receptor agonists is favorable in most clinical settings, provided their use is accompanied by adequate monitoring and therapeutic individualization.

5 CONCLUSION

GLP-1 analogues have been consolidated as an important therapeutic strategy in the management of type 2 diabetes mellitus and obesity, demonstrating consistent efficacy in glycemic control and body weight reduction, in addition to additional metabolic benefits widely described in the literature. These factors have contributed to its increasing incorporation into clinical practice.

However, the possible association with acute pancreatitis remains a controversial topic. Although observational studies and clinical reports suggest a possible increased risk, evidence from systematic reviews and meta-analyses does not demonstrate a consistent causal association, indicating that the absolute risk described is low.

In this context, the available findings suggest that the benefit-risk profile of GLP-1 analogues is globally favorable in most clinical scenarios, provided that their use is carried out in a judicious and individualized manner. Caution is advised in patients with a prior history of pancreatitis or with multiple predisposing factors, in whom the indication should be carefully evaluated.

Finally, the need for additional studies with greater methodological rigor and long-term follow-up is highlighted, in order to elucidate more definitively the possible relationship between the use of these drugs and pancreatic events, contributing to a safer and evidence-based clinical practice.

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MAXILLARY SINUS LIFT: COMPARISON BETWEEN THE LATERAL WINDOW TECHNIQUE AND THE TRANSCRESTAL TECHNIQUE

LEVANTAMENTO DE SEIO MAXILAR: COMPARAÇÃO ENTRE A TÉCNICA DA JANELA LATERAL E A TÉCNICA TRANSCRESTAL

ELEVACIÓN DEL SENO MAXILAR: COMPARACIÓN ENTRE LA TÉCNICA DE VENTANA LATERAL Y LA TÉCNICA TRANSCRESTAL



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ABSTRACT

Maxillary sinus lift is a widely used procedure to enable dental implant placement in the posterior maxilla in cases of reduced bone height. Among the available techniques, the lateral window approach and the transcrestal technique stand out, presenting differences regarding invasiveness, bone gain, and postoperative morbidity. This study aimed to perform an integrative literature review comparing these two techniques in terms of indications, advantages, limitations, and clinical outcomes. The search was conducted in PubMed, SciELO, and ScienceDirect databases using specific descriptors combined with Boolean operators. Clinical studies, randomized trials, systematic reviews, and observational studies published between 2012 and 2025 were included. The results showed that both techniques present high implant survival and success rates. The lateral window technique demonstrated superior bone gain, especially in cases of severe atrophy, whereas the transcrestal technique showed lower morbidity and greater patient comfort. It is concluded that the choice of technique should be individualized, considering anatomical factors, residual bone height, and case complexity.

Keywords: Maxillary Sinus Lift. Dental Implants. Lateral Window Technique. Transcrestal Technique. Bone Graft.

RESUMO

O levantamento de seio maxilar é um procedimento amplamente utilizado para viabilizar a instalação de implantes dentários na região posterior da maxila em casos de altura óssea reduzida. Dentre as técnicas disponíveis, destacam-se a abordagem pela janela lateral e a técnica transcrestal, que apresentam diferenças quanto à invasividade, ganho ósseo e morbidade pós-operatória. O presente estudo teve como objetivo realizar uma revisão integrativa da literatura, comparando essas duas técnicas quanto às suas indicações, vantagens, limitações e resultados clínicos. A busca foi realizada nas bases de dados PubMed, SciELO e ScienceDirect, utilizando descritores específicos combinados por operadores booleanos. Foram incluídos estudos clínicos, ensaios randomizados, revisões sistemáticas e estudos observacionais publicados entre 2012 e 2025. Os resultados demonstraram que ambas as técnicas apresentam elevadas taxas de sucesso e sobrevivência dos implantes. A técnica da janela lateral mostrou-se superior em termos de ganho ósseo, especialmente em casos de atrofia severa, enquanto a técnica transcrestal apresentou menor morbidade e maior conforto ao paciente. Conclui-se que a escolha da técnica deve ser individualizada, considerando fatores anatômicos, altura óssea residual e complexidade do caso clínico.

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Palavras-chave: Levantamento de Seio Maxilar. Implantes Dentários. Janela Lateral. Técnica Transcrestal. Enxerto Ósseo.

RESUMEN

El levantamiento de seno maxilar es un procedimiento ampliamente utilizado para permitir la colocación de implantes dentales en el maxilar posterior en casos de altura ósea reducida. Entre las técnicas disponibles, destacan el abordaje por ventana lateral y la técnica transcrestal, que difieren en cuanto a invasividad, ganancia ósea y morbilidad postoperatoria. Este estudio tuvo como objetivo realizar una revisión bibliográfica integradora, comparando estas dos técnicas en cuanto a sus indicaciones, ventajas, limitaciones y resultados clínicos. La búsqueda se realizó en las bases de datos PubMed, SciELO y ScienceDirect, utilizando descriptores específicos combinados con operadores booleanos. Se incluyeron estudios clínicos, ensayos aleatorizados, revisiones sistemáticas y estudios observacionales publicados entre 2012 y 2025. Los resultados demostraron que ambas técnicas presentan altas tasas de éxito y supervivencia de los implantes. La técnica por ventana lateral demostró ser superior en términos de ganancia ósea, especialmente en casos de atrofia severa, mientras que la técnica transcrestal mostró menor morbilidad y mayor comodidad para el paciente. Se concluye que la elección de la técnica debe individualizarse, considerando factores anatómicos, altura ósea residual y la complejidad del caso clínico.

Palabras clave: Elevación del Seno Maxilar. Implantes Dentales. Ventana Lateral. Técnica Transcrestal. Injerto Óseo.

1 INTRODUCTION

The present study is characterized as an integrative review of the literature, of a qualitative nature and descriptive approach, conducted according to the methodological assumptions described by Whitemore and Knafl (2005), with the objective of analyzing and comparing the techniques of maxillary sinus lifting through the lateral window and the transcrestal approach, based on available scientific evidence.

The search for scientific articles was carried out in the electronic databases PubMed, SciELO and ScienceDirect, selected for their relevance in the health area and wide indexing of national and international scientific journals. For the search strategy, the following descriptors were used: "maxillary sinus lift", "lateral window technique", "transcrestal sinus lift", "osteotome technique" and "sinus floor elevation", combined by means of the Boolean operators AND and OR, according to the structured strategy: ("maxillary sinus lift" OR "sinus floor elevation") AND ("lateral window technique" OR "transcrestal sinus lift" OR "osteotome technique").

As inclusion criteria, articles published between 2012 and 2025, available in full, in English and Portuguese, involving clinical studies in humans and that directly addressed maxillary sinus lift and the comparison between lateral and transcrestal window techniques, were selected. Clinical trials, randomized studies, systematic reviews, and observational studies were included. Exclusion criteria included duplicate articles, studies that did not have a direct relationship with the proposed theme, isolated case reports with no comparative relevance, in vitro studies, and publications with restricted access to the full text.

The study selection process was carried out in stages. Initially, the titles and abstracts of the articles identified in the databases were read, followed by the complete reading of the potentially eligible studies. After applying the eligibility criteria, the articles that made up the final sample of this review were selected.

For data extraction and analysis, the following variables were considered: clinical indications, residual bone height, bone gain obtained, implant survival rate, postoperative morbidity, associated complications, type of biomaterial used, and follow-up time of the studies.

The data were organized in a descriptive and comparative way, allowing a critical analysis of the evidence available in the literature and the construction of a discussion about the advantages, disadvantages and clinical applicability of maxillary sinus lift techniques.

2 RESULTS AND DISCUSSION

The analysis of the selected studies shows that maxillary sinus lifting, both by the lateral window technique and by the transcrestal technique, is a highly predictable and consolidated procedure in rehabilitation with implants in the posterior region of the maxilla. Such predictability is directly related to the ability of these techniques to promote vertical augmentation of the alveolar ridge, enabling the installation of implants even in conditions of severe bone atrophy, as widely described in recent literature (TSAI et al., 2020; ZHOU et al., 2020; LYU et al., 2023).

2.1 IMPLANT SURVIVAL

The data analyzed demonstrate that both techniques have high implant survival rates, with no statistically significant differences in most of the clinical studies and systematic reviews available (DEL FABBRO et al., 2012; PIJETURSSON et al., 2008; WALLACE; FROUM, 2003). These findings reinforce the predictability of maxillary sinus lift as a reliable procedure for posterior maxillary rehabilitation.

Tsai et al. (2020) reported an overall survival rate of 98.9% in severely atrophic maxillae, regardless of the technique employed, including one- and two-stage approaches. Similarly, Zhou et al. (2020) observed a clinical success rate of 100% after 24 months of follow-up, both for the transcrestal technique and for the lateral window technique, with maintenance of peri-implant bone stability throughout the period evaluated.

Additional studies corroborate these results, demonstrating that the survival rate of implants in maxillary sinus lift procedures remains high in the long term, even under unfavorable anatomical conditions (JENSEN; TERHEYDEN, 2009; POMMER et al., 2012). These data suggest that the success of osseointegration is more related to the correct indication of the technique, surgical planning, and the primary stability of the implant than to the type of approach used.

Thus, although there are differences between the techniques in terms of invasiveness and bone gain, the literature is consistent in demonstrating that both provide predictable and safe clinical results regarding implant survival. Thus, the choice of technique should not be based exclusively on the success rate, but rather on an individualized analysis that considers anatomical factors, extent of the bone defect, systemic conditions of the patient, and experience of the professional (LYU et al., 2023).

2.2 BONE GAIN

Regarding vertical bone gain, the literature shows a consistent trend towards superiority of the lateral window technique, especially in cases of greater bone involvement and lower residual bone height (DEL FABBRO et al., 2012; PIJETURSSON et al., 2008). This approach allows greater surgical access and direct control of the sinus cavity, favoring the creation of an adequate subantral space for the insertion of a larger volume of biomaterial.

Comparative clinical studies corroborate this evidence. Zhou et al. (2020) observed that endosinus bone gain was significantly higher in the lateral window technique after 24 months of follow-up, evidencing greater volumetric stability of the graft over time. Similarly, Tsai et al. (2020) demonstrated that, in situations of residual bone height ≤ 3 mm, the two-stage lateral approach provided superior bone gain when compared to the transcrestal technique.

From a biological point of view, this superiority can be explained by the greater manipulation capacity of the Schneider membrane and the formation of a more stable three-dimensional space, delimited by the lateral wall of the maxillary sinus, the alveolar bone crest, and the elevated sinus membrane. This environment favors bone neoformation and the maintenance of graft volume over time (LYU et al., 2023).

However, despite the greater amount of bone obtained with the lateral technique, histological studies indicate that the quality of the newly formed bone tissue is similar between the techniques. Esfahanizadeh et al. (2012) demonstrated that there are no significant differences in the formation of vital bone, connective tissue, and residual material between the lateral approach and the osteotome technique.

In addition, the transcrestal technique has shown satisfactory clinical results in terms of bone gain in well-selected cases, especially when associated with technological advances, such as hydraulic systems and precision instruments (TORRES et al., 2017; DI FRISCHIA et al., 2025). These features allow greater control of the elevation of the sinus membrane, expanding the indications for this technique even in situations of lower residual bone height.

Thus, although the lateral window technique is superior in terms of absolute bone gain and predictability in severe cases, the transcrestal technique can provide adequate clinical results when correctly indicated. Thus, the choice of technique should consider not only the desired bone volume, but also the complexity of the case, the anatomical conditions, and the surgeon's experience.

2.3 POSTOPERATIVE MORBIDITY

Regarding postoperative morbidity, the literature consistently demonstrates that the transcrestal technique has significant advantages when compared to the lateral window approach, especially in terms of less discomfort and faster patient recovery (FARINA et al., 2018; STACCHI et al., 2017).

In a randomized clinical trial, Farina et al. (2018) observed a lower incidence of edema, ecchymosis, and nosebleeds in patients undergoing the transcrestal technique, in addition to a lower impact on daily activities in the postoperative period. These findings are corroborated by systematic reviews that indicate lower morbidity associated with minimally invasive techniques, especially when compared to the traditional lateral approach (STACCHI et al., 2017).

This difference can be explained by the less invasive nature of the transcrestal technique, which does not require the creation of a lateral bone window and significantly reduces the extent of mucoperiosteal detachment, resulting in less surgical trauma and shorter operative time. Consequently, there is a reduction in the inflammatory response and an improvement in the patient's postoperative experience.

On the other hand, the transcrestal technique has important limitations, especially related to the absence of direct visualization of the sinus membrane, which characterizes it as a technique dependent on the operator's skill. This condition can increase the risk of perforation of Schneider's membrane, particularly in cases with unfavorable anatomy or lower residual bone height (SCHNEIDER et al., 2014; LYU et al., 2023).

On the other hand, the lateral window technique, although associated with greater morbidity, offers better visual control of the procedure, allowing greater predictability in complex cases and reducing the risk of intraoperative complications when performed properly. However, this approach is related to a higher incidence of edema, postoperative discomfort, and longer recovery time, as described in the literature (STACCHI et al., 2017).

Thus, a clinical balance is observed between lower morbidity and lower visual control in the transcrestal technique, in contrast to greater invasiveness and greater surgical predictability in the lateral window technique. Thus, the choice of approach should consider not only the technical aspects, but also the patient's profile, the complexity of the case, and the surgeon's experience, aiming to optimize clinical results and minimize complications.

2.4 CLINICAL INDICATIONS AND ANATOMICAL FACTORS

The selection of the maxillary sinus lift technique is directly related to the patient's anatomical conditions, and residual bone height is one of the main determining factors for

the choice of surgical approach. Traditionally, the transcrestal technique is indicated in cases with residual bone height greater than 5–6 mm, while the lateral window technique is preferred in situations of more severe atrophy, in which there is a need for greater vertical bone gain (TSAI et al., 2020; ZHOU et al., 2020; DEL FABBRO et al., 2012).

However, recent evidence suggests that the clinical decision should not be based solely on residual bone height. Additional anatomical factors, such as the thickness of the lateral wall of the maxillary sinus, the presence of sinus septa, the shape of the sinus cavity, and the characteristics of the Schneider membrane, play a key role in the predictability of the procedure and the risk of intraoperative complications (LYU et al., 2023; SCHNEIDER et al., 2014).

The presence of sinus septa, for example, can make it difficult to elevate the membrane and increase the risk of perforation, especially in the transcrestal technique, which does not allow direct visualization of the operative field. Similarly, the thickness of the sinus membrane and its structural integrity are critical factors that directly influence the success of the procedure and the stability of the graft (STACCHI et al., 2017).

In addition, the shape of the maxillary sinus and the degree of pneumatization can interfere with the ability to create and maintain the subantral space, impacting the volume of graft required and the choice of the most appropriate technique. In cases with complex anatomy or extremely low bone height, the lateral window technique tends to be more indicated, due to greater surgical control and better visualization of the sinus cavity (PIJETURSSON et al., 2008; WALLACE; FROUM, 2003).

On the other hand, recent technological advances have expanded the indications of the transcrestal technique, allowing its use in situations previously considered limiting. The use of hydraulic systems, piezoelectric instruments, and minimally invasive techniques has contributed to greater precision in the elevation of the sinus membrane and reduced risk of complications, enabling its application even in cases with lower residual bone height (TORRES et al., 2017; DI FRISCHIA et al., 2025).

Thus, the choice of technique should be based on a multifactorial analysis, which considers not only the residual bone height, but also the anatomical characteristics of the maxillary sinus, the complexity of the clinical case, the systemic conditions of the patient, and the surgeon's experience. This individualized approach allows optimizing clinical outcomes, reducing the occurrence of complications, and increasing the predictability of treatment with implants in the posterior region of the maxilla.

2.5 COMPARATIVE SYNTHESIS, LIMITATIONS AND CLINICAL IMPLICATIONS

The integrated analysis of the studies shows that both techniques are effective and predictable, but have different clinical profiles. The lateral window technique stands out for its greater bone gain and greater predictability in cases of severe atrophy, and is considered the approach of choice in complex situations. On the other hand, the transcrestal technique has lower morbidity, shorter surgical time, and greater patient comfort, and is indicated in cases with favorable anatomical conditions.

However, it is important to highlight that the studies analyzed have relevant limitations, such as methodological heterogeneity, variations in surgical protocols, differences in the biomaterials used, and diversity in follow-up periods. These factors can directly influence the results and make it difficult to compare studies directly.

Thus, the choice of technique should be individualized and based on a careful evaluation of anatomical factors, the extent of bone loss, the surgeon's experience, and the patient's expectations. Evidence-based decision-making, combined with the advancement of available techniques and technologies, allows for the optimization of clinical outcomes and minimization of complications, contributing to the long-term success of rehabilitation with posterior maxillary implants.

3 CONCLUSION

It is concluded that the techniques of maxillary sinus lift by lateral window and transcrestal approach are effective, safe and highly predictable approaches for rehabilitation with implants in the posterior region of the maxilla, presenting high success rates when correctly indicated.

The lateral window technique stands out for its greater potential for bone gain and greater predictability in situations of severe maxillary atrophy, being more indicated in cases that require greater volume of bone regeneration and expanded surgical control. On the other hand, the main advantages of the transcrestal technique are less invasiveness, reduction of postoperative morbidity, and greater patient comfort, being preferable in scenarios with favorable anatomical conditions.

In this sense, the choice of technique should be individualized and based on a comprehensive evaluation, which considers not only the residual bone height, but also anatomical factors of the maxillary sinus, complexity of the clinical case, and surgeon's experience. In addition, technological advances have contributed to the expansion of the indications for the transcrestal technique, expanding its clinical applicability.

Finally, the need for clinical studies with greater methodological standardization and long-term follow-up is highlighted, in order to strengthen the available evidence and improve evidence-based clinical decision-making.

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ACUTE MYOCARDIAL INFARCTION WITH CORONARY OCCLUSION WITHOUT ST-SEGMENT ELEVATION: A SYSTEMATIC LITERATURE REVIEW

INFARTO AGUDO DO MIOCÁRDIO COM OCLUSÃO CORONARIANA SEM SUPRADESNIVELAMENTO DE SEGMENTO ST: UMA REVISÃO DE LITERATURA SISTEMÁTICA

INFARTO AGUDO DE MIOCARDIO CON OCLUSIÓN CORONARIA SIN ELEVACIÓN DEL SEGMENTO ST: UNA REVISIÓN SISTEMÁTICA DE LA LITERATURA



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ABSTRACT

The current paradigm for Acute Myocardial Infarction (AMI), based on the STEMI/NSTEMI dichotomy, fails to identify approximately 30% of acute coronary occlusions (ACO) that do not present with millimeter ST-segment elevation. Objective: To analyze the literature on Myocardial Occlusion (ACO) without ST-segment elevation, comparing its morbidity and mortality and diagnostic criteria with the traditional model. Methodology: Systematic literature review following the PRISMA protocol in the PubMed and SciELO databases (2015-2026), using the terms "Occlusion Myocardial Infarction", "NSTEMI" and "STEMI equivalents". Results: Studies were included that demonstrate that STEMI criteria have a sensitivity of only 43% to 62% for detecting acute occlusion. Patients with non-ST-segment elevation myocardial infarction (NSTEMI-negative) suffer significant delays in catheterization (median > 400 min vs. 41 min in STEMI) and have a 30-day mortality rate of 7.29%, statistically higher than patients without occlusion. New electrocardiographic patterns (Aslanger, De Winter, Precordial Whirlpool) and artificial intelligence show superior accuracy. Conclusion: The transition to the NSTEMI/NSTEMI paradigm is urgent to mitigate the undertreatment of critically ill patients erroneously classified as low risk.

Keywords: Myocardial Infarction. Coronary Occlusion. Non-ST-Segment Elevation Myocardial Infarction. Electrocardiography.

RESUMO

O paradigma atual de Infarto Agudo do Miocárdio (IAM), baseado na dicotomia STEMI/NSTEMI, falha em identificar cerca de 30% das oclusões coronarianas agudas (OCA) que não apresentam supradesnivelamento milimétrico do segmento ST. Objetivo: Analisar a literatura sobre o Infarto com Oclusão Miocárdica (OCA) sem

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supradesnívelamento do segmento ST, comparando sua morbimortalidade e critérios diagnósticos com o modelo tradicional. Metodologia: Revisão sistemática da literatura seguindo protocolo PRISMA nas bases PubMed e SciELO (2015-2026), utilizando os termos "Occlusion Myocardial Infarction", "NSTEMI" e "STEMI equivalents". Resultados: Foram incluídos estudos que demonstram que critérios de STEMI têm sensibilidade de apenas 43% a 62% para detectar oclusão aguda. Pacientes com OCA sem supra (OMI STEMI-negativo) sofrem atrasos significativos no cateterismo (mediana > 400 min vs. 41 min no STEMI) e apresentam mortalidade em 30 dias de 7,29%, estatisticamente superior aos pacientes sem oclusão. Novos padrões eletrocardiográficos (Aslanger, De Winter, Redemoinho Precordial) e inteligência artificial apresentam acurácia superior. Conclusão: A transição para o paradigma OCA/NOCA é urgente para mitigar o subtratamento de pacientes graves erroneamente classificados como baixo risco.

Palavras-chave: Infarto do Miocárdio. Oclusão Coronariana. Infarto do Miocárdio Sem Supradesnível do Segmento ST. Eletrocardiografia.

RESUMEN

El paradigma actual para el Infarto Agudo de Miocardio (IAM), basado en la dicotomía STEMI/NSTEMI, no logra identificar aproximadamente el 30% de las oclusiones coronarias agudas (OCA) que no presentan elevación del segmento ST de milímetros. Objetivo: Analizar la literatura sobre Oclusión Miocárdica (OCA) sin elevación del segmento ST, comparando su morbilidad y mortalidad y criterios diagnósticos con el modelo tradicional. Metodología: Revisión sistemática de la literatura siguiendo el protocolo PRISMA en las bases de datos PubMed y SciELO (2015-2026), utilizando los términos "Oclusión Miocárdica Infarto", "NSTEMI" y "equivalentes de STEMI". Resultados: Se incluyeron estudios que demuestran que los criterios STEMI tienen una sensibilidad de solo 43% a 62% para detectar oclusión aguda. Los pacientes con infarto de miocardio sin elevación del segmento ST (NSTEMI negativo) sufren retrasos significativos en la cateterización (mediana > 400 min frente a 41 min en STEMI) y presentan una tasa de mortalidad a 30 días del 7,29 %, estadísticamente superior a la de los pacientes sin oclusión. Los nuevos patrones electrocardiográficos (Aslanger, De Winter, Remolino Precordial) y la inteligencia artificial demuestran una mayor precisión. Conclusión: La transición al paradigma NSTEMI/NSTEMI es urgente para mitigar el infratratamiento de pacientes críticos clasificados erróneamente como de bajo riesgo.

Palabras clave: Infarto de Miocardio. Oclusión Coronaria. Infarto de Miocardio Sin Elevación del Segmento ST. Electrocardiografía.

1 INTRODUCTION

Cardiovascular diseases (CVD) have consolidated themselves as the main cause of global mortality in the twenty-first century, representing a significant epidemiological transition. While at the beginning of the twentieth century deaths from infectious diseases and malnutrition predominated, today chronic non-communicable diseases, particularly CVD, account for the largest share of deaths. According to the 2021 Global Burden of Disease (GBD), CVD was responsible for 19.4 million deaths, with ischemic heart disease as the main cause in individuals over 50 years of age. This scenario is especially critical in low-income countries, where limited access to appropriate treatments and the high prevalence of uncontrolled risk factors, such as hypertension and diabetes, result in high mortality rates (IHME, 2021; Bonow et al., 2012).

In Brazil, CVD is a serious public health problem, accounting for approximately 28% of deaths in people over 30 years of age (Bonow et al., 2012). Within this context, acute coronary syndrome (ACS) stands out as one of the most serious manifestations, with more than 100 thousand deaths annually related to ischemic heart disease, equivalent to 43% of CVD deaths in the country (Nascimento et al., 2025).

However, Alencar et al. (2024) describe an additional critical condition: acute coronary occlusion (OCA), characterized by total or near-total blockage of a coronary artery, which can lead to significant myocardial ischemia and infarction, even in the absence of ST-segment elevation on the ECG. It is estimated that 30% to 50% of OCA cases do not present ST elevation, and are often underdiagnosed. Patients with non-ST OCA have mortality and infarction extent comparable to those of STEMI, highlighting the need to identify alternative electrocardiographic signs early, such as hyperacute T waves, "De Winter" pattern, and ST-specific depressions (Alencar et al., 2024).

By defining the disease exclusively by an imprecise aspect (the elevation of the ST segment on the ECG), it ends up neglecting the true pathophysiology of OCA. This creates the so-called "no false negative" paradox: when a patient has OCA but does not have ST elevation, they are not classified as STEMI and therefore are not considered a false negative for STEMI. This gap in the literature ends up hindering clinical decision-making, as physicians are forced to use criteria that may not be the most appropriate to address Acute Coronary Syndrome (Alencar et al., 2024).

However, this study aims to review the scientific literature on AMI with non-ST-segment elevation coronary occlusion, with emphasis on its clinical characteristics, diagnostic methods, therapeutic strategies, and prognostic implications.

2 THEORETICAL FRAMEWORK

According to Rao et al. (2025), acute coronary syndromes occur due to the rupture or erosion of an unstable atherosclerotic plaque, leading to the formation of thrombi and microemboli that reduce blood flow to the myocardium, resulting in ischemia. These syndromes encompass three clinical conditions of progressive severity: unstable angina (UA), non-ST-elevation acute myocardial infarction (NSTEMI), and ST-elevation acute myocardial infarction (STEMI). The diagnosis and classification of these conditions are based on the patient's clinical history, symptoms, ECG analysis, and measurement of cardiac biomarkers, such as cardiac troponins I and T.

While unstable angina is characterized by transient episodes of myocardial ischemia without significant necrosis, acute myocardial infarction involves prolonged and intense ischemia, with elevated biomarkers. In NSTEMI, arterial obstruction is partial, causing subendocardial ischemia, while in STEMI there is complete coronary occlusion, resulting in extensive transmural ischemia (Rao et al., 2025).

The approach proposed by the OCA-NOCA paradigm emphasizes the urgency of reperfusion (catheterization or thrombolysis) in all cases of OCA, regardless of ECG, aiming to reduce irreversible myocardial damage and improve clinical outcomes. This perspective challenges current guidelines and reinforces the importance of integrating anatomical and physiological criteria in the diagnosis of AMI (Alencar et al., 2024).

Despite the widespread use of ECG as an initial diagnostic tool in ACS, its sensitivity to identify non-ST-elevation OCA remains limited. Research has shown that about 30% to 50% of patients with angiographically confirmed OCA do not meet the classic criteria for STEMI, being erroneously classified as NSTEMI. Meta-analyses reveal that the sensitivity of ST-segment elevation for detecting OCA is only 43.6%, whereas other electrocardiographic markers, such as hyperacute T waves, are more accurate. Such findings reinforce the need for a more comprehensive diagnostic approach, incorporating not only ECG but also ultrasensitive biomarkers and imaging methods, in order to reduce underdiagnosis and improve the prognosis of these patients (Alencar et al., 2024).

The electrophysiological rationale for the failure of the STEMI (ST-Segment Elevation Myocardial Infarction) paradigm lies in the vector physics and spatial limitation of the conventional 12-lead electrocardiogram. As discussed in the manifesto, ST-segment elevation is a result of the direction of the injury current in relation to the electrodes; If the occlusion vector points to regions of the myocardium not directly covered by the standard leads, the phenomenon may not be registered as a classic "supra". This concept explains why acute occlusions, which pathophysiologically represent the same risk, are often

neglected when they do not produce vector changes that reach the arbitrary millimetric thresholds of the guidelines (Meyers; Weingart; Smith, 2018).

A critical example of this limitation occurs in circumflex artery occlusions, which are responsible for supplying the low and posterior lateral wall of the left ventricle. The article emphasizes that such events are commonly "muted" on standard ECG, as the resulting injury vectors target areas where there are no corresponding leads on the anterior thoracic surface. By misclassifying these cases as NSTEMI (Non-ST-Segment Elevation Myocardial Infarction), the current model ignores the anatomical reality of a total arterial obstruction, delaying emergency reperfusion therapy for patients who have subtle or isolated electrocardiographic evidence of coronary occlusion (Meyers; Weingart; Smith, 2018).

According to Meyers, Weingart and Smith (2018), the traditional classification of infarctions, based on the distinction between STEMI and NSTEMI, is pointed out as an insufficient and conceptually flawed nomenclature, as it prioritizes millimetric electrocardiographic criteria to the detriment of the pathophysiology of acute coronary occlusion. According to the manifesto that proposes the new paradigm, the term "STEMI" constitutes an error that limits clinical progress, since it fails to identify about 25% to 30% of patients with total arterial obstruction who do not have classic elevation. Instead, the authors advocate the transition to the OCA/NOCA model (Occlusion Infarction vs. Infarction without Occlusion), whose objective is to redirect the focus of the diagnosis to the presence of mechanical occlusion that requires immediate reperfusion, regardless of whether the electrocardiogram tracing complies with the current formal definitions.

Reinforcing this need for transition, a retrospective study by Meyers et al. (2021) demonstrated that patients with acute coronary occlusion who do not meet the criteria for STEMI (hollow STEMI) have areas of infarction and mortality rates equivalent to those with evident ST elevation. However, the study showed that this group suffers significant diagnostic delays, with a median time for catheterization more than twice that recorded in STEMI patients(+). These findings suggest that the use of more accurate electrocardiographic findings for OCA would allow the rapid and noninvasive identification of these patients, enabling emergency reperfusion and mitigating myocardial damage that is currently neglected by the conventional protocol.

De Winter et al. (2008) described a distinct electrocardiographic pattern, observed in about 2% of cases of previous infarction, characterized by a ST-segment depression of 1 to 3 mm at point J with an upward slope in the precordial leads (V1 to V6). This morphology progresses to high, symmetrical, positive T waves, often accompanied by a slight elevation of the ST segment in the aVR lead. Unlike transient hyperacute T waves, this signal

manifests statically and is associated with total vessel occlusion, implying a risk of significant myocardial loss and the need for immediate reperfusion therapy.

Hyperacute T waves are often the first electrocardiographic sign of an acute coronary occlusion (OCA), appearing even before ST-segment elevation. According to Ricci et al. (2025), these waves are not defined only by their amplitude, but mainly by being wide, broad-based, "bulky" and symmetrical in relation to the preceding QRS complex. Their identification is critical, as they represent a very early phase of infarction, and are now formally recognized as an equivalent of STEMI that requires immediate reperfusion, since the relationship between T wave amplitude and QRS is a more sensitive marker than the isolated height of the wave.

The diagnosis of left ventricular posterior wall infarction is often overlooked in the standard 12-lead electrocardiogram due to the absence of leads on the dorsal chest wall. As explained by Ayyad et al. (2025), the occlusion affecting this region is manifested through a mirror image in the anterior precordial leads (V1 to V4), characterized by horizontal depression of the ST segment, prominent and positive T waves, and wide R waves. Ricci et al. (2025) corroborate that any ST-segment depression, even if less than 1 mm, when maximum in leads V1 to V4, has a specificity of 97% for the diagnosis of OCA, and should be treated with the same urgency as a classic elevation.

The Aslanger pattern describes a specific presentation of lower myocardial occlusion in patients with multivessel coronary artery disease. According to Ricci et al. (2025), this pattern is identified by an isolated ST-segment elevation in lead DIII (lead III), associated with a diffuse depression in leads V4 to V6, but with the ST-segment in V1 greater than in V2. Although it does not meet the traditional criteria for STEMI, which require elevation in two contiguous leads, this finding indicates an acute occlusion of the right circumflex or coronary artery with concomitant subendocardial ischemia, representing a high-risk condition.

The presence of Left Bundle Branch Block (LBB) or pacemaker rhythm traditionally makes it difficult to diagnose acute infarction due to changes in ventricular repolarization. However, Ricci et al. (2025) highlight that the Sgarbossa Criteria Modified by Smith overcome this limitation by introducing the concept of proportionality. The modification replaces the absolute criterion of 5 mm of discordance with a ratio between ST-segment elevation and S-wave (ST/S ratio) less than or equal to -0.25 (or 25%). This change significantly increased the sensitivity for detecting acute coronary occlusion in patients with LBB, allowing for early interventions that the original criteria failed to indicate.

Distinguishing between benign early repolarization and a subtle anterior descending artery (ADA) occlusion is a common challenge in the emergency room. According to Ricci et al. (2025), the presence of "QRS Terminal Distortion", defined by the absence of both the S wave and the notch at the J point in leads V2 or V3, is a highly specific marker of ADA occlusion. The presence of this sign indicates that the elevation, even if subtle and does not meet the traditional millimetric criteria, is of malignant ischemic origin and not a benign variant.

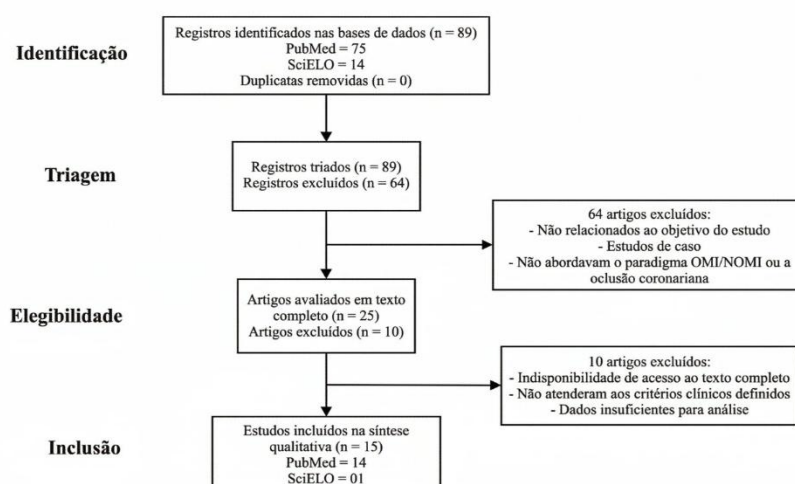
There are specific patterns that point to occlusions of important arterial branches that do not generate the classic pattern of STEMI. Ayyad et al. (2025) describe the "South African Flag Sign" as an indicator of occlusion of the first diagonal branch of the anterior descending artery, manifesting by elevation in leads D1, aVL, and V2, combined with depression in D3. Additionally, Batubara et al. (2025) and Ricci et al. (2025) cite the "Precordial Swirl Sign" (Precordial Swirl), characterized by elevation or hyperacute T waves in leads V1 and V2 with reciprocal depression in V5 and V6, indicating a proximal occlusion of the anterior descending artery that requires immediate catheterization.

3 METHODOLOGY

For this study, a systematic review of the literature was carried out based on the PRISMA protocol (Figure 1) (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*), aiming to analyze the transition from the traditional paradigm to the Myocardial Occlusion Infarction (OCA) model in patients initially classified as NSTEMI.

Figure 1

Prism flowchart



Source: Authors, 2026.

3.1 DEFINITION OF THE SURVEY QUESTION (PEAK)

The guiding question was structured through the PICO strategy: Patients with non-ST-segment ACS; Identification of signs of acute occlusion (STEMI equivalents); Comparison with the traditional millimetric criterion; Occlusion confirmed by coronary angiography.

3.2 SEARCH STRATEGY AND DATABASES

The search was conducted in the PubMed and SciELO databases, using controlled descriptors (MeSH and DeCS) and Boolean operators to maximize the sensitivity of the search:

("Acute Myocardial Infarction" OR "Acute Coronary Syndrome") AND ("NSTEMI" OR "Non-ST Elevation Myocardial Infarction" OR "OMI" OR "Occlusion Myocardial Infarction") AND ("Coronary Occlusion" OR "Total Occlusion" OR "ECG" OR "Electrocardiography" OR "Troponin" OR "Sgarbossa" OR "De Winter") ("Myocardial Infarction" OR "Acute Coronary Syndrome") AND ("Non-ST Elevation" OR "NSTEMI" OR "Coronary Occlusion").

3.3 INCLUSION AND EXCLUSION CRITERIA

Articles published between 2015 and 2026, in English, Portuguese, or Spanish, that address clinical characteristics, diagnostic methods, therapeutic strategies, and prognostic implications of NSTEMI, were selected. Articles that do not present clear information on the topic or that are limited to case studies will be excluded.

3.4 DATA ANALYSIS AND SYNTHESIS

The identified studies underwent a two-stage screening (title/abstract and full text). The methodological quality of the selected studies was evaluated according to the guidelines of Evidence-Based Medicine. The extracted data were synthesized in comparative tables, highlighting the sensitivity of the new diagnostic criteria in relation to the old paradigm.

4 RESULTS

The search resulted in 89 studies identified, 75 in the PubMed database and 14 in SciELO. No duplicates were found. After screening by title and abstract, 64 studies were excluded because they did not meet the inclusion criteria. Thus, 25 articles were selected for full reading, of which 10 were excluded due to unavailability of access to the full text or for not meeting the established clinical criteria. In the end, 15 studies were included in the review.

Table 1

Autoria e Ano	Revista / Base de Dados / DOI	Título do Artigo	Objetivo Central	Métodos
Kos et al. (2026)	World J Cardiol / PubMed / 10.4330/wjc.v18.i1.111736	Impact of total occlusion of the infarct-related coronary artery on mortality of 2483 patients...	Avaliar o impacto da oclusão total da artéria coronária na mortalidade de pacientes com IAM, independentemente do supra de ST.	Estudo de coorte prospectivo com 2.483 pacientes com IAM, comparando desfechos entre artérias ocluídas e não ocluídas.
Meyers et al. (2025)	Eur Heart J Acute Cardiovasc Care / PubMed / [DOI no texto]	Failure of standard contemporary STEMI ECG criteria to reliably identify acute occlusion of the LAD...	Avaliar a sensibilidade dos critérios padrões de STEMI para detectar oclusão aguda da artéria descendente anterior (ADA).	Estudo de caso-controle retrospectivo comparando critérios de STEMI versus achados de OMI em pacientes com oclusão da ADA confirmada.
Ricci et al. (2025)	Ann Emerg Med / PubMed / 10.1016/j.annemergmed.2024	ECG Patterns of Occlusion Myocardial Infarction: A Narrative Review	Descrever e revisar os padrões eletrocardiográficos sutis que indicam Oclusão Coronariana Aguda (OMI) sem critérios de STEMI.	Revisão narrativa da literatura focada em padrões de ECG (De Winter, Aslanger, Ondas T hiperagudas, etc.).
Ayyad et al. (2025)	Curr Cardiol Rep / PubMed / [DOI no texto]	Reevaluating STEMI: The Utility of the Occlusive Myocardial Infarction Classification...	Discutir a utilidade e a necessidade da transição da classificação STEMI/NSTEMI para o paradigma OMI/NOMI.	Revisão da literatura abordando limitações do modelo atual e benefícios da nova classificação baseada na oclusão.
Batubara et al. (2025)	Egypt Heart J / PubMed / 10.1186/s43044-025-00688-2	A case series of OMI: time for revisiting STEMI/NSTEMI ECG criteria	Demonstrar através de casos clínicos a falha dos critérios STEMI e a eficácia dos sinais de OMI.	Série de casos clínicos ilustrando padrões de ECG de OMI (Aslanger, Sgarbossa, etc.) e revisão da literatura.
Frick et al. (2025)	Adv Interv Cardiol / PubMed / [DOI no texto]	Occlusion myocardial infarction: a revolution in acute coronary syndrome	Analisar a mudança de paradigma em curso na classificação das síndromes coronarianas agudas.	Editorial / Artigo de opinião baseado em evidências recentes sobre o conceito de OMI.

Alencar et al. (2024)	Arq Bras Cardiol / SciELO / 10.36660/abc.20230733	Além do Paradigma IAMCSST-IAMS SST: Proposta do Instituto Dante Pazzanese para o Diagnóstico de OCA	Propor a adoção do modelo "Oclusão Coronariana Aguda (OCA)" em substituição à dicotomia baseada apenas no supra de ST.	Artigo de Revisão e Posicionamento Institucional analisando evidências e propondo novo fluxograma de atendimento.
Kola et al. (2024)	J Clin Med / PubMed / 10.3390/jcm13175201	OMI/NOMI: Time for a New Classification of Acute Myocardial Infarction	Avaliar a necessidade de reclassificação do IAM baseada na oclusão e não apenas na elevação do segmento ST.	Revisão abrangente da literatura discutindo a fisiopatologia e as falhas dos critérios atuais.
Bae et al. (2023)	JACC Cardiovasc Interv / PubMed / 10.1016/j.jcin.2022.09.027	Early Invasive Strategy Based on the Time of Symptom Onset of Non-ST-Segment Elevation MI	Investigar o impacto da estratégia invasiva precoce baseada no tempo do início dos sintomas em NSTEMI.	Estudo de coorte prospectivo multicêntrico (KAMIR-NIH) analisando mortalidade e tempo de intervenção.
Tsai et al. (2022)	Dis Markers / PubMed / [DOI no texto]	Troponin I Cutoff for Non-ST-Segment Elevation	Determinar o ponto de corte ideal de Troponina I para diagnóstico e risco em NSTEMI.	Análise retrospectiva de dados de laboratoriais e desfechos clínicos.
Meyers et al. (2021)	J Emerg Med / PubMed / 10.1016/j.jemerm.2020.10.026	Comparison of the STEMI vs. NSTEMI and Occlusion MI (OMI) vs. NOMI paradigms of acute MI	Comparar a precisão diagnóstica e tempos de tratamento entre os paradigmas STEMI/NSTEMI e OMI/NOMI.	Estudo retrospectivo comparativo analisando tempos de cateterismo e desfechos em coorte de IAM.
Meyers et al. (2021)	IJC Heart & Vasc / PubMed / 10.1016/j.ijcha.2021.100767	Accuracy of OMI ECG findings versus STEMI criteria for diagnosis of acute coronary occlusion MI	Testar a acurácia dos achados de ECG de OMI versus critérios milimétricos de STEMI para diagnosticar oclusão.	Estudo caso-controle retrospectivo (DOMI ARIGATO) comparando interpretação de ECG por especialistas e critérios padrões.

Baro et al. (2019)	Clin Cardiol / PubMed / 10.1002/cle.23130	High-sensitivity cardiac troponin T as a predictor of acute total occlusion in patients with NSTEMI-ACS	Avaliar a Troponina T de alta sensibilidade como preditor de oclusão total em pacientes com NSTEMI.	Estudo observacional transversal analisando níveis de troponina e achados angiográficos.
Khan et al. (2017)	Eur Heart J / PubMed / 10.1093/eurheartj/ehx418	Impact of total occlusion of culprit artery in acute non-ST elevation myocardial infarction	Determinar o impacto prognóstico da oclusão total da artéria culpada em pacientes diagnosticados como NSTEMI.	Revisão sistemática e meta-análise de estudos observacionais comparando NSTEMI com e sem oclusão total.
de Winter et al. (2008)	N Engl J Med / PubMed / [DOI no texto]	A New ECG Sign of Proximal LAD Occlusion	Descrever um novo padrão de ECG associado à oclusão da artéria descendente anterior proximal sem supra de ST.	Estudo observacional retrospectivo de ECGs e angiografias identificando o padrão "De Winter".

Source: Authors, 2026.

Analysis of the selected studies revealed consistent data that challenge the effectiveness of the current binary model. According to research conducted by Meyers et al. (2025), focused on anterior descending artery occlusions, traditional STEMI criteria failed to identify 38% of angiographically confirmed TIMI 0 (total occlusion) flow cases. In terms of global accuracy, previous reviews, such as the one by Meyers et al. (2021), have already pointed out that the sensitivity of ST-segment elevation criteria for the detection of acute occlusion is around 41%, contrasting with the interpretation based on the OCA concept, which can double this sensitivity while maintaining high specificity.

Regarding prognosis and mortality, data compiled by Kos et al. (2026) in a cohort of 2,483 patients demonstrated that the presence of total occlusion of the culprit artery is an independent predictor of 30-day mortality, with a rate of 7.29% in the group with occlusion (OCA) versus 3.52% in the group without occlusion (NOCA), regardless of the initial electrocardiographic presentation. These findings are corroborated by the meta-analysis by Khan et al. (2017), which indicated that approximately 25% of patients initially diagnosed as NSTEMI had a fully occluded artery, resulting in a significantly elevated mortality risk when compared to non-occluded patients.

Regarding the treatment time, the literature analyzed indicates a critical disparity. Patients classified as non-ST-elevation OCA face substantial delays to catheterization, with median times often exceeding 90 minutes or, in more severe cases, exceeding 400 minutes to intervention, while patients with classic STEMI criteria are seen, on average, within 41 to 60 minutes. In addition, recent studies on the use of artificial intelligence, such as the models

validated by Meyers et al. (2025) and cited by Batubara et al. (2025), have shown that algorithms trained on the OCA concept achieved 100% sensitivity in detecting proximal occlusions of the anterior descending artery on the first electrocardiogram, surpassing the standard human capacity and the criteria of the current guidelines.

5 DISCUSSIONS

A critical analysis of the contemporary literature shows that the current paradigm for the classification of acute myocardial infarction, based on the dichotomy between ST-segment elevation infarction (STEMI) and non-elevation infarction (NSTEMI), presents severe structural flaws when using the surface electrocardiogram (ECG) as the sole arbiter for the decision of emergency reperfusion. As Frick et al. (2025) argue, this classification creates a "paradox of no false negative", where the absence of millimetric criteria for elevation in a patient with total occlusion is not recognized as a failure of the diagnostic test, but rather categorized as a distinct clinical entity (NSTEMI), masking the urgency of the underlying pathology.

The ineffectiveness of the traditional criteria is quantitatively alarming. Meyers et al. (2021) demonstrated that the sensitivity of STEMI criteria for detecting acute coronary occlusion (OCA) is only 41%. More recent data reinforce this limitation: in a study focused specifically on total occlusions of the anterior descending artery (ADA) — the lesion with the highest lethality potential — Meyers et al. (2025) identified that 38% of patients with TIMI 0 flow (total occlusion) did not meet the criteria for STEMI at any time during electrocardiographic monitoring. These findings are corroborated by Kola et al. (2024), who in their cohort observed that 40% of angiographically confirmed patients with OCA did not meet the classic criteria for hemodynamic activation.

The direct consequence of this diagnostic gap is the systematic therapeutic delay for the group called "STEMI(-) OCA" (Unsupra Occlusion). Ayyad et al. (2025) and Batubara et al. (2025) highlight that these patients suffer significant delays in door-to-balloon time, with medians often exceeding 90 minutes, in contrast to the 40 to 60 minutes observed in the classic STEMI group. The prognostic impact of this delay is devastating: the meta-analysis by Khan et al. (2017) revealed that the 25.5% of patients diagnosed as NSTEMI who have a fully occluded artery have a mortality risk 1.67 times higher than NSTEMI without occlusion. In addition, Bae et al. (2023) demonstrated that 3-year mortality almost doubles (13.4% vs 7.3%) when the time between symptom onset and catheterization ("symptom-to-catheter time") exceeds 48 hours, reinforcing that the conservative or delayed strategy for false-NSTEMI is deleterious.

To mitigate these flaws, the transition to the OCA paradigm proposes the valorization of subtle but specific electrocardiographic patterns that precede or replace the classic elevation. Ricci et al. (2025) extensively reviewed these patterns, emphasizing the importance of hyperacute (wide and symmetrical) T waves, which are often the first sign of occlusion, and terminal QRS distortion, which differentiates benign repolarization from ADA occlusion. Additionally, signs such as the "South African Flag Sign" (elevation at D1, aVL and V2 with infra at D3) and the "Precordial Whirlpool Sign" (supra at V1-V2 with infra at V5-V6) were identified by Batubara et al. (2025) and Ayyad et al. (2025) as critical markers of proximal occlusions requiring immediate intervention, despite not meeting the standard millimeter criteria.

In addition to the technical limitations, the current paradigm carries implicit demographic biases. Ricci et al. (2025) point out that ST-segment elevation thresholds were derived mostly from male populations of Western ancestry. Women, who physiologically have a lower elevation of the basal J-point, may experience acute occlusions without meeting the strict cut-off criteria (such as 1.5 mm or 2.0 mm), resulting in disproportionate underdiagnosis. Applying proportionality-based criteria, such as the Smith-modified Sgarbossa criteria for Left Bundle Branch Block, helps correct these distortions when assessing the patient's voltage-relative ischemia, rather than using absolute measures.

The reliance on biomarkers, such as troponin, for risk restratification in the absence of ST elevation also presents pitfalls. Although Baro et al. (2019) demonstrated that high-sensitivity troponin T levels above 1000 ng/L are highly predictive of total occlusion, waiting for this elevation contradicts the fundamental principle of "time is muscle", since such levels take hours to manifest. In this context, ECG interpreted from the perspective of OCA offers an instantaneous screening tool that troponin cannot provide in the hyperacute phase, allowing the distinction between the true NSTEMI patient (NOCA) and the occluded patient (OCA) who requires immediate catheterization.

Given the complexity of recognizing these subtle patterns, artificial intelligence (AI) emerges as a promising solution to democratize the diagnosis of excellence. Meyers et al. (2025) demonstrated that an AI model trained on the concept of OCA was able to detect 100% of acute anterior descending artery occlusions in the first ECG performed, drastically exceeding the sensitivity of 62% of STEMI criteria and equaling the performance of human experts. Batubara et al. (2025) reinforce that the integration of machine learning algorithms into clinical practice can reduce the variability of human interpretation and ensure that patients with patterns such as the "Precordial Whirlpool" or "Aslanger" do not have their treatment delayed due to lack of technical recognition.

In summary, the accumulated evidence indicates that the STEMI/NSTEMI classification has become insufficient for the decision of emergency reperfusion, failing to protect a significant portion of patients with acute coronary occlusion. The adoption of the OCA/NOCA paradigm, supported by the recognition of advanced electrocardiographic patterns and the aid of artificial intelligence, presents itself as the necessary evolution to ensure that all patients with myocardium at risk receive reperfusion therapy at the appropriate time. As Frick et al. (2025) suggest, cardiology should evolve from a diagnostic tool-focused approach to a pathology-focused approach, ensuring that the absence of a millimeter sign on paper is not a preventable myocardial necrosis sentence.

6 CONCLUSION

This review critically analyzed acute myocardial infarction with non-ST-segment elevation coronary occlusion, highlighting relevant limitations of the traditional STEMI/NSTEMI paradigm. Studies have shown that a significant part of patients classified as NSTEMI have total coronary occlusion, associated with greater myocardial necrosis, delayed reperfusion, and increased mortality.

The exclusive dependence on ST-segment millimetric criteria is insufficient to identify acute occlusions, especially in view of the limitations of the conventional electrocardiogram. The incorporation of advanced electrocardiographic standards and new diagnostic tools increases clinical sensitivity and can reduce therapeutic delays.

In this context, the OCA/NOCA paradigm emerges as a proposal more aligned with the anatomical and pathophysiological reality of acute coronary syndrome. Evidence shows that the absence of ST-segment elevation should not be interpreted as absence of coronary occlusion. The evolution of contemporary cardiology requires that clinical decision-making be centered on the pathology underlying coronary obstruction, and not only on the electrocardiographic manifestation based on millimetric criteria.

Thus, the transition to an occlusion-based model represents a strategic advance, capable of reducing potentially avoidable myocardial necrosis and improving clinical outcomes in acute myocardial infarction.

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USE OF THE *ALLIUM CEPA* BIOASSAY AS AN INDICATOR OF CYTOTOXICITY OF PESTICIDES IN VITICULTURE

UTILIZAÇÃO DO BIOENSAIO *ALLIUM CEPA* COMO INDICADOR DE CITOTOXICIDADE DE PRAGUICIDAS DA VITICULTURA

UTILIZACIÓN DEL BIOENSAYO DE *ALLIUM CEPA* COMO INDICADOR DE CITOTOXICIDAD DE PLAGUICIDAS EN LA VITICULTURA



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ABSTRACT

Objectives: To evaluate the cytotoxic effect of pesticides used in grape cultivation in Marialva-Paraná through the *Allium cepa* bioassay.

Methods: Different concentrations of pesticides were tested: imidacloprid, Metiram+Pyraclostrobin, Metalaxyl-m+Mancozeb and Tetraconazole. The test solutions were prepared based on the recommended doses for grape cultivation and also with variations in these concentrations. Cytotoxicity was assessed by calculating the mitotic index.

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Results: Macroscopic analysis showed that, with increasing concentration tested, there was an increase in fragility and a decrease in root size. For all substances tested, there was a significant reduction in the size of the roots compared to the substances with the respective negative controls. Cytotoxicity was confirmed by calculating the mitotic index. Furthermore, during the counting of cells that presented different phases of cell division, some abnormalities were observed in the genetic material indicative of genotoxicity.

Conclusions: This study confirmed the cytotoxicity of all active ingredients tested, and the information presented aims to contribute to the development of additional research to relate cytogenotoxicity in humans.

Keywords: Mitotic Index. Biological Assay. Onions. Agrochemical.

RESUMO

Objetivo: Avaliar os efeitos citotóxicos de praguicidas usados no cultivo da uva em Marialva-Paraná por meio do bioensaio com *Allium cepa*.

Método: Foram testadas diferentes concentrações dos praguicidas: imidacloprido, Metiram+Piraclostrobina, Metalaxil-m+Mancozebe e Tetraconazol. As soluções-teste foram preparadas com base nas doses recomendadas para cultura da uva e também com variações nestas concentrações. A citotoxicidade foi avaliada por meio do cálculo do índice mitótico.

Resultados: Análise macroscópica mostrou que, com o aumento da concentração testada houve aumento da fragilidade e diminuição no tamanho das raízes. E para todos os ativos testados, houve redução significativa entre o tamanho das raízes em comparação dos ativos com os respectivos controles negativos. A citotoxicidade foi confirmada pelo cálculo do índice mitótico. Ademais, durante a contagem das células que apresentavam diferentes fases da divisão celular, foram observadas algumas anormalidades no material genético indicativas de genotoxicidade.

Conclusão: Este estudo confirmou a citotoxicidade de todos os ativos testados e as informações apresentadas visam contribuir para o desenvolvimento de pesquisas adicionais para relacionar a citogenotoxicidade em seres humanos.

Palavras-chave: Índice Mitótico. Bioensaio. Cebolas. Agroquímicos.

RESUMEN

Objetivo: Evaluar los efectos citotóxicos de plaguicidas utilizados en el cultivo de uva en Marialva, Paraná, mediante el bioensayo con *Allium cepa*.

Método: Se probaron diferentes concentraciones de los plaguicidas imidacloprid, Metiram + Piraclostrobina, Metalaxil-M + Mancozeb y Tetraconazol. Las soluciones de prueba se prepararon con base en las dosis recomendadas para el cultivo de la uva, así como con variaciones de dichas concentraciones. La citotoxicidad se evaluó mediante el cálculo del índice mitótico.

Resultados: El análisis macroscópico mostró que, con el aumento de la concentración, hubo mayor fragilidad y disminución del tamaño de las raíces. Para todos los principios activos evaluados, se observó una reducción significativa en el tamaño de las raíces en comparación con sus respectivos controles negativos. La citotoxicidad fue confirmada mediante el cálculo del índice mitótico. Además, durante el conteo de las células en

diferentes fases de la división celular, se observaron algunas anomalías en el material genético indicativas de genotoxicidad.

Conclusión: Este estudio confirmó la citotoxicidad de todos los principios activos evaluados, y los hallazgos buscan contribuir al desarrollo de futuras investigaciones para relacionar la citogenotoxicidad en seres humanos.

Palabras clave: Índice Mitótico. Bioensayo. Cebollas. Agroquímicos.

1 INTRODUCTION

Pesticides are widely used to combat pests and diseases to increase agricultural productivity. According to the annual bulletin of the Brazilian Institute of the Environment and Renewable Natural Resources (1), in 2022 more than 800 tons of formulated products were sold in the country.

The System for the Control of Trade and Use of Pesticides in the State of Paraná (SIAGRO) receives the sales declarations of all companies in the State, and in 2023, it registered more than 138 thousand tons of assets sold in Paraná. The municipality of Marialva was responsible for the sales of 544.6 tons of pesticides in the same year (2). In the last 3 years (2021, 2022 and 2023), pesticide sales have increased by more than 70 thousand tons (2), demonstrating that this sector is growing.

The update of the toxicological classification of pesticides by the National Health Surveillance Agency (3) added to the transformations in agricultural processes, indicate that the consumption of pesticides in Brazil should be intensified in the coming years. Insufficient occupational protection and monitoring measures in the area of agriculture increase and aggravate the public health problems caused by the wide exposure of the population and rural workers to pesticides. In particular, family farmers who are in a situation of social vulnerability (4).

Bioassays using higher plants are excellent indicators of cytotoxicity and genotoxicity of chemical substances, being used mainly in the detection of environmental pollutants (5). *Allium cepa*, commonly known as onion, is one of the species widely used in bioassays due to its ease of access, low cost, and low complexity in cultivation (6, 7). This species is indicated to evaluate several genetic parameters, having 16 large chromosomes, which facilitates the visualization of chromosomal abnormalities. In addition, the analysis of the cell cycle of *Allium cepa* roots allows the cytotoxic activity of different substances to be determined by evaluating the decrease in the frequency of cell division (8).

In addition, the bioassay with *Allium cepa* has great sensitivity in the evaluation of cellular toxicity and chromosomal alterations, contributing to the establishment of direct and/or indirect risks in the human population (9). Thus, the objective of this work was to evaluate the cytotoxic effects of pesticides used in grape cultivation in the region of Marialva in Paraná.

2 MATERIAL AND METHODS

2.1 BIOASSAY WITH *ALLIUM CEPA*

The onions (*Allium cepa*) used for the test were purchased commercially at a street market in Maringá-PR, from the same supplier. Bulbs with a diameter of approximately 3 centimeters were selected. All onions were sanitized with running water and the surface skins were removed.

2.2 TEST SOLUTIONS

All the pesticides tested were donated by a local producer, from Marialva-PR, who removed from the commercial packaging, the amount necessary to carry out the bioassay. Table 1 shows the trade name, active ingredient, classification as to purpose and toxicity of the pesticides tested. The information was obtained from the database of the Agricultural Defense Agency of Paraná (10).

Table 1

List of pesticides used for the Allium cepa bioassay

Trade name	Active	Class	Toxicological classification
Cabrio Top®	Metiram + Pyraclostrobin	Fungicide	4 - Slightly toxic
Proved 200 SC®	Imidacloprid	Insecticide	4 - Slightly toxic
Ridomil Gold- MZ®	Metaxyl-m+mancozeb	Fungicide	5 - Unlikely to Cause Acute Damage
Domark 100 EC®	Tetraconazole	Fungicide	4 - Slightly toxic

The pesticides tested are used during grape cultivation in the North Central region of Paraná. Therefore, the concentrations selected for this study were based on the doses recommended for grape cultivation, and concentrations lower and higher than those used for some cases were also used. Concentrations with cytotoxic and/or genotoxic effects described in the literature were also selected, as shown in Table 2. The lower concentrations were used to verify if, at these concentrations, the active ingredient still presented cytotoxic effects. The higher concentrations were used as a positive control, and it was expected to find a cytotoxic effect. All test solutions were prepared in a properly calibrated volumetric flask, taking into account the guidelines described in the package insert for the preparation of the mixture.

Table 2

Concentrations of each active ingredient used for the Allium cepa bioassay

Active	Concentration	Reason for the choice
Metiram + Pyraclostrobin	4g/L	Concentration of use for grape cultivation
	8g/L	Concentration 2 times higher than that of use

	16g/L	Concentration 4 times higher than that of use
Imidacloprid	0.2ml/L	Concentration of use for grape cultivation
	0.25ml/L	Concentration of use for grape cultivation
	0.40ml/L	Concentration of use for grape cultivation
	0.50ml/L	Concentration of use for grape cultivation
	8.75 ml/L	Concentration described in the article by Fioresi et al. (27) as potentially genotoxic
Metaxyl-m+mancozeb	6.25g/L	Concentration 4 times lower than that of use
	12.5g/L	Concentration 2 times lower than that of use
	25g/L	Concentration of use for grape cultivation
	50g/L	Concentration 2 times higher than that of use
	100g/L	Concentration 4 times higher than that of use
Tetraconazole	0.125mL/L	Concentration 4 times lower than the lowest concentration of use
	0.250mL/L	Concentration 2 times lower than the lowest concentration of use
	0.500mL/L	Concentration of use for grape cultivation
	0.750mL/L	Concentration of use for grape cultivation
	3,000 mL/L	Concentration 4 times higher than that of use

2.3 METHOD

This experiment was carried out in quadruplicate for each concentration of the actives, inside an exhaust hood and in the dark. Initially, the bulbs were placed in distilled water for 48 hours at room temperature to stimulate the development of the root meristem. After this period, the bulbs were placed in containers containing distilled water (negative control) and the test solutions. Each active ingredient was tested individually, according to the concentrations described in table 2.

The bulbs remained immersed in these solutions for a period of 72 hours, as described by Rank and Nielsen (11). After this period, a macroscopic analysis was performed, observing the morphological aspect of the roots, and then the length of the roots immersed in the test solutions was measured and compared with the negative control and the occurrence of cytotoxicity was considered when there was a statistically significant difference in the length of the roots submitted to growth in the test solutions in relation to the growth observed in the negative control. For this statistical evaluation, the Kruscal-Wallis test was used.

After measurement, the roots were collected and fixed in ethanol:acetic acid solution in the proportion of 3:1 for 6 hours and stored in 70% ethanol in a refrigerator (4°C) for later cytogenetic analysis.

For the preparation of the slides, Feulgen staining was used, where the roots were subjected to acid hydrolysis with 1N HCl for 8 minutes at 60°C, washed again in distilled water, stained with Schiff Reagent for 45 minutes in the dark, and then submitted to manual crushing on a glass slide for cytogenetic analysis. 2,000 cells of each replicate were analyzed

with the aid of a light microscope. The number of dividing cells observed in each reading was noted and later used to calculate the mitotic index (MI) by the following formula:

$$IM = \frac{\text{number of cells in division}}{\text{number of cells counted}} \times 100 \quad (1)$$

When any abnormality was observed in the cells during the reading, the abnormality was photographed using an optical microscope with a camera attached.

3 RESULTS AND DISCUSSION

Regarding the morphological aspect of the roots, the negative control presented the typical fasciculate root system, formed by adventitious roots with a healthy appearance and firm consistency. While the root system immersed in different concentrations of the test solutions also presented adventitious roots, but with a softer consistency. In general, as the concentration of the pesticide increased, the roots became more fragile, making it difficult to manipulate. Figure 1 shows the roots of *Alium strain* from the negative control and also from the different concentrations of test solutions of Provado 200 SC® (imidachlorid), but it should be noted that the other pesticides tested also showed similar macroscopic changes.

Figure 1

Evaluation of the development of the root meristem of A. cepa after immersion in containers containing distilled water as a negative control (a) and test solutions of Provado 200 SC® at different concentrations (b-f) for 72 hours at room temperature

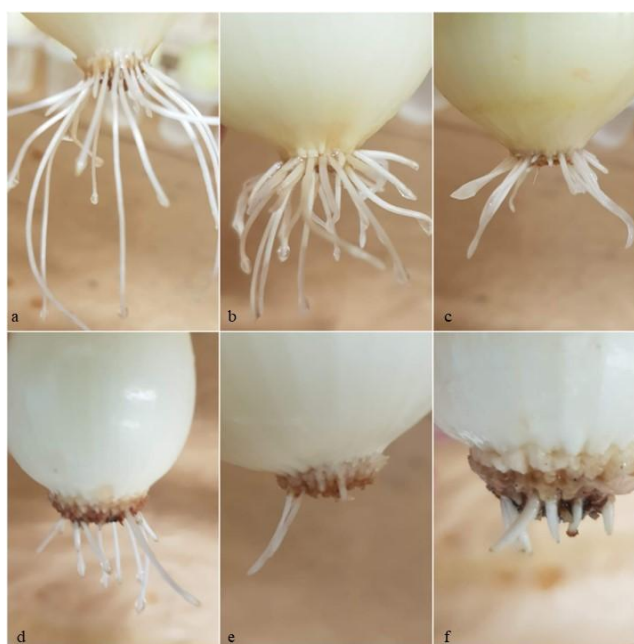


Figure 1 also shows the difference in the length of the roots of the negative control and the different concentrations tested, strongly suggesting that the pesticide has a cytotoxic effect. However, it is necessary to calculate the mitotic index, which is an indicator of the cytotoxic effect, as it is a marker of cell proliferation.

Table 3 presents the results of the mitotic index, as well as the number and length of the roots of all the active ingredients and their respective negative controls. All active ingredients, from the lowest concentrations, showed a reduction in root length compared to the negative control, presenting a statistically significant difference (p value less than 0.05).

Table 3

Mean size and quantity of roots and mitotic index for the different concentrations of the active ingredients compared to the respective negative controls (distilled water)

Active	Concentration	Average length (cm)	p-value *	Quantity	Mitotic index
Negative control	-	2,39	-	26,5	31,16%
They put in + pyraclostrobin	4g/L	1,1	< 0.05	30	31,61%
	8g/L	0,32	< 0.05	43	15,80%
	16g/L	0,92	< 0.05	43	1,32%
Active	Concentration	Average length (cm)	p-value *	Quantity	Mitotic index
Negative control	-	4,23	-	13,5	53,06%
Imidacloprid	0.2ml/L	1,33	< 0.05	13,5	50,46%
	0.25ml/L	1,86	< 0.05	7,75	45,02%
	0.40ml/L	1,3	< 0.05	6,25	39,61%
	0.50ml/L	1,07	< 0.05	5,25	34,85%
	8.75 ml/L	0,91	< 0.05	7	25,29%
Metalaxyl-M + Mancozeb	6.25g/L	1,85	< 0.05	6	14,39%
	12.5g/L	1	< 0.05	5,75	4,81%
	25g/L	1,09	< 0.05	6,5	3,50%
	50g/L	1,36	< 0.05	8,25	4,99%
	100g/L	1,44	< 0.05	6	0,00%
Active	Concentration	Average length (cm)	p-value *	Quantity	Mitotic index
Negative control	-	2,32	-	44	35,50%
Tetraconazole	0.125mL/L	0,95	< 0.05	14,5	33,21%
	0.250mL/L	0,9	< 0.05	19,25	31,35%
	0.500mL/L	0,82	< 0.05	26,5	30,46%
	0.750mL/L	0,9	< 0.05	19	21,26%
	3,000 mL/L	1,57	< 0.05	22,5	19,77%

Number of roots and size are presented as mean and the p-value, referring to the size of the roots, was calculated by the Kruskal-Wallis test.

Also in Table 3, most of the concentrations of the active ingredients tested showed a reduction in the mitotic index compared to the negative control and the higher the concentration of the active ingredient tested, the lower the mitotic index. The concentration

of metiram + pyraclostrobin use did not show a great difference in the percentage value of the mitotic index when compared to the negative control. However, when the concentration increased, the mitotic index reduced by 49.3% to 2 times the concentration of use and from 95.8% to 4 times the concentration of use.

For imidacloprid, the difference in the percentage value of the mitotic index when compared to the negative control was small (4.9%) for the first concentration of use, but increased to 15.2%, 25.3% and 34.3% in subsequent concentrations. This demonstrates the occurrence of cytotoxic effect at higher concentrations.

The farmer, when preparing the active ingredients for application in the crop, may come into contact with higher concentrations of the pesticide, and in this case, have a risk of poisoning if he is not properly using the Personal Protective Equipment (PPE).

For the active ingredients metalaxyl-m+mancozeb and tetraconazole, lower concentrations were also tested in relation to those used in viticulture. The lowest tested concentration of the active ingredient metalaxyl-m+mancozeb showed a mitotic index of 14.39%, a reduction of 72.9% in relation to the negative control, demonstrating to be a concentration with a high cytotoxic effect on *Allium cepa* roots. However, the lowest concentrations of tetraconazole presented percentage values of the mitotic index very close to those found in the negative control with a reduction of 6.5%. While for the highest concentrations of tetraconazole there was a decrease in the percentage values of the mitotic index in relation to the negative control, and for the highest concentration tested, there was a reduction of 44.3%. This decrease may probably be related to the action of this active ingredient in the suppression of DNA replication or to failure in the G2 phase of the cell cycle (12-14).

It is important to emphasize that the active ingredients selected for this study are all of a toxicological classification of low risk for acute poisoning, a fact that induces the farmer to handle these substances without due care, that is, without the proper use of the recommended PPE, it should be emphasized that the absence of risk of acute poisoning does not imply the absence of risk due to chronic exposure (15).

The fungicides Ridomil Gold-MZ® and Cabrio Top® are classified as unlikely to cause acute damage and little toxicity, respectively, but studies show that prolonged exposure to fungicides of the dithiocarbamates class, to which these fungicides belong, can lead to the appearance of respiratory allergies, dermatitis, or even more serious diseases such as Parkinson's disease and cancers (15).

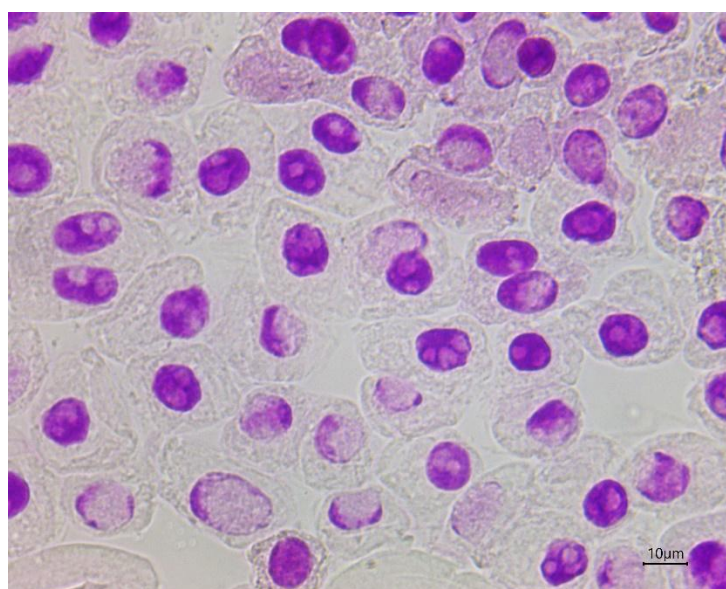
The package insert of Domark 100 EC® (tetraconazole) itself warns of liver damage due to chronic exposure. For Provado 200 SC® (imidacloprid) the effects of chronic exposure

are related to liver and thyroid decrease, as well as delayed bone calcification. This evidence was found in animal studies (16, 17).

Although there was no report of mutagenic or carcinogenic potential in the package insert of the substances tested(16-19). During the counting of cells that presented different phases of cell division, some abnormalities were observed in the genetic material such as binucleated cells, presence of nuclear vacuole and alterations related to the cell death process (pycnosis, karyorexis and karyolysis). Figure 2 shows the cells in the process of cell death and with nuclear vacuole.

Figure 2

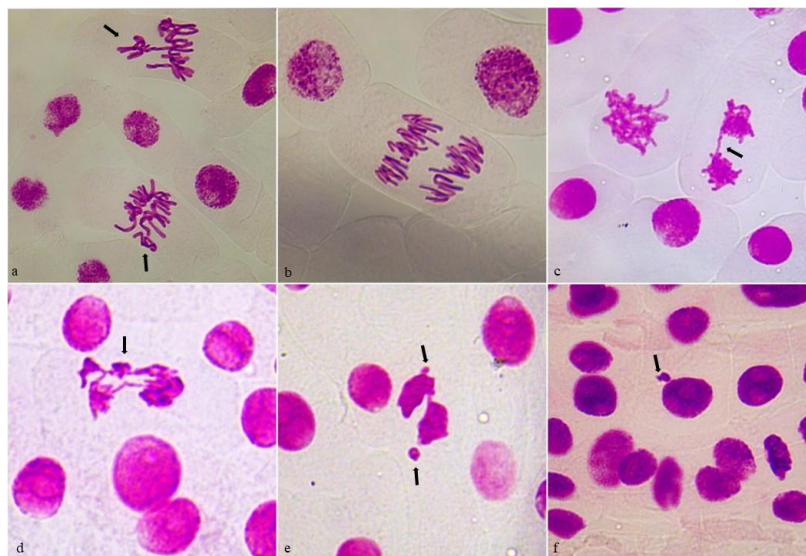
Allium cepa cells in the process of cell death after immersion in a Cabrio Top® test solution (Metiram + pyraclostrobin)



Also during the cell count, the occurrence of micronuclei, nuclear shoots, and chromosomal adhesion was observed. Metaphasic alterations such as c-metaphase, anaphasic alterations such as: anaphase bridge, multipolar anaphase, and telophasic alterations such as: telophase bridge; and other nuclear alterations such as pleomorphic nuclei. Figures 3 and 4 present images of some of the changes observed.

Figure 3

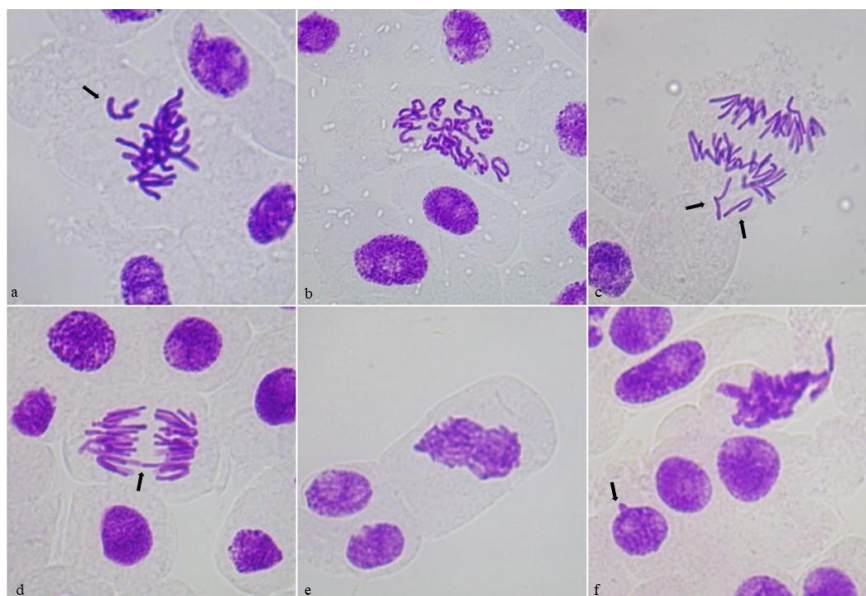
Abnormalities Observed in Allium Cepa Cells After Immersion in Test Solution of Provado 200 SC® (Imidacloprid)



a: upper arrow indicates cell with bridge in anaphase and with irregular division of DNA and lower arrow indicates genetic material outside the spindle in a cell in metaphase; b: cell in multipolar anaphase; c: arrow indicates telophase bridge and on the left side it is possible to observe a cell with chromosomal adhesion; d: arrow indicates two telophase bridges with pleomorphic nuclei; and: the arrows indicate micronuclei in a cell in telophase with pleomorphic nuclei; f: arrow indicates micronucleus in interphase cell.

Figure 4

Abnormalities observed in Allium cepa cells after immersion in Cabrio Top® (Metiram+pyraclostrobin) (a-d) and Domark 100 EC® (Tetraconazole) (e-f) test solution



a: arrow indicates genetic material outside the spindle in metaphase cell; b: c-metaphase; c: arrows indicate genetic material outside the spindle in a cell in multipolar anaphase; d: arrow indicates bridge in anaphase; e: telophase cell with adhesion; F: Arrow indicates nuclear bud in interphase cell and on the upper right it is possible to observe a cell with adhesion, possibly in metaphase.

Specifically for the active ingredient imidacloprid, the occurrence of micronuclei, shoots, and chromosomal adhesion was mainly observed. But c-metaphase, bridge in anaphase, multipolar anaphase, and genetic material outside the spindle in metaphase and anaphase were also observed. Genotoxicity of imidacloprid has been reported in studies conducted with amphibians (20), human lymphocytes (21), HepG2 cells (22), fish (23), and plants (24). This genotoxic activity may be related to the fact that the active ingredient imidacloprid is a compound that has an electronegative pharmacophore, therefore, favoring the binding with the DNA molecule, and can generate genotoxic damage. This DNA damage can occur through oxidative stress that generates reactive oxygen species in large quantities, and is highly toxic to the body. Abnormal condensation of fibers leads to adhesion of chromosomal fibers, which can cause cell death or chromosomal abnormalities, such as micronuclei, for cases in which they persist until anaphase (25).

The active ingredient imidacloprid is used as an insecticide, showing efficacy in controlling pest insects. However, it is classified as harmful to the environment, and can be toxic to non-target organisms such as bees that are pollinators, and can also affect humans if used on a large scale (26-27).

The most frequently observed chromosomal abnormalities after the tetraconazole test were nuclear vacuole and chromosomal adhesion, which had a relationship between the increase in the occurrence of these abnormalities and the increase in the concentrations of the test solutions. The nuclear vacuole can lead to nuclear deformation, and its occurrence is indicative of suppression in DNA synthesis during the S phase of mitosis (28). Chromosomal adhesion is an irreversible abnormality caused by the degradation or depolymerization of chromosomal DNA, being associated with pesticides, and may even lead to cell death (29).

The occurrence of micronucleus was also observed with the increase in the concentrations of the test solutions, demonstrating that higher concentrations can present clastogenic or aneugenic effects, since micronuclei are described as resulting from these two basic phenomena in mitotic cells. Being formed by the acentric chromosomes or fragments of broken chromosomes or whole chromosomes or chromatids that delay in anaphase and are excluded from the daughter nucleus in telophase (30).

These chromosomal abnormalities may be related to the fact that tetraconazole is classified as a "potentially carcinogenic compound in humans", according to data from the Environmental Protection Agency (31). In addition to being a potentially carcinogenic compound, tetraconazole can trigger endocrine diseases in humans and animals by affecting the biosynthesis of steroid hormones (32).

Fungicides used to protect plants against fungal pathogens are widely used, but knowledge about the possible effects on organisms other than fungi is still insufficient (33). The bioassay using *A. cepa* proved to be a sensitive and reliable method, because by showing the occurrence of chromosomal abnormalities and micronuclei, it is a tool capable of indicating the clastogenicity of agrochemicals with a pesticidal effect (34). In addition, the determination of the mitotic index can be used as a bioindicator of cytotoxicity (35).

In this study, chromosomal abnormalities were observed. However, the genotoxic evaluation was not performed, through the calculation of the index of cellular abnormalities of the root meristem in contact with the test solutions and the negative control, in order to obtain more robust results in relation to the genotoxic effect.

Root growth may vary between different onion bulbs. In view of this situation, it is suggested that the contact of the bulb with the distilled water be maintained until the length of the root reaches 2 centimeters and not for a certain time (24 or 48 hours), so that a growth pattern can be maintained before the contact of the root with the active ingredient to be tested, allowing a better evaluation of cytotoxicity. The negative control should continue to be kept immersed in distilled water until the end of the test, as a guarantee that the conditions of the experiment did not influence the growth of the root.

The bioassay with *Allium cepa* showed cytotoxicity results for all the active ingredients tested, and the active ingredients imidacloprid and tetraconazole when used in concentrations higher than those indicated in grape cultivation promoted the formation of micronuclei and adherent chromosomes. This information is of great value, contributing to the development of additional research, using laboratory animals to relate cytogenotoxicity in humans. The results obtained also serve as a warning for rural workers to be made aware of the proper use of PPE during the handling and application of pesticides, especially those from family farming in the North Central Region of Paraná.

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CLINICAL AND EPIDEMIOLOGICAL CHARACTERIZATION, ANESTHETIC-SURGICAL PROCEDURE, AND INTRAOPERATIVE PHARMACOLOGICAL MANAGEMENT: ELECTIVE CRANIOPLASTY

CARACTERIZAÇÃO CLÍNICO-EPIDEMIOLÓGICA, ATO ANESTÉSICO-CIRÚRGICO E ABORDAGEM FARMACOLÓGICA INTRAOPERATÓRIA: CRANIOPLASTIA ELETIVA

CARACTERIZACIÓN CLÍNICO-EPIDEMIOLÓGICA, ACTO ANESTÉSICO-QUIRÚRGICO Y ABORDAJE FARMACOLÓGICO INTRAOPERATORIO: CRANEOPLASTIA ELECTIVA



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ABSTRACT

Elective cranioplasty is a complex neurosurgical procedure aimed at reconstructing cranial defects resulting from trauma, tumor resections, post-craniectomy syndromes, and other neurological conditions. Although planned, this intervention involves relevant physiological challenges, particularly regarding anesthetic management and the maintenance of hemodynamic stability, which are essential factors to ensure adequate cerebral perfusion and prevent perioperative complications. In light of the above, this study aims to describe the clinical-epidemiological profile, anesthetic-surgical act, and intraoperative pharmacological approach. This is a cross-sectional study conducted in a tertiary hospital, including patients who underwent elective cranioplasty between January 2020 and December 2022, whose data were collected from electronic medical records. In the sample (n = 53), the following characteristics were highlighted: female sex (58.5%), age equal to or greater than 60 years (34.0%), white skin color (100.0%), current or previous smoking (22.6%), current or previous alcohol consumption (54.7%), non-eutrophic patients (62.5%), with comorbidities (98.1%) and previous surgeries (84.9%). In the anesthetic-surgical act, surgical time between 241 and 320 minutes (37.7%), general anesthesia (100.0%), orotracheal intubation (100.0%),

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and dorsal decubitus (92.5%) were observed. The most commonly administered intraoperative medications were propofol, remifentanyl, sevoflurane, intravenous lidocaine, cisatracurium, neostigmine, and levobupivacaine, and a high use of ondansetron, cefazolin, ephedrine, dexamethasone, mannitol, and metaraminol was also observed. Patients undergoing elective cranioplasty in the neurosurgery service in question are predominantly women, older adults, non-eutrophic, with comorbidities and previous surgeries, undergoing procedures in dorsal decubitus, with prolonged surgical time, general anesthesia, and orotracheal intubation. The proper integration of patient clinical characteristics, surgical technique, anesthetic management, and pharmacological approach in elective cranioplasties is essential to optimize perioperative care, in-hospital safety, and clinical prognosis.

Keywords: Neuroanesthesia. Neurosurgery. Hospital Care. Perioperative Period. Health Profile.

RESUMO

A cranioplastia eletiva é um procedimento neurocirúrgico complexo destinado à reconstrução de defeitos cranianos decorrentes de traumatismos, ressecções tumorais, síndromes pós-craniectomia e outras condições neurológicas. Embora planejada, essa intervenção envolve desafios fisiológicos relevantes, sobretudo no que se refere ao manejo anestésico e à manutenção da estabilidade hemodinâmica, fatores essenciais para garantir perfusão cerebral adequada e prevenir complicações perioperatórias. Diante do exposto, este estudo tem como objetivo descrever perfil clínico-epidemiológico, ato anestésico-cirúrgico e abordagem farmacológica intraoperatória. Trata-se de um estudo transversal, desenvolvido em um hospital terciário, com pacientes submetidos à cranioplastia eletiva entre janeiro de 2020 e dezembro de 2022, cujos dados foram coletados de prontuários eletrônicos. Na amostra (n = 53), destacaram-se sexo feminino (58,5%), idade igual ou superior a 60 anos (34,0%), cor de pele branca (100,0%), tabagismo atual ou prévio (22,6%), consumo de bebida alcoólica atual ou anterior (54,7%), pacientes não-eutróficos (62,5%), com comorbidades (98,1%) e cirurgias prévias (84,9%). No ato anestésico-cirúrgico, evidenciaram-se tempo cirúrgico entre 241 e 320 minutos (37,7%), com anestesia geral (100,0%), intubação orotraqueal (100,0%) e decúbito dorsal (92,5%). Os medicamentos intraoperatórios mais administrados foram propofol, remifentanil, sevoflurano, lidocaína endovenosa, cisatracúrio, neostigmina e levobupivacaína e, foi observado uso elevado de ondansetrona, cefazolina, efedrina, dexametasona, manitol e metaraminol. Os pacientes submetidos à cranioplastia eletiva no serviço de neurocirurgia em questão são, predominantemente, mulheres, com idade avançada, não-eutróficos, com comorbidades e cirurgias prévias, submetidos a procedimentos em decúbito dorsal, com tempo cirúrgico elevado, anestesia geral e intubação orotraqueal. A integração adequada entre características clínicas do paciente, técnica cirúrgica, ato anestésico e abordagem farmacológica em cranioplastias eletivas é essencial para otimizar o cuidado perioperatório, a segurança intra-hospitalar e o prognóstico clínico.

Palavras-chave: Neuroanestesia. Neurocirurgia. Assistência Hospitalar. Período Perioperatório. Perfil de Saúde.

RESUMEN

La craneoplastia electiva es un procedimiento neuroquirúrgico complejo destinado a la reconstrucción de defectos craneales derivados de traumatismos, resecciones tumorales, síndromes post-craniectomía y otras condiciones neurológicas. Aunque planificada, esta intervención implica desafíos fisiológicos relevantes, especialmente en lo que respecta al manejo anestésico y al mantenimiento de la estabilidad hemodinámica, factores esenciales para garantizar una perfusión cerebral adecuada y prevenir complicaciones perioperatorias. Ante lo expuesto, este estudio tiene como objetivo describir el perfil clínico-epidemiológico,

el acto anestésico-quirúrgico y el abordaje farmacológico intraoperatorio. Se trata de un estudio transversal, desarrollado en un hospital terciario, con pacientes sometidos a craneoplastia electiva entre enero de 2020 y diciembre de 2022, cuyos datos fueron recolectados de historias clínicas electrónicas. En la muestra ($n = 53$), se destacaron: sexo femenino (58,5%), edad igual o superior a 60 años (34,0%), color de piel blanca (100,0%), tabaquismo actual o previo (22,6%), consumo de alcohol actual o previo (54,7%), pacientes no eutróficos (62,5%), con comorbilidades (98,1%) y cirugías previas (84,9%). En el acto anestésico-quirúrgico, se evidenciaron tiempo quirúrgico entre 241 y 320 minutos (37,7%), con anestesia general (100,0%), intubación orotraqueal (100,0%) y decúbito dorsal (92,5%). Los medicamentos intraoperatorios más administrados fueron propofol, remifentanilo, sevoflurano, lidocaína intravenosa, cisatracurio, neostigmina y levobupivacaína, y se observó un alto uso de ondansetrón, cefazolina, efedrina, dexametasona, manitol y metaraminol. Los pacientes sometidos a craneoplastia electiva en el servicio de neurocirugía en cuestión son predominantemente mujeres, de edad avanzada, no eutróficos, con comorbilidades y cirugías previas, sometidos a procedimientos en decúbito dorsal, con tiempo quirúrgico prolongado, anestesia general e intubación orotraqueal. La adecuada integración entre las características clínicas del paciente, la técnica quirúrgica, el acto anestésico y el abordaje farmacológico en craneoplastias electivas es esencial para optimizar el cuidado perioperatorio, la seguridad intrahospitalaria y el pronóstico clínico.

Palabras clave: Neuroanestesia. Neurocirugía. Atención Hospitalaria. Período Perioperatorio. Perfil de Salud.

1 INTRODUCTION

Elective cranioplasty is a highly complex neurosurgical procedure aimed at repairing cranial defects that may result from trauma, tumor resections, post-craniectomy syndromes, and congenital anomalies. In addition to restoring the physical and aesthetic integrity of the skullcap, cranioplasty has important functional implications, including improved brain protection and potential influence on cerebrovascular dynamics and intracranial pressure (ICP) post-craniectomy. Recent studies indicate that elective cranial reconstructive procedures, although planned, present relevant physiological challenges, especially related to anesthetic management and intraoperative hemodynamic stability, requiring therapeutic approaches strictly based on the best available evidence (MEE *et al.*, 2022; ZANUTO *et al.*, 2024).

In this scenario, it is noteworthy that the maintenance of hemodynamic stability is one of the main intraoperative challenges in elective cranioplasty. Abrupt variations in blood pressure can occur during different stages of the procedure, especially in anesthetic induction, cranial bed manipulation, and implant positioning (MEE *et al.*, 2022; ZANUTO *et al.*, 2024). Such alterations can compromise adequate cerebral perfusion and require strict control of mean arterial pressure, volume and anesthetic depth. Thus, continuous hemodynamic monitoring and precise titration of anesthetic and vasoactive agents become central elements to ensure adequate cerebral perfusion and patient safety during the procedure (COTTRELL; PATEL, 2017; PETERSEN *et al.*, 2003; HALDAR *et al.*, 2015).

The literature has increasingly explored the specific anesthetic aspects of elective neurosurgical interventions, emphasizing that adequate maintenance of cerebral perfusion and control of mean arterial pressure are crucial to prevent cerebral ischemia and other perioperative complications. Anesthesia for cranioplasty and other elective intracranial neurosurgery often involves techniques that optimize anesthetic depth, minimize harmful increases in ICP, and stabilize the patient's hemodynamics, and are often performed under general anesthesia with orotracheal intubation. The anesthetic approach can vary between total intravenous anesthesia (TIVA) or combined with inhalational agents, depending on the clinical presentation and individual anesthetic goals (ANDRABI *et al.*, 2017; LIU *et al.*, 2025).

From the pathophysiological point of view, neurosurgical procedures imply potential alterations in cerebral autoregulation and circulatory homeostasis, which makes integrated anesthetic planning essential to optimize cerebral blood flow and maintain a stable hemodynamic profile. The management of anesthesia in elective cranioplasties should consider, for example, the cardiovascular response to anesthetic induction, surgical

manipulations, and nociceptive stimuli, as well as specific strategies for brain relaxation and prevention of ICP elevations (CHUI *et al.*, 2014).

The literature also highlights that the proper management of anesthesia includes the balance between effective analgesia and minimization of adverse events. The use of opioids, with rapid pharmacokinetics, allows control of the sympathetic response to intubation and surgical stimuli, in addition to contributing to hemodynamic stability and anesthetic titration. Along with neuromuscular blockers, sedatives, antiemetic agents, or adjunctive analgesics, this therapeutic arsenal should be considered within a multimodal protocol guided by the best available evidence, in order to reduce adverse events and optimize clinical outcomes (BHATIA *et al.*, 2019; KIANIAN *et al.*, 2024).

Regarding epidemiology, the profile of patients undergoing elective cranioplasty is heterogeneous, and is often composed of individuals with multiple comorbidities, chronic use of medications, and varied demographic characteristics, which can influence both the anesthetic-surgical procedure and the pharmacological response. Comorbidities such as oncological disease, hypertension, neurological disease, and psychiatric disorder require detailed preoperative evaluation and individualized anesthetic planning to maintain adequate cerebral perfusion, avoid significant hemodynamic fluctuations, and provide a favorable postoperative recovery (EYELADE *et al.*, 2016; FERREIRA *et al.*, 2024).

In this context, it is evident that anesthetic practice in elective cranioplasty should be based on principles of evidence-based medicine, combining physiological knowledge with up-to-date clinical data to guide therapeutic decisions at all stages of perioperative care.

Therefore, this study aims to describe the sociodemographic, behavioral, and health aspects of patients undergoing elective cranioplasty, as well as to characterize the anesthetic-surgical procedure and the intraoperative pharmacological approach.

2 METHODOLOGY

This was a cross-sectional study conducted in a tertiary hospital located in Passo Fundo, Rio Grande do Sul, Brazil, with ethical approval (opinion No°. 6,282,730) and compliance with the Declaration of Helsinki. The study and the results were described according to the guidelines of *the Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE - VON ELM *et al.*, 2007).

To compose the sample, a list of the hospitalization management system was obtained, considering the data on hospitalization by medical specialty. Patients who underwent elective cranioplasty between January 2020 and December 2022, of both sexes,

aged 18 years or older, and with documents descriptive of the surgery available in the electronic medical record, were defined as eligible for this study.

Data collection covered two hospitalization periods: the clinical-epidemiological profile was analyzed in the medical records of the hospital admission consultation, while the anesthetic-surgical procedure and the pharmacological approach were investigated intraoperatively.

The clinical-epidemiological profile included sex, age, skin color, marital status, origin, exercise of paid activity, education, religion, smoking, alcoholism, use of illicit drugs, nutritional status classified by body mass index (BRASIL, 2011), drug atopy, continuous use medications, comorbidities and previous surgeries. The anesthetic-surgical procedure included surgical time, anesthetic technique, orotracheal intubation, and patient positioning. The intraoperative pharmacological approach included sedatives, opioid anesthetics, inhalational anesthetics, adjuvant analgesics, neuromuscular blockers, neuromuscular blockade reversers, local anesthetics for conductive or regional anesthesia, and other medications used during the surgical procedure.

For data analysis, descriptive statistics were used based on mean and standard deviation estimates for numerical variables, and absolute (n) and relative (%) frequencies for categorical variables.

3 RESULTS

The final sample was composed of 53 participants, from 37 municipalities, predominantly from the north of Rio Grande do Sul. As shown in Table 1, the following stood out: female (58.5%), age 60 years or older (34.0%; 51.7 ± 2.0 years), white skin color (100.0%), individuals with a spouse (58.5%), from municipalities other than Passo Fundo (81.1%), with paid activity (60.0%), 9 years or less of schooling (63.3%), and Catholics (67.9%). Regarding behavioral aspects, 22.6% were or were smokers, 54.7% reported current or previous consumption of alcoholic beverages and 100.0% had never used illicit drugs. Regarding health, 62.5% had non-eutrophic nutritional status, 13.2% had drug atopy, 45.3% used 3 to 6 daily medications (mean 3.2 ± 0.3 daily medications) and 98.1% had comorbidities, especially oncological disease (69.8%), systemic arterial hypertension (49.1%), neurological disease (46.5%), psychiatric disorder (37.7%) and cerebrovascular disease (18.9%). In addition, 83.0% had the simultaneous presence of two or more comorbidities and 84.9% had undergone previous surgeries.

Table 1

Clinical-epidemiological profile of patients undergoing elective cranioplasty at a tertiary hospital in Passo Fundo, Rio Grande do Sul, Brazil, 2020 - 2022 (n = 53)

Variables	n	%
Gender		
Male	22	41,5
Women	31	58,5
Age, in full years		
18 - 39	12	22,6
40 - 49	10	18,9
50 - 59	13	24,5
≥ 60	18	34,0
Skin color		
White	53	100,0
Other	0	0,0
Marital status		
With spouse	31	58,5
No spouse	22	41,5
Provenance		
Passo Fundo	10	18,9
Other municipalities	43	81,1
Paid activity (n = 45)		
Yes	27	60,0
No/not informed	18	40,0
Schooling, in years of study (n = 49)		
≤ 9	31	63,3
10 - 12	16	32,6
≥ 13	2	4,1
Religion		
Catholic	36	67,9
Other/Not Informed	17	32,1
Smoking		
Yes	6	11,3
Former smoker	6	11,3
No/not informed	41	77,4
Alcoholism		
Yes	25	47,2
Former drinker	4	7,5
No/not informed	24	45,3
Illicit drug use		
Yes	0	0,0
Former user	0	0,0
No/not informed	53	100,0
Nutritional status (n = 48)		
Eutrophic	18	37,5
Non-eutrophic	30	62,5
Drug atopy		
Yes	7	13,2
No/not informed	46	86,8
Number of medicines for continuous use		
0	6	11,3
1 - 2	19	35,9
3 - 6	24	45,3
≥ 7	4	7,5
Comorbidity		
Yes	52	98,1
No	1	1,9
Comorbidities		
Oncological disease	37	69,8
Systemic arterial hypertension	26	49,1

Neurological disease	24	45,3
Psychiatric disorder	20	37,7
Cerebrovascular disease	10	18,9
Diabetes mellitus	8	15,1
Dyslipidemia	7	13,2
Cardiovascular disease	7	13,2
Endocrine disease	6	11,3
Obesity	4	7,5
Liver disease	2	3,8
Lung disease	1	1,9
Haematological disease	1	1,9
Renal disease	1	1,9
Number of comorbidities		
0 - 1	9	17,0
≥ 2	44	83,0
Previous surgeries		
Yes	45	84,9
No/not informed	8	15,1

Regarding the anesthetic-surgical procedure, described in Table 2, the predominance of surgical time between 241 and 320 minutes (37.7%), general anesthesia (100.0%), orotracheal intubation (100.0%) and supine (92.4%) was observed.

Table 2

Characterization of the anesthetic-surgical procedure of patients undergoing elective cranioplasty at a tertiary hospital in Passo Fundo, Rio Grande do Sul, Brazil, 2020 - 2022 (n = 53)

Variables	n	%
Surgical time, in minutes		
≤ 60	0	0,0
61 - 120	5	9,4
121 - 180	7	13,2
181 - 240	6	11,4
241 - 320	20	37,7
> 320	15	28,3
Anesthetic technique		
General anesthesia	53	100,0
Local anesthesia	35	66,0
Sedation	0	0,0
Orotracheal intubation		
Yes	53	100,0
No	0	0,0
Patient positioning		
Supine position	49	92,4
Prone position	0	0,0
Lateral decubitus	2	3,8
Other positioning	2	3,8

Regarding the intraoperative medications shown in Table 3, the most commonly used sedative, opioid anesthetic, inhalational anesthetic, and adjuvant analgesic were, respectively, propofol (98.1%), remifentanil (98.1%), sevoflurane (3.8%), and intravenous lidocaine (98.1%). The most frequent neuromuscular blocker, neuromuscular blockade

reverser, and local anesthetic were, respectively, cisatracurium (94.3%), neostigmine (13.2%), and levobupivacaine (73.6%). In addition, other intraoperative drugs showed high use, such as ondansetron (98.1%), cefazolin (96.2%), ephedrine (88.7%), dexamethasone (73.6%), mannitol (69.8%) and metaraminol (58.5%).

Table 3

Intraoperative pharmacological approach to patients undergoing elective cranioplasty at a tertiary hospital in Passo Fundo, Rio Grande do Sul, Brazil, 2020 - 2022 (n = 53)

Variables	n	%
Sedatives		
Propofol	52	98,1
Midazolam	10	18,9
Diazepam	1	1,9
Clonazepam	1	1,9
Etomidate	0	0,0
Other	1	1,9
Intraoperative opioid anesthetics		
Remifentanil	52	98,1
Sulfentanil	47	88,7
Fentanyl	4	7,5
Alfentanil	0	0,0
Methadone	0	0,0
Other	0	0,0
Intraoperative inhalational anesthetics		
Sevoflurane	2	3,8
Intraoperative adjunctive analgesics		
Intravenous lidocaine	52	98,1
Dipyrone	49	92,5
Ketoprofen	43	81,1
Dexmedetomidine	13	24,5
Morphine	12	22,6
Clonidine	7	13,2
Ketamine	5	9,4
Magnesium Sulfate	0	0,0
Acetaminophen	0	0,0
Other	0	0,0
Neuromuscular Blockers		
Cisatracurium	50	94,3
Succinylcholine	3	5,7
Rocuronium	1	1,9
Atracurium	0	0,0
Pancuronium	0	0,0
Vecuronium	0	0,0
Other	0	0,0
Neuromuscular Blockade Reversers		
Neostigmine	7	13,2
Sugammadex	0	0,0
Other	0	0,0
Local anesthetics for conductive or regional anesthesia		
Levobupivacaine	39	73,6
Bupivacaine	5	9,4
Lidocaine	3	5,7
Ropivacaine	1	1,9
Mepivacaine	0	0,0
Other	0	0,0
Other medicines		

Ondansetron	52	98,1
Cefazolin	51	96,2
Ephedrine	47	88,7
Dexamethasone	39	73,6
Mannitol	37	69,8
Metaraminol	31	58,5
Pantoprazole	22	41,5
Gentamicin	15	28,3
Heparin	14	26,4
Atropine	13	24,5
Aminophylline	6	11,3
Phenytoin	5	9,4
Hydrocortisone	5	9,4
Furosemide	4	7,5
Bromopride	2	3,8
Epinephrine	1	1,9
Cefoxitin	1	1,9
Ciprofloxacin	1	1,9
Phenobarbital	1	1,9
Clindamycin	1	1,9
Ceftriaxone	1	1,9
Ethylephrine	1	1,9
Droperidol	1	1,9
Naloxone	1	1,9
Tranexamic acid	0	0,0
Methylprednisolone	0	0,0
Vancomycin	0	0,0
Thrombin	0	0,0
Clopidogrel	0	0,0
Protamine	0	0,0
Millrinone	0	0,0
Isosorbide	0	0,0
Metoprolol	0	0,0
Scopolamine	0	0,0
Tirofiban	0	0,0

4 DISCUSSION

The clinical-epidemiological characterization of individuals undergoing elective cranioplasty revealed a predominance of females, a finding that differs from that described in most of the literature, in which a higher frequency of men is observed (COELHO *et al.*, 2023; DO *et al.*, 2022; MUSTAFA *et al.*, 2025; LEATHERS *et al.*, 2025). This difference may be related to the profile of the population included in the study, composed exclusively of patients undergoing elective procedures, in which there is a lower participation of traumatic causes that are more prevalent in males (MUNIVENKATAPPA *et al.*, 2016).

The age profile identified in this sample is compatible with that described in the literature on elective cranioplasty (NAM *et al.*, 2022; MUSTAFA *et al.*, 2025), as well as the predominance of individuals with nine years of schooling or less (COELHO *et al.*, 2023; MUSTAFA *et al.*, 2025). This characteristic may be related to the higher barriers to access to health services faced by populations with lower levels of education, favoring late diagnosis and, consequently, the indication of specialized surgical treatment (BOCCOLINI; DE SOUZA JUNIOR, 2016; ZAJACOVA; LAWRENCE, 2018). Similarly, the higher frequency of white

individuals has also been described in previous studies involving elective cranial surgeries (LEATHERS *et al.*, 2025). There was also a predominance of patients with a spouse and in the exercise of paid activity, findings also reported in national and international investigations on elective cranial procedures (DE ARAÚJO *et al.*, 2022; FILIPOVIĆ *et al.*, 2025). As for religious aspects, the adoption of Catholicism as the predominant belief was also identified in populations undergoing neurosurgical interventions (REI *et al.*, 2023).

With regard to behavioral aspects, the higher proportion of non-smokers observed in the present sample is supported by the previously published literature (LEATHERS *et al.*, 2025). On the other hand, with regard to the consumption of alcoholic beverages, the results of this study differ from those reported by Leathers *et al.* (2025), who identified a lower prevalence of alcohol use among patients undergoing cranioplasty. This discrepancy may be related to differences in the care context and in the sociodemographic characteristics of the populations analyzed.

With regard to health conditions, the predominance of non-eutrophic nutritional status observed in this sample is supported by a North American study (MOYA *et al.*, 2023). In addition, the high prevalence of oncological disease, systemic arterial hypertension, neurological disease, psychiatric disorder, and cerebrovascular disease is compatible with findings described in the scientific literature on patients undergoing elective cranioplasty (NAM *et al.*, 2022; MOYA *et al.*, 2023; LEATHERS *et al.*, 2025; MUSTAFA *et al.*, 2025). A high frequency of multimorbidity and history of previous surgeries was also observed, which may be related to the particularities of the scenario studied, characterized as a macro-regional reference center for the performance of medium and high complexity procedures.

Regarding the anesthetic-surgical procedure, the operative time observed in this study was higher than that described in the international literature on cranioplasty (ANDRABI *et al.*, 2017; CHEN *et al.*, 2023). This result may reflect the variability inherent to the cranioplasty technique, whose duration is influenced by multiple factors not measured in this study, including particularities of the reconstructive method employed, the need for intraoperative adjustments of the implant, and the time dedicated to the fixation and hemostasis stages. In addition, differences related to the institutional context and care routines may contribute to a longer duration of the procedure, without this necessarily representing an increase in complications or inadequacy of the surgical approach.

With regard to anesthetic management, cranioplasty under general anesthesia, with orotracheal intubation and supine positioning, is in line with the practice described in the national and international literature on elective cranial neurosurgery. These elements are widely adopted as standard in this type of procedure, as they allow safe airway control,

adequate mechanical ventilation, and hemodynamic stability, in addition to favoring surgical access to the operative field, especially in surgeries of longer duration (ANDRABI *et al.*, 2017; CHEN *et al.*, 2023; DA SILVA; PEREIRA; BROCHADO, 2014; COTTRELL; PATEL, 2017; ZANUTO *et al.*, 2024)

Conducting neurosurgery requires the preservation of cerebral perfusion and the reduction of intraoperative risks, which requires adequate preoperative evaluation and careful planning of the intervention, considering its effects on neurophysiology (COTTRELL; PATEL, 2017). In this context, the choice of anesthetic agents (including hypnotics, analgesics, and neuromuscular blockers) directly influences cerebral hemodynamic stability during the procedure (DA SILVA; PEREIRA; BROCHADO, 2014), since variations in intraoperative blood pressure can compromise cerebral perfusion pressure, one of the main challenges in cranioplasty surgeries, reinforcing the need for continuous monitoring and careful titration of anesthetic agents throughout surgery (COTTRELL; PATEL, 2017).

The use of TIVA, based on propofol associated with remifentanil, has been widely used in neurosurgical procedures because it favors greater cerebral hemodynamic control and faster anesthetic recovery, with limited interference on neurophysiological parameters (COTTRELL; PATEL, 2017; NGUYEN *et al.*, 2023). This strategy allows early neurological evaluation in the postoperative period and is justified by the pharmacological characteristics of these agents (COTTRELL; PATEL, 2017). The association between propofol and short-acting opioids, especially remifentanil, promotes adequate hypnosis, amnesia, and attenuation of responses to surgical stimulation, in addition to contributing to a lower incidence of adverse events, such as nausea, vomiting, and seizures, reinforcing the benefits of its intraoperative use and the high frequency observed in this study (ZHONG *et al.*, 2025; COLES *et al.*, 2000)

Although inhalational anesthetics, such as sevoflurane, are widely used in neurosurgical procedures and have beneficial effects on cerebral blood flow, in addition to possible neuroprotective properties, their use may be associated with limitations when compared to TIVA (ZHOU *et al.*, 2021). Among these restrictions are the greater occurrence of residual effects, less precise control of anesthetic depth, and increased risk of postoperative nausea and vomiting (WU *et al.*, 2023). These characteristics may explain the lower frequency of sevoflurane use in the present sample (3.8%), especially when contrasted with the predominant use of propofol (98.1%).

The intravenous administration of lidocaine is consistently part of multimodal analgesia protocols in neurosurgical procedures, acting to attenuate the sympathetic response associated with laryngoscopy and orotracheal intubation (COTTRELL; PATEL,

2017; MAISSAN *et al.*, 2022). This effect contributes to greater hemodynamic stability and to the prevention of intracranial pressure elevations in the intraoperative period, in addition to helping to control postoperative pain (ZEILER *et al.*, 2015; CHANDRA *et al.*, 2022), which may explain the high frequency of use observed in this study (98.1%).

Neuromuscular blockade in the patients in the sample was predominantly performed with cisatracurium, an agent widely used in surgical procedures because it favors adequate conditions for orotracheal intubation and muscle relaxation, with preservation of hemodynamic stability and greater intraoperative safety (HUMMAD, 2025). In addition, this drug is associated with faster and more predictable recovery of motor function in the postoperative period, maintaining comparable rates of adverse events and clinical outcomes in relation to other neuromuscular blockers (HUMMAD, 2025; PARVATI *et al.*, 2024), which explains its high frequency of use found in the study (94.3%). It is also noteworthy that the mechanism of action of cisatracurium, based on the competitive blockade of neuromuscular transmission, allows pharmacological reversal with acetylcholinesterase inhibitors, such as neostigmine (STRAWBRIDGE, 2023), justifying the administration of this drug in 13.2% of cases.

Levobupivacaine, a long-acting local anesthetic, has been widely used for infiltration of the surgical wound because it promotes effective blockade of sensory and motor neural conduction (BAJWA; KAUR, 2013). Compared to other local anesthetics, it has a lower potential for cardiovascular and neurological toxicity, which confers a more favorable safety profile (KORAT; KAPUPARA, 2017). Although it shares pharmacokinetic characteristics similar to those of racemic bupivacaine, its better clinical tolerability has supported the increasing use in surgical procedures, including neurosurgical interventions (ATHAR *et al.*, 2016), which may explain the high frequency observed in the sample (73.6%).

Prophylactic regimens for postoperative nausea and vomiting, based mainly on ondansetron and dexamethasone, play a central role in reducing associated complications, such as bronchial aspiration, bleeding, and surgical wound involvement, positively impacting outcomes in elective neurosurgery (GAN *et al.*, 2014; THONGRONG *et al.*, 2018). Such clinical relevance may explain the significant use of ondansetron (98.1%) and dexamethasone (73.6%) in the sample analyzed. In addition to its antiemetic efficacy, dexamethasone stands out for its anti-inflammatory and pain-modulating effects, which have been widely explored in the perioperative neurosurgical context (DE OLIVEIRA JR *et al.*, 2013). This synthetic corticosteroid also contributes to the control of encephalic edema and to the attenuation of intracranial pressure, favoring neurological recovery. Even so, its

indication must carefully consider the individual clinical profile, weighing potential benefits and risks (GAN *et al.*, 2014; GUPTA *et al.*, 2014).

Intraoperative antimicrobial prophylaxis was predominantly performed with cefazolin, an antibiotic widely used in neurosurgical procedures due to its coverage against cutaneous pathogens and favorable safety profile. Its use aims to reduce the occurrence of surgical site infections and prevent adverse repercussions on the central nervous system (BRATZLER *et al.*, 2013; NGUYEN *et al.*, 2019), which may explain the high frequency in the analyzed sample (96.2%).

Regarding vasoactive drugs, ephedrine is one of the preferable vasopressors for the treatment of hypotension in the intraoperative period of neurosurgery due to its adrenergic agonist mechanism of action and its positive chronotropic and inotropic effects (MENG; RASMUSSEN, 2025; UEMURA *et al.*, 2023), which may explain the high prevalence (88.7%) in this study. In addition, metaraminol is a pharmacological agent indicated for the treatment and prevention of intraoperative hypotension, especially in situations in which general or regional anesthesia promotes a decrease in systemic vascular resistance (COTTRELL; PATEL, 2017). Metaraminol acts mainly as an alpha-1 adrenergic agonist, promoting peripheral vasoconstriction and increased mean arterial pressure, which translates into maintenance of adequate cerebral perfusion in elective cranial surgeries and avoids episodes of pressure drop that compromise oxygenation and perfusion of brain tissue (MILLER *et al.*, 2020), corroborating the important use (58.5%).

In the context of intracranial pressure modulation during elective intracranial procedures, mannitol stands out as the most commonly used osmotic agent in neuroanesthetic practice. Its use is associated with obtaining more favorable intraoperative brain relaxation, facilitating exposure to the surgical field and reducing risks related to the handling of the brain parenchyma in cranial surgeries, including cranioplasties (RANGWALA *et al.*, 2024). The therapeutic effect results from the establishment of an osmotic gradient between the intravascular space and the brain tissue, promoting water mobilization from the extracellular brain compartment to the systemic circulation, with a consequent reduction in brain volume and intracranial pressure, which contributes to greater technical safety and intraoperative predictability (LI *et al.*, 2020). Additionally, the use of mannitol in anesthetic management is pertinent due to its ability to promote a consistent reduction in intracranial pressure in the pre-opening period or during the initial stages of cranial access, favoring more stable surgical conditions (ZHANG *et al.*, 2019). This effect contributes to minimizing transient increases in intracranial pressure and the formation of cerebral edema, situations

that can negatively interfere with anesthetic conduction and intraoperative safety (MILLER *et al.*, 2020), which is possibly related to the high frequency observed in the sample (69.8%).

In summary, the findings of this study contribute to the literature by integrating the analysis of the clinical-epidemiological profile, aspects related to the anesthetic-surgical procedure, and pharmacological strategies adopted in the intraoperative period of patients undergoing elective cranioplasty. The detailed characterization of these variables allows a better understanding of the care context of these individuals and provides relevant subsidies for the improvement of personalized therapeutic conducts, with a potential positive impact on functional outcomes and perioperative safety.

It is noteworthy that the research was developed in a hospital institution classified as a macro-regional reference for medium and high complexity procedures, which was reflected in a diversified sample, composed of 53 patients from 37 different municipalities. In addition, the results obtained are in line with evidence previously described in the national and international literature, giving scientific solidity to the findings. In this sense, the methodological design employed and the systematic analysis of the information reinforce the potential of the study to support the planning of anesthetic-surgical care and support evidence-based decision-making processes.

However, it is important to recognize limitations inherent to the study. Among them, possible information and selection biases stand out, since the data were extracted from electronic medical records filled out by different professionals, which restricts control over the standardization and completeness of the records. In addition, the sample is limited to a single hospital center, which may limit the extrapolation of the results to other care settings, and should be interpreted with caution in the context of generalization.

5 CONCLUSION

The results indicate that patients undergoing elective cranioplasty are mostly women, aged 60 years or older, white, who consume alcoholic beverages, have non-eutrophic nutritional status, comorbidities and previous surgeries. In the anesthetic-surgical procedure, there is a predominance of surgical time between 241 and 320 minutes, associated with general anesthesia, orotracheal intubation, and supine position. The most commonly used intraoperative medications are propofol, remifentanyl, sevoflurane, intravenous lidocaine, cisatracurium, neostigmine, and levobupivacaine. In addition, high administration of ondansetron, cefazolin, ephedrine, dexamethasone, mannitol, and metaraminol is observed. Finally, the results are consistent with the scientific literature and offer relevant contributions to the qualification of anesthesiology and neurosurgery services, with benefits related to the

improvement of patient care, the optimization of resources, and the scientific support of care decisions.

6 AUTHOR CONTRIBUTIONS

Lucas Dalla Maria: conception and planning of the study; data collection and processing; statistical analysis of the collected data and interpretation, conception and writing of the manuscript; critical review of the literature; critical revision of the manuscript; final approval of the manuscript.

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Marcelo Augusto Landim Arteiro de Oliveira: conception and writing of the manuscript; critical review of the literature; critical revision of the manuscript; final approval of the manuscript.

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Shana Ginar da Silva: conception and planning of the study; critical review of the literature; critical revision of the manuscript; final approval of the manuscript.

Ivana Loraine Lindemann: conception and planning of the study; statistical analysis of the collected data and interpretation, conception and writing of the manuscript; critical review of the literature; critical revision of the manuscript; final approval of the manuscript.

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PHYSIOLOGICAL CHANGES DURING AGING

ALTERAÇÕES FISIOLÓGICAS DURANTE O ENVELHECIMENTO

CAMBIOS FISIOLÓGICOS DURANTE EL ENVEJECIMIENTO



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ABSTRACT

Population aging is a growing global phenomenon, marked by a significant increase in the proportion of older adults, driven by declining fertility rates and rising life expectancy. In Brazil, this process is occurring rapidly, bringing important implications for public health and social organization. Aging is characterized by progressive, heterogeneous, and multifactorial changes that affect various body systems, including the nervous, sensory, immune, endocrine, cardiorespiratory, musculoskeletal, gastrointestinal, urinary, and integumentary systems. These changes involve functional decline, structural alterations, and reduced adaptive capacity, directly impacting individuals' autonomy, quality of life, and functionality. Among other aspects, there is a reduction in neural plasticity, sensory changes (vision,

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hearing, smell, and taste), sleep fragmentation, immunosenescence, hormonal imbalances, decreased cardiorespiratory capacity, and loss of muscle mass and bone density. Additionally, socioeconomic, cultural, and individual factors significantly influence how aging manifests. Thus, understanding the physiological changes associated with senescence is essential for developing strategies for prevention, health promotion, and maintenance of functionality, contributing to healthy and active aging.

Keywords: Older Adults. Health. Functionality.

RESUMO

O envelhecimento populacional constitui um fenômeno global crescente, marcado pelo aumento expressivo da proporção de pessoas idosas, impulsionado pela redução das taxas de fecundidade e pelo aumento da expectativa de vida. No Brasil, esse processo ocorre de forma acelerada, trazendo importantes implicações para a saúde pública e para a organização social. O envelhecimento é caracterizado por alterações progressivas, heterogêneas e multifatoriais, que afetam diversos sistemas do organismo, incluindo os sistemas nervoso, sensorial, imunológico, endócrino, cardiorrespiratório, musculoesquelético, gastrointestinal, urinário e tegumentar. Essas mudanças envolvem declínio funcional, alterações estruturais e redução da capacidade adaptativa, impactando diretamente a autonomia, a qualidade de vida e a funcionalidade dos indivíduos. Destacam-se, entre outros aspectos, a redução da plasticidade neural, alterações sensoriais (visão, audição, olfato e paladar), fragmentação do sono, imunossenescência, desequilíbrios hormonais, diminuição da capacidade cardiorrespiratória e perda de massa muscular e densidade óssea. Além disso, fatores socioeconômicos, culturais e individuais influenciam significativamente a forma como o envelhecimento se manifesta. Dessa forma, compreender as alterações fisiológicas associadas à senescência é fundamental para o desenvolvimento de estratégias de prevenção, promoção da saúde e manutenção da funcionalidade, contribuindo para um envelhecimento saudável e ativo.

Palavras-chave: Idosos. Saúde. Funcionalidade.

RESUMEN

El envejecimiento poblacional constituye un fenómeno global creciente, caracterizado por el aumento significativo de la proporción de personas mayores, impulsado por la reducción de las tasas de fecundidad y el aumento de la esperanza de vida. En Brasil, este proceso ocurre de forma acelerada, lo que genera importantes implicaciones para la salud pública y la organización social. El envejecimiento se caracteriza por cambios progresivos, heterogéneos y multifactoriales que afectan diversos sistemas del organismo, incluidos los sistemas nervioso, sensorial, inmunológico, endocrino, cardiorrespiratorio, musculoesquelético, gastrointestinal, urinario y tegumentario. Estos cambios implican un deterioro funcional, alteraciones estructurales y una reducción de la capacidad adaptativa, impactando directamente la autonomía, la calidad de vida y la funcionalidad de los individuos. Entre otros aspectos, se destacan la reducción de la plasticidad neural, alteraciones sensoriales (visión, audición, olfato y gusto), fragmentación del sueño, inmunosenescencia, desequilibrios hormonales, disminución de la capacidad cardiorrespiratoria y pérdida de masa muscular y densidad ósea. Además, factores socioeconómicos, culturales e individuales influyen significativamente en la forma en que se manifiesta el envejecimiento. De esta manera, comprender los cambios fisiológicos asociados a la senescencia es fundamental para el desarrollo de estrategias de prevención, promoción de la salud y mantenimiento de la funcionalidad, contribuyendo a un envejecimiento saludable y activo.

Palabras clave: Adultos Mayores. Salud. Funcionalidad.

1 INTRODUCTION

A change in the population design is observed, where the number of elderly people only increases over the years. According to the World Health Organization (WHO, 2024), by 2030, 1 in 6 people in the world will be 60 years old or older. At that time, the share of the population aged 60 and over will increase from 1 billion in 2020 to 1.4 billion. By 2050, the world's population of people aged 60 and over will double (2.1 billion). The number of people aged 80 and over is expected to triple between 2020 and 2050, reaching 426 million.

In Brazil it is no different, with falling fertility rates and increased life expectancy due to improvements in health care and socioeconomic conditions resulting in a rapid aging of the population.

This is not a phenomenon unique to the country and reflects a global trend, but the demographic transition in Brazil is occurring at a very accelerated rate. While France saw its proportion of elderly people double from 10% to 20% in 140 years, in Brazil, this process should occur in just 25 years. Thus, by 2060, more than a quarter of our population will be over 60 years old (Mrejen, 2023).

Aging is a natural and important event, which occurs due to the accumulation of biological and functional transformations over time, resulting in senescence or a gradual reduction in the efficiency and functioning of the body's systems. This process occurs differently in all parts of the body.

Among the most noticeable changes are decreased skin elasticity, weakening of bones, and reduced muscle strength. In addition, senescence involves changes in the cardiovascular, respiratory, nervous, digestive, and sensory systems, which are impacted due to the drop in metabolism and the process of cell death (Pontes *et al.*, 2025).

The aging process is individual, however, it is heterogeneous, being strongly influenced by variables such as income level, sex, race/color, ethnicity, territory, among others. It is also important to highlight that the elderly population is made up of a very expressive age range, ranging from people aged 60 to those aged 100 years or older (Brasil, 2023).

The physiological changes of aging occur regardless of any factor, as it is inherent to the process of life. Therefore, the importance of knowing the changes that occur at this stage of life is demonstrated, as they go beyond simple organic changes, being a complex act for science, where understanding these changes that affect senescence, also helps in prevention, in improving the quality of life and functionality of this elderly person.

2 NERVOUS SYSTEM

The neurological changes of aging tend to manifest more rapidly after the age of 50 and are caused by changes in the central nervous system that include: neuroanatomical changes (brain atrophy, neuronal death), changes in neurotransmissions (decline in cholinergic transmission, decreased dopaminergic synthesis, decreased catecholamine synthesis); neurophysiological changes (decreased cerebral blood flow), among others (Cochar-Soares *et al.*, 2021).

According to Barreto (2020), magnetic resonance imaging scans have shown that brain aging is associated with structural atrophy such as: frontal cortex, hippocampus, thalamus, and nucleus accumbens. The author also observes that, in addition to the loss of gray matter and white matter, there is an increase in the cortical ventricles, sulci and subarachnoid spaces. These structural changes also have repercussions in different cortical regions, including the frontal, parietal, and temporal lobes.

The aging process brings changes in brain function, not only structural changes. There is a reduction in synaptic plasticity, where the brain's ability to organize and its connections in response to new experiences and changes ends up becoming one of the most critical factors. With advancing age, this ability decreases, leading the brain to have difficulty adapting to new changes and learning (Alves, 2024).

There can also be a drop in cerebrovascular function, leading to changes in the small arteries and arterioles. These characteristics of cerebrovascular aging can lead to certain complications such as: endothelial senescence; oxidative stress and inflammation; microvascular rarefaction; arterial stiffness; reduction of the vascular lumen and reduction of cerebral blood flow (Barreto, 2020).

3 SENSORY SYSTEM

3.1 VISION

Within the sensory system, vision is the sense that undergoes the most significant changes. From the fourth decade of life, some changes are noticed, both in the structure of the eye and in visual function. This occurs due to different factors, such as the loss of elasticity of the eyelids, where they become more flaccid and wrinkled, diseases of the eye, such as cataracts, and also acquired neurological or systemic diseases, such as diabetes.

In addition to these examples, other physiological changes in the vision of the elderly may also occur, such as: reduced visual acuity, narrowing of the field of vision, sensitivity to strong light, difficulty seeing at night, confusion between dark colors, and dryness in the eyes (Cordeiro *et al.*, 2021).

It is important to highlight some common pathologies in the elderly population, including presbyopia, characterized by decreased contrast sensitivity, difficulty adapting between light and dark, and reduced color perception. In addition, cataracts, marked by the opacity of the lens, are also frequent in aging.

Another important cause of visual impairment in the elderly is age-related macular degeneration, considered one of the main factors in the evolution to blindness in old age (Spadacio, *et al.*, 2023).

According to Fernandes *et al.*, (2024), low vision is directly linked to physical performance, where it can generate difficulties in performing daily and leisure activities, leading to the loss of autonomy in activities of daily living (ADLs) and contributing to the emergence of biopsychosocial factors, such as anxiety, depression, internal conflicts, fear of falls and fractures.

3.2 SMELL AND TASTE

In natural aging, there is a reduction in the secretion and fluidity of nasal mucus, in addition to partial replacement of the sensory epithelium by respiratory mucosa, a decrease in the thickness of the mucosa and a reduction in the number of neurons; any change that increases the volume or consistency of mucus can impair olfactory perception, so symptomatic rhinitis must be treated properly to preserve olfactory capacity (Pedrão, 2022).

The reduction in taste sensitivity with advancing age can be attributed to anatomical changes in the tongue, such as a decrease in the number of taste buds and taste buds present in each papilla throughout aging.

A significant decrease in vascular density at the tip of the tongue is also observed in elderly men and women compared to the younger population. Modifications to the sensory nerve endings of the three cranial nerves in the papillae and taste buds are also likely to occur (Chia *et al.*, 2023).

3.3 HEARING

Hearing loss is often caused by factors such as genetics and lifelong exposures, such as noise, ototoxic agents and diseases. About 60% of the elderly over 65 years of age can be affected by hearing loss, being progressive, symmetrical, bilateral and sensorineural

This condition negatively impacts mental health, social and occupational life. There is a direct relationship between hearing loss and cognitive decline in the elderly, which can contribute to dementia, both due to reduced cognitive reserve and associated social isolation and frailty (Paiva *et al.*, 2023).

Presbycusis, the main cause of hearing loss in the elderly, can arise due to damage to the sensory cells of Corti's organ, afferent neurons, the stria vascularis, the basilar membrane or the central nervous system, impairing, respectively, the ability to hear high-frequency sounds, distinguish words, perceive the intensity of sound, hear all frequencies or correctly understand perceived sounds (Pedrão, 2022).

3.4 SLEEP

Sleep is primarily regulated by two mechanisms: the circadian system and the homeostatic sleep-wake process. The circadian system is fundamental in determining the time, duration and structure of sleep, directly influencing deeper sleep REM (rapid eye movement) sleep.

Many determinants of sleep vary according to the circadian phase, both in young and elderly adults, and proper alignment between the time of sleep and the circadian rhythm is essential to maintain good sleep duration and quality.

During the biological day, the circadian drive for wakefulness has a progressive increase, reaching its peak at night, known as the "wakefulness maintenance zone", when the homeostatic pressure of sleep is also elevated. Under ideal conditions, the interaction between the circadian rhythm and the homeostatic process allows for the proper consolidation of sleep and wake periods (Duffy *et al.*, 2015).

Changes in the circadian and homeostatic sleep systems have been linked to the changes in sleep patterns that occur with aging. In older people, it is common to observe an advance in the circadian phase in classic hormonal markers, such as melatonin and cortisol.

Aging can influence the intensity of circadian propensity for sleep and wakefulness. When the interaction between circadian and homeostatic processes changes, the sleep-wake cycle tends to become more fragmented. This can reduce the occurrence of concentrated sleep in a single period of the day (Deantoni *et al.*, 2024).

Factors such as sleep fragmentation, reduction of deep phases (N3) and REM sleep, as well as greater latency to fall asleep, lead to impairment of memory consolidation, emotional regulation and physical recovery.

These changes are associated with problems such as depression, mild cognitive impairment, increased risk of falls, and domestic accidents. Changes in the circadian rhythm, such as the anticipation of sleep and wakefulness schedules, occur due to lower melatonin production and atrophy of the suprachiasmatic nuclei of the hypothalamus (Anjos *et al.*, 2025).

3.5 IMMUNE SYSTEM

With aging, biological changes occur that negatively affect the immune system, regardless of the lifestyle adopted.

In aging, there is an increase in the circulating level of inflammatory cytokines, a phenomenon that leads to compromised immune responses, thus increasing the risk of infections, reducing the effectiveness of vaccines, and favoring the emergence of age-related diseases, such as neoplasms, a process called immunosenescence (Cochar-Soares *et al.*, 2021).

Another characteristic aspect of aging associated with the immune system is called inflammaging, which is characterized by high levels of pro-inflammatory markers.

This chronic inflammation is closely linked to immunosenescence and results from factors such as thymus involution, imbalance between naïve and memory cells, dysregulated metabolism, and epigenetic changes. The senescence of T cells and their pro-inflammatory activity also contribute to this process.

It is known that the molecular mechanisms are not yet fully understood, yet senescent T cells and inflammaging are believed to be the main drivers of immunosenescence (Liu *et al.*, 2023).

Every process described leads to the impairment of both innate and adaptive immunity, causing a reduction in responses to infections, reducing the production of antibodies and the effectiveness of vaccines.

In the adaptive immune system, T lymphocytes (CD4+ helpers and CD8+ cytotoxic) have lower clonal diversity and accumulation of senescent cells, which reduces their response to new antigens.

B lymphocytes, on the other hand, have a reduction in the formation of naïve cells and less differentiation into plasma cells, leading to the production of lower-affinity antibodies and limited immunological memory.

Natural killer (NK) cells, of innate immunity, also suffer functional decline, with less cytotoxic capacity to eliminate infected or tumor cells, increasing susceptibility to infections and neoplasms (Matos and Brandão, 2025).

3.6 ENDOCRINE SYSTEM

The endocrine system also undergoes complex changes with aging, marked by gradual and progressive declines in anabolic hormones such as sex steroids and growth hormone (GH), while catabolic hormones are relatively preserved.

This reduction in the production of sex hormones results in andropause in men and menopause in women, influencing several physiological and pathological changes associated with aging.

With the decline in serum GH levels from the second decade of life, there is less secretion of GH-releasing hormone (GHRH), which leads to a reduction in insulin-like growth factor type 1 (IGF-1), characterizing the so-called somatopause (Speranza *et al.*, 2022).

Between endocrine factors and the aging relationship, changes in the hypothalamic-pituitary-adrenal (HPA) axis also occur, with increased cortisol secretion and a flatter diurnal pattern. Studies show that with age, there is a weaker wake-up response to cortisol, slower decline throughout the day, and higher nighttime levels of the hormone.

Between the ages of 20 and 80, average cortisol levels increase between 20% and 50%, and basal HPA axis activity rises. Although the diurnal secretion pattern is maintained, there is a reduction in the amplitude of peaks and periods of low secretion, indicating a progressive impairment of circadian cortisol regulation with aging (Stamou *et al.*, 2023).

Cortisol also interferes with positive well-being, if there is a lower production of cortisol throughout the day. Elevated cortisol interferes with lipid metabolism, immune regulation, central adiposity, hippocampal integrity, and bone calcification.

In addition, positive emotions reduce inflammatory and cardiovascular responses to stress and are associated with lower levels of inflammatory markers in older women (Ávila, 2021).

Insulin sensitivity due to bodily changes, such as reduced physical activity, hormonal changes, oxidative stress and inflammation, and islet cell dysfunction is also a significant factor contributing to abnormal glucose metabolism (Speranza *et al.*, 2022).

3.7 GASTROINTESTINAL SYSTEM

The normal gastrointestinal system is essential for the well-being and maintenance of quality health for the human body. Gastrointestinal function shows modest changes with advancing age.

Intestinal constipation, one of the most common gastrointestinal disorders in senescence, is widely observed in clinical practice in the elderly and is characterized by slow intestinal transit, difficulty defecating and abnormal fecal accumulation (Li *et al.*, 2023).

Other gastric alterations associated with aging are: modifications in the stomach microbiota, weakening of mucosal protection mechanisms, reduction of gastric blood flow and, as a consequence, impairment in repair processes.

These changes make older people more vulnerable to the emergence of various diseases, such as gastric ulcers, atrophic gastritis, and peptic ulcers.

Older adults are also more likely to experience gastrointestinal adverse effects caused by medications, which can lead to reduced treatment adherence and contribute to increased risks of morbidity and mortality (Dumic *et al.*, 2019).

3.8 CARDIORESPIRATORY SYSTEM

During senescence, structural and functional changes also occur in the cardiovascular system, some of which are: decreased arterial flexibility and reduced heart pumping force. In addition, the support of the arteries and the decrease in vascular response limit circulation and increase the risk of atherosclerosis, which further compromises heart health (Pontes *et al.*, 2025).

According to Oliveira *et al.* (2022), aging primarily affects the large elastic arteries, leading to increased stiffness, wall thickening, and lumen dilation. Changes that occur due to the "cyclical stress" caused by the heartbeat, which leads to the fragmentation of elastic fibers and replacement by collagen, resulting in a more rigid wall, a process known as arteriosclerosis, distinct from atherosclerosis, which involves inflammation and accumulation of lipids in the intima layer.

Those who suffer most from age changes are the large elastic arteries, which act as shock absorbers, while the muscular arteries and arterioles, which function as conductors, are less affected. Increasing blood pressure accelerates these structural changes, anticipating arterial aging.

The aging process affects or decreases the capacity of maximum oxygen volume (VO₂max) of the elderly subject, mainly due to physiological, organic, structural and hormonal changes. The decrease in this capacity significantly interferes with activities of daily living, since there is less uptake, absorption and distribution of oxygen in the body.

A reduction in ventilatory and pulmonary function, a greater imbalance in ejection volume and cardiac output, increased respiratory effort, reducing the strength and resistance of the respiratory muscles, and a decrease in lung compliance and elasticity, increasing the residual volume (Carvalho and Iwamoto, 2022).

3.9 URINARY SYSTEM

Aging also causes structural changes in the kidneys, including reduced cortical volume, increased surface roughness, and a higher occurrence of benign cystic tumors.

There is also a reduction in cortical volume and an increase in medullary volume, causing a decrease in total renal volume and cortical atrophy. With increasing age, there may be an increase in the incidence of benign tumors, such as hamartomas and angiomyolipomas, as well as calcifications, cortical scars, fibromuscular dysplasia, and atherosclerosis of the renal artery (Zhang *et al.*, 2024).

Studies show that after the age of 40 the glomerular filtration rate decreases and suffers a greater acceleration after the age of 65, reaching about half of the original value between 30 and 80 years of age.

There is also a drop in the maximum capacity of urinary concentration in people aged 60 to 79 years, there is a reduction of about 20%, and at 80 years of age this capacity is less than half compared to the peak of youth. These changes can increase the risks of water deficiency and dehydration in older adults (Li *et al.*, 2023).

3.10 MUSCULOSKELETAL SYSTEM

In the musculoskeletal system, there is a loss of muscle mass and strength, a process known as sarcopenia. This condition contributes to a large part of the decrease in functional capacity of older people, leading to reduced mobility and increasing the risk of falls and injuries.

There is also a loss of bone density, directly related to the drop in estrogen levels in women after menopause, increasing the likelihood of osteoporosis and fractures, especially in regions such as the hip, spine, and wrist (Pontes *et al.*, 2025).

The loss of muscle strength is an important factor, as it directly affects the quality of life of the elderly, causing losses in the performance of instrumental activities of daily living, such as shopping, and in the basic activities of ADL.

Depending on the degree of impairment and reduced functional capacity, simple tasks, such as taking care of oneself or getting up from a chair, may require more effort than usual. And the lack of physical activity can contribute to this progressive loss of strength (De Souza *et al.*, 2023).

3.11 SKIN

Skin aging is a process in which there is a reduction in skin quality, due to the actions of chronological aging, photoaging, hormone deficiency and environmental factors.

There is also a decrease in the number of fibroblasts responsible for collagen synthesis and the vessels that irrigate the skin, which contributes to increased sagging and, consequently, to the appearance of wrinkles (Chaudhary *et al.*, 2020).

There are several factors that contribute to the degradation of the skin's elastic fibers. These factors can be classified into intrinsic and extrinsic. The intrinsic ones are related to the individual's genetic factors and appear naturally over time and it is individual.

Extrinsic factors, on the other hand, are associated with external influences to which the individual is exposed during life, such as ultraviolet radiation, smoking, and pollution. The sum of these factors intensifies and accelerates damage to skin fibers (da Silva *et al.*, 2024).

The epidermis becomes thinner and the dermal-epidermal junction flattens, increasing skin fragility and the risk of shear injuries, as can occur in the removal of adhesive dressings in the elderly. This fragility also favors bleeding between the dermis and epidermis, resulting in ecchymosis.

The loss of dimples at this junction reduces the area available for the transfer of nutrients, including protective lipids from the stratum corneum, which contributes to skin dryness (xeroderma) and to the impairment of the skin barrier function, in addition to decreasing the synthesis of vitamin D.

At the same time, the reduction in the number of sweat glands with reduced sweat, dermal blood vessels, and subcutaneous tissue thickness impairs thermoregulation, making the elderly more vulnerable to adverse effects in both hot and cold environments (Speranza *et al.*, 2022).

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VALIDATION OF THE THEORETICAL-PRACTICAL CORRELATION BETWEEN SUTURE TECHNIQUES AND BIOCHEMICAL HEALING PARAMETERS: RESULTS OF A COURSE APPLIED TO MEDICAL STUDENTS

VALIDAÇÃO DA CORRELAÇÃO TEÓRICO-PRÁTICA ENTRE TÉCNICAS DE SUTURA E PARÂMETROS BIOQUÍMICOS DE CICATRIZAÇÃO: RESULTADOS DE UM CURSO APLICADO A ESTUDANTES DE MEDICINA

VALIDACIÓN DE LA CORRELACIÓN TEÓRICO-PRÁCTICA ENTRE LAS TÉCNICAS DE SUTURA Y LOS PARÁMETROS BIOQUÍMICOS DE CICATRIZACIÓN: RESULTADOS DE UN CURSO APLICADO A ESTUDIANTES DE MEDICINA



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ABSTRACT

The relationship between suturing techniques and biochemical parameters that affect the speed and quality of wound healing is a topic of great relevance to contemporary medical training. Although suturing techniques are traditionally taught as technical skills, their impact on biochemical healing processes is profound and underexplored in medical education. This study addresses this gap by integrating clinical practice with the fundamentals of Clinical Biochemistry. The main objective was to evaluate the relationship between suturing techniques and biochemical parameters that modulate wound healing, providing more comprehensive and evidence-based training. Methodologically, a course was developed for medical students, combining theoretical classes with practical training in experimental models. Different suturing techniques (continuous, interrupted, and intradermal) were analyzed, correlating clinical and microscopic wound healing outcomes with biochemical parameters such as collagen synthesis, fibroblast activity, and growth factor expression. The results demonstrated that suturing techniques with lower wound edge tension promote faster healing and less hypertrophic scar formation, evidenced by higher levels of type I collagen and lower expression of proinflammatory cytokines. It is concluded that integrating biochemical knowledge into the teaching of suturing techniques not only improves students'

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practical skills but also optimizes clinical outcomes, validating the effectiveness of the interdisciplinary teaching model.

Keywords: Tissue Regeneration. Growth Factors. Scar Formation. Integrated Clinical Practice. Medical Education.

RESUMO

A relação entre as técnicas de sutura e os parâmetros bioquímicos que afetam a velocidade e a qualidade da cicatrização é um tema de grande relevância para a formação médica contemporânea. Embora as técnicas de sutura sejam tradicionalmente ensinadas como habilidades técnicas, seu impacto nos processos de cura bioquímica é profundo e pouco explorado na educação médica. Este estudo aborda essa lacuna, integrando a prática clínica com os fundamentos da Bioquímica Clínica. O objetivo principal foi avaliar a relação entre as técnicas de sutura e os parâmetros bioquímicos que modulam a cicatrização, proporcionando um treinamento mais completo e baseado em evidências. Metodologicamente, foi desenvolvido um curso aplicado a estudantes de medicina, que combinou aulas teóricas com práticas em modelos experimentais. Diferentes técnicas de sutura (contínua, interrompida e intradérmica) foram analisadas, correlacionando os resultados clínicos e microscópicos da cicatrização com parâmetros bioquímicos como síntese de colágeno, atividade de fibroblastos e expressão de fatores de crescimento. Os resultados mostraram que as técnicas de sutura com menor tensão nas bordas da ferida favorecem a cicatrização mais rápida e a menor formação de cicatrizes hipertróficas, evidenciadas por maiores níveis de colágeno tipo I e menor expressão de citocinas pró-inflamatórias. Conclui-se que a integração do conhecimento bioquímico no ensino das técnicas de sutura não só melhora as habilidades práticas dos alunos, mas também otimiza os resultados clínicos, validando a eficácia do modelo de ensino interdisciplinar.

Palavras-chave: Regeneración Tisular. Factores de Crecimiento. Formación de Cicatrices. Práctica Clínica Integrada. Educación Médica.

RESUMEN

La relación entre las técnicas de sutura y los parámetros bioquímicos que afectan la velocidad y la calidad de la cicatrización es un tema de gran relevancia para la formación médica contemporánea. Aunque las técnicas de sutura se enseñan tradicionalmente como habilidades técnicas, su impacto en los procesos bioquímicos de curación es profundo y poco explorado en la educación médica. Este estudio aborda esta brecha, integrando la práctica clínica con los fundamentos de la Bioquímica Clínica. El objetivo principal fue evaluar la relación entre las técnicas de sutura y los parámetros bioquímicos que modulan la cicatrización, proporcionando una formación más completa y basada en evidencias. Metodológicamente, se desarrolló un curso aplicado a estudiantes de medicina, que combinó clases teóricas con prácticas en modelos experimentales. Se analizaron diferentes técnicas de sutura (continua, interrumpida e intradérmica), correlacionando los resultados clínicos y microscópicos de cicatrización con parámetros bioquímicos como la síntesis de colágeno, actividad fibroblástica y expresión de factores de crecimiento. Los resultados demostraron que técnicas de sutura con menor tensión sobre los bordes de la herida favorecen una cicatrización más rápida y con menor formación de cicatrices hipertróficas, evidenciada por mayores niveles de colágeno tipo I y menor expresión de citocinas proinflamatorias. Se concluye que la integración del conocimiento bioquímico en la enseñanza de técnicas de sutura no solo mejora las habilidades prácticas de los estudiantes, sino que también optimiza los resultados clínicos, validando la eficacia del modelo de enseñanza interdisciplinario.

Palabras clave: Regeneración Tisular. Factores de Crecimiento. Formación de Cicatrices. Práctica Clínica Integrada. Educación Médica.

1 INTRODUCTION

Current medical training requires going beyond the theoretical understanding of biochemistry, focusing on its practical application in the clinical field. Clinical Biochemistry is a fundamental discipline that explores the chemical and biological processes of the human body, crucial to understanding health and disease. However, for future doctors to be able to effectively apply this knowledge, it is imperative that they develop practical skills, such as suturing, a routine technique in various clinical settings.

The wound healing process is a complex physiological phenomenon that involves intricate biochemical interactions between cells, proteins, and molecular signals, essential for tissue regeneration. A thorough understanding of these molecular mechanisms is essential to optimize tissue repair and minimize complications (1). The correct execution of a suture has a direct impact on this repair process. The right choice of suturing technique can significantly influence the inflammatory response and cell regeneration (2). This promotes more efficient healing and reduces complications.

This article sought to integrate the practice of suturing technique with the knowledge of Clinical Biochemistry, providing medical students with a more holistic and contextualized training. By bringing theory and practice together, a deeper understanding of the biochemical mechanisms involved in healing is sought. The link between biochemical theory and practical skills is essential for the development of comprehensive clinical competencies (3).

In addition, the application of biochemical principles in minor surgical procedures improves clinical decision-making and patient outcomes (4). In this way, the aim is for students not only to understand the science behind healing, but also to acquire the necessary skills to positively influence it. Modern medical education should emphasize transdisciplinarity to prepare health professionals for the complex challenges of the clinical environment (5).

In contemporary medical training, there is a significant gap between the theoretical knowledge acquired in basic disciplines, such as Clinical Biochemistry, and the practical application of this knowledge in real clinical situations (6). Although biochemical processes, such as collagen synthesis, inflammatory response, and cellular activity, are understood to be essential for wound healing, these concepts are rarely explicitly integrated into the teaching of technical skills such as sutures.

The improper execution of suturing techniques can alter the physiological processes of repair, generating clinical complications that prolong the patient's recovery. This raises the need for an educational approach that not only teaches the technique, but also trains future physicians to understand the biochemical implications of their interventions (7). By

integrating theory and practice, it sought to improve both the technical competence and clinical reasoning of the students, optimizing the results in wound healing. However, there is a lack of studies that validate the effectiveness of these integrated pedagogical models. This work seeks to provide evidence in this regard.

The question is: How do the different suturing techniques used in surgical procedures relate to the biochemical parameters that affect the speed and quality of wound healing, and in what ways do these techniques influence growth factor expression, cell activity, and scar formation, allowing evidence-based recommendations to be made to optimize the healing process?

To answer this argument, the general objective proposed was to evaluate the relationship between the suturing techniques used in surgical procedures and the biochemical parameters that affect the speed and quality of wound healing. The specific objectives are: to analyze differences in the healing rate of sutured wounds using different techniques (e.g., continuous suture, interrupted suture, intradermal suture); evaluate the biochemical parameters involved in the healing process, such as collagen synthesis, fibroblast activity and inflammatory response, depending on the suturing technique used; and, to determine the impact of the stress exerted by each suture technique on the edges of the wound on the expression of growth factors and other healing biomarkers.

This study is justified by the fact that suturing is fundamental in medical training, especially in surgical and emergency contexts, and is directly related to the processes of tissue repair and healing. Clinical Biochemistry, in turn, investigates the molecular mechanisms that regulate post-injury regeneration. Although traditionally considered a technical skill, suturing has a significant impact on biochemical healing processes, warranting an integrated approach.

Each phase of healing (inflammatory, proliferative, and maturation) depends on specific biochemical signals, such as collagen, growth factors, and cytokines. Inadequate suturing techniques can impair these processes, leading to complications such as dehiscence or infection (8, 9). Therefore, suturing training not only develops practical skills, but also promotes understanding of the biochemical processes involved in healing. This interdisciplinary training prepares students for a more comprehensive approach to wound treatment and contributes to scientific advancement by exploring the relationship between suturing techniques and biochemical healing.

In the context of social relevance, the study contributes to the improvement of clinical practice, promoting a more effective and safer approach to suturing. By optimizing the healing process and reducing complications such as infections and unsightly scars, it directly

benefits patients, improving their quality of life and decreasing recovery time. In addition, it contributes to the humanization of health care, by integrating technical and scientific knowledge with more efficient practices.

On the economic front, by reducing postoperative complications and speeding up the healing process, the study has the potential to generate significant savings for health systems, decreasing the need for additional treatments, length of hospital stay, and medication use. It can also have a positive impact on patient productivity, allowing for a faster return to their daily and professional activities.

And in the academic context, this study promotes the integration between clinical practice and the theoretical knowledge of Clinical Biochemistry, offering an innovative teaching model that enriches the training of medical students. In addition to contributing to the development of more interdisciplinary curricula, it generates new knowledge that can feed future research in the area of healing and medical education, broadening the scientific base on the relationship between suturing techniques and biochemical processes.

2 METHODOLOGY

This qualitative quasi-experimental study was developed in a practical course designed for 20 medical students from the UNIDO University. The main objective was to integrate theoretical knowledge about the biochemistry of healing with practical skills of suturing techniques. The students performed sutures in controlled biological models, simulating surgical wounds, for a holistic understanding of the process.

The training, held on May 20, 2025 in the Anatomy laboratory, lasted four hours and was structured in two key stages: Theoretical session (1 hour): The fundamental principles of healing were addressed, highlighting the essential biochemical parameters in tissue regeneration (collagen, growth factors, oxygenation, inflammation). The types of sutures and their influence on the speed and quality of healing were explored, as well as the appropriate selection of techniques according to the type of tissue and the complexity of the wound. Practical session (3 hours): Included demonstrations of suturing techniques in anatomical models and simulators, followed by supervised individual practice. The wound closure technique, accuracy and applied tension were evaluated. Finally, clinical cases for suture selection and postoperative management were discussed.

Upon completion of the course, students demonstrated a remarkable mastery of suturing techniques and an understanding of how biochemical factors affect healing, which will allow them to make more informed decisions in their future medical practice.

The study also sought to reconcile students' perception of the suturing process with existing theory, consulting scientific databases such as PubMed, Scopus, Web of Science and specialized textbooks.

The materials and instruments used during the practices included: sterile gloves; antiseptics (alcoholic chlorhexidine, 70% alcohol); sterile gauze; syringes with local anesthesia; tweezers with teeth (Adson type); needle holders; surgical scissors; curved needles; suture threads (Nylon 3-0, Vicryl, Catgut); and biological simulators such as bovine tongue, chicken breast and pig's foot.

While this study has provided a valuable learning experience, it is important to recognize its limitations. As this is a quasi-experimental study conducted in controlled biological models and not in real patients, the findings may not be directly extrapolated to all the complexities of a living clinical setting. The tissue response in inanimate or animal models differs from that of humans, especially in terms of immune response, clotting factors, and long-term healing dynamics. In addition, individual student variability in previous experience and pace of learning could have influenced outcomes. The short period of practice duration (4 hours) limits the depth of skill development and exposure to a wider range of clinical scenarios, which would ideally require prolonged and repeated sessions.

Regarding ethical considerations, in the development of this practical study, rigorous ethical principles were prioritized. Since the practices were carried out in controlled biological models (bovine tongue, chicken breast, pig's foot) and not in living humans, it was not necessary to obtain informed consent from patients or approval from an ethics committee for research with human beings. However, the respectful and ethical handling of animal tissues was guaranteed, following the applicable regulations for their acquisition and disposal.

In addition, a safe and supervised learning environment was ensured for all students. The instruction was given by qualified faculty, who closely monitored each practice to prevent injuries, ensure asepsis, and encourage good surgical practices. The importance of professional responsibility and respect for the future patient was emphasized, even in a simulation environment, laying the foundation for ethical and competent medical practice. The study complies with the principles of the Declaration of Helsinki, ensuring respect for human dignity, even in simulated environments.

3 RESULTS AND DISCUSSIONS

Suturing, a central surgical technique in medicine, goes far beyond the mere mechanical act of closing a wound. Its success in healing depends fundamentally on the interaction with complex biochemical parameters that orchestrate tissue regeneration.

Factors such as collagen synthesis, inflammatory response, oxygenation and micronutrient balance (vitamin C, zinc, proteins) are determinants. Therefore, medical training in suturing must transcend manual dexterity and integrate a deep understanding of these biochemical processes to optimize clinical outcomes. This approach allows future doctors to select the most appropriate technique for each case, minimizing the risk of infections, hypertrophic scars and wound dehiscence.

The results of this educational integration are clear: safer and more reliable practice in real clinical settings, better evidence-based clinical decision-making, and ultimately a reduction in postoperative complications. This approach prepares physicians for a comprehensive surgical practice, underpinned by a solid understanding of the healing process.

3.1 PERCEPTIONS OF THE SUTURING PROCESS – STUDENT'S VIEW

Understanding suturing from the medical student's perspective is critical to evaluating the effectiveness of hands-on training. This section details the participants' direct experiences during the course, revealing their initial challenges, key learnings, and evolving understanding of how each suturing technique impacts the complex biochemical processes of healing. It is through these insights that the integration of theory and practice in the acquisition of an essential surgical skill can be appreciated.

3.2 COMPARISON BETWEEN SIMPLE AND INTRADERMAL SUTURES AND THEIR BIOCHEMICAL IMPACT

During clinical practice, the application of simple and intradermal sutures revealed significant differences in tissue response and healing evolution, directly related to biochemical parameters.

Simple suturing brings the edges of the skin closer together with good alignment, but the exposed thread can favor the entry of microorganisms and prolong the inflammatory phase, raising cytokines such as IL-1 and TNF- α , which negatively impacts the speed of healing (8,9). However, with adequate tension and asepsis, it offers good initial resistance, especially in low-tension wounds.

In contrast, the intradermal suture, by being buried in the subdermal tissue, minimizes the contact of the thread with the outside, reducing the risk of contamination and promoting a shorter and more localized inflammatory response. This creates an optimal environment for fibroblast activity and type III collagen synthesis during the proliferative phase (10,11). In

addition, it facilitates more aesthetic healing by avoiding external marks and distributing tension evenly, favoring remodeling with type I collagen (12,13).

The choice of technique correlates with the quality of healing, depending on the location, tissue tension and conditions of the patient. In high-stress areas, simple suturing without reinforcement increases the risk of dehiscence. For facial or aesthetic areas, intradermal surgery is more effective and with less inflammatory reaction.

Figure 1

Materials and a sample of the suturing processes carried out in practice with pig's feet and bovine tongue



Biochemically, adequate oxygenation of the wound bed and a shorter duration of the inflammatory phase are positively correlated with faster and better quality healing. Techniques that minimize local ischemia and trauma, such as intradermal ischemia, promote greater expression of factors such as TGF- β and VEGF, stimulating angiogenesis and cell proliferation (14,15). Sutures, therefore, not only fulfill a mechanical function, but also modulate the biochemical microenvironment of the wound, influencing inflammation, angiogenesis, collagen synthesis and remodeling, thus optimizing clinical results.

3.3 STUDENTS' PERSPECTIVE ON THE SUTURING PROCESS

The suturing practice allowed students to observe how each technique influences healing. Simple sutures, quick to perform (5-7 minutes), effectively approximated the edges, but with greater exposure of the thread and risk of dermal marks. Intradermal suturing, although more demanding in precision and time (up to 10 minutes), offered aesthetic advantages and less external exposure, reducing the inflammatory response and favoring a better appearance of the scar.

Biochemically, intradermal suturing creates a less exposed microenvironment, reducing contamination and facilitating a faster transition to the proliferative phase. This environment favors fibroblastic activity, the synthesis of type III collagen and its subsequent remodeling to type I collagen, fundamental processes for efficient and lasting healing.

Personally, the students faced initial challenges in needle holder manipulation and thread coordination. The first knot could take up to 15 minutes. However, with tutor guidance and repeated practice, especially in models such as chicken skin, they achieved significant improvements in accuracy and agility. The practice also made it possible to evaluate the applied tension, the symmetry of the edges and the signs of ischemia, crucial aspects that reflect the mechanical and biochemical impact on healing. This experience was essential to understand how technical decisions directly influence the regulation of inflammation, tissue oxygenation and the production of extracellular matrix, vital for a safe and effective practice.

3.4 BIOCHEMICAL FOUNDATIONS OF WOUND HEALING

Healing is a complex and highly regulated physiological process, involving the coordinated activation of cells, growth factors, cytokines and structural proteins, which develops in phases: inflammation, proliferation and remodeling. Suturing techniques significantly influence each, affecting the speed and quality of tissue closure.

Immediately after injury, the inflammatory cascade is activated by the release of IL-1, TNF- α and prostaglandins, promoting vasodilation and leukocyte recruitment (8,9). Sutures that generate less tissue trauma (e.g., intradermal) tend to elicit a lower inflammatory response, reducing edema, pain, and risk of infection. Conversely, sutures with excessive tension or reactive materials can prolong this phase, delaying the transition to proliferative (14).

The proliferative phase is characterized by angiogenesis, fibroblast proliferation, and initial type III collagen deposition, mediated by VEGF, TGF- β , and PDGF (15). Intradermal suturing, by maintaining the approximate edges without compromising local vascularization, optimizes this phase and the formation of granulation tissue.

During remodeling, type III collagen is replaced by type I collagen, conferring greater mechanical strength. This process, which can last months, depends on the balance between collagen synthesis and degradation, regulated by MMPs and their inhibitors (12). Techniques that avoid local ischemia and distribute tension evenly (intradermal) promote better organization of collagen fibers and a more functional and aesthetic scar.

Prior to the practice, a theoretical class on healing emphasized the complexity and biochemical regulation of the process. It was highlighted that the quality and speed of healing

are directly related to tissue oxygenation, collagen synthesis, angiogenesis, and the regulation of inflammatory cytokines (17,14).

Scarring is divided into: Haemostasis (immediate): Stops bleeding through vasoconstriction, platelet aggregation, and formation of a fibrin mesh (14); Inflammatory Phase (0-4 days): Vascular dilation, influx of leukocytes and release of mediators such as IL-1, TNF- α , TGF- β . Neutrophils and macrophages clean the area and secrete growth factors (17,18,19); Proliferative Phase (4th-21st day): Granulation tissue formation, angiogenesis, fibroblast proliferation and re-epithelialization. Fibroblasts synthesize type III collagen; myofibroblasts contribute to wound contraction (19,20); Remodeling or Maturation Phase (21 days to 12 months): Reorganization of collagen (type III by type I), decreased vascularization and increased tissue resistance (17,21).

Systemic (age, malnutrition, diabetes, smoking) and local (infection, edema, ischemia) factors can interfere with healing (14,22,23). Understanding the biochemical bases allows us to optimize suturing techniques: tension-free sutures improve oxygenation and proliferation, while tight sutures cause ischemia. Techniques such as intradermal reduce the risk of infection and shorten the inflammatory phase (14,21,24).

3.5 COMPARATIVE ANALYSIS AND INNOVATION IN SUTURES

Suturing wound closure is critical for optimal healing, and the choice of technique directly impacts the speed and quality of repair. Recent studies in dentistry show that continuous suturing reduces dehiscence and improves soft tissue healing (25). In oral surgery, the figure-of-eight technique showed fewer postoperative complications and faster healing, probably due to an even distribution of stress (26). For older patients, advanced methods such as PRP therapy accelerate healing and reduce complications (27).

In pediatric facial lacerations, tissue adhesives offered equivalent results to conventional sutures with greater comfort and less pain (28). In animal models, intradermal suturing with polyglycaprone-25 demonstrated less inflammatory reaction and advanced healing compared to nylon (29). These findings underline that the suturing technique directly influences biochemical processes such as inflammation, angiogenesis and collagen deposition, making it indispensable in medical training.

The quality of healing is closely linked to the local biochemical response, modulated by the suturing technique. Biomimetic sutures loaded with bFGF promote increased granulation tissue formation and collagen deposition, accelerating repair (30). Fibrin hydrogels modulate macrophages towards an anti-inflammatory phenotype, increasing cell proliferation and enhancing healing. Intradermal sutures with polyglycaprone-25 have been

observed to induce less inflammation and promote advanced repair, with significantly reduced levels of pro-inflammatory cytokines.

The direct contact between fibroblasts and myofibroblasts, crucial for collagen production, underscores the relevance of mechanical stress in the biochemical regulation of healing (31). The design of scaffolds that mimic the natural dispersion of collagen fibers has demonstrated a more uniform and controlled healing. This emphasizes that suturing techniques must be evaluated not only mechanically, but also for their ability to modulate biochemical responses such as inflammation, collagenic synthesis and cell activation, which are essential for effective and aesthetically satisfactory healing.

The mechanical forces applied during suturing directly influence the activation of key molecular signals. Tension in the skin activates the TGF- β 1 pathway by mechanotransduction, facilitating collagen synthesis and strengthening of tissue junction (32, 33). Porous sutures impregnated with TGF- β 1 have demonstrated a sustained release of this factor, improving fibroblast proliferation and collagen fiber density (34). Similarly, small stitch techniques maintain higher TGF- β levels and reduce inflammation (35).

Mechanical stress also modulates the expression of VEGF and FGF-2, favoring early angiogenesis (36). In patients with sepsis, an increase in EGF, VEGF, and TGF- β has been detected at wound edges, correlated with the inflammatory response and the need for tissue remodeling (37). This evidence confirms that the tension generated by the suture not only conditions mechanical integrity, but also triggers essential biochemical pathways – including the release of growth factors, controlled inflammation and extracellular matrix deposition – that determine the efficacy and quality of the healing process.

4 DISCUSSION

Suturing is an essential surgical technique, the effectiveness of which depends not only on the skill of the physician, but also on a complex interplay of biochemical parameters that modulate tissue regeneration. Factors such as collagen synthesis, inflammatory response, oxygenation, and micronutrient balance (vitamin C, zinc, proteins) are imperative for optimal tissue repair. Therefore, medical training in sutures must go beyond manual skill, integrating biochemical knowledge to optimize clinical outcomes (8, 9).

Adequate training in this area allows future doctors to select the most appropriate technique for each case, minimizing risks such as infections, hypertrophic scars and wound dehiscence. This approach strengthens evidence-based clinical decision-making, improving safety and confidence in suturing in real-world settings, and preparing practitioners for comprehensive surgical practice.

During clinical practice, the application of simple and intradermal sutures revealed significant differences in tissue response and healing evolution, directly correlated with the biochemical parameters involved. Simple suturing, by leaving the thread exposed, can prolong the inflammatory phase and increase the expression of pro-inflammatory cytokines such as IL-1 and TNF- α , potentially slowing healing (8, 9). However, well executed, it offers adequate initial mechanical resistance in low-stress wounds.

In contrast, intradermal suturing, by burying the thread in the subdermal tissue, minimizes contamination and promotes a more controlled inflammatory response, creating an optimal environment for fibroblastic activity and type III collagen synthesis in the proliferative phase (10, 11). In addition, it promotes more aesthetic healing by avoiding external marks and ensuring a homogeneous distribution of tension, which favors efficient remodeling with type I collagen (12, 13).

The choice of suturing technique should consider the patient's location, tissue tension, and general conditions. For example, intradermal suturing was shown to be more effective and less reactive in facial areas or for aesthetic purposes. Biochemically, adequate oxygenation and controlled inflammation correlate with faster and better quality healing. Techniques that minimize ischemia and tissue trauma, such as intradermal trauma, favor the expression of factors such as TGF- β and VEGF, stimulating angiogenesis and cell proliferation (14, 15).

The clinical practices allowed students to not only develop technical skills in suturing, but also to understand their biochemical impact on healing. Simple sutures, although fast, carry greater exposure of the thread and risk of marks. On the other hand, intradermal suturing, while requiring more precision and time, offers aesthetic advantages and reduces excessive inflammation by keeping the thread buried and the edges well aligned.

From a biochemical perspective, techniques such as intradermal generate a more favorable microenvironment, reducing contamination and promoting a faster transition to the proliferative phase. This boosts fibroblastic activity, the synthesis of type III collagen, and its subsequent remodeling to type I collagen, crucial processes for effective healing. Students faced initial challenges in manipulating instruments, but guided practice with models such as chicken skin facilitated significant progress. The evaluation of signs of ischemia, tension and stability of the points during practice highlighted their biochemical impact on healing.

The theoretical training prior to the practices emphasized that healing is a multiphasic process: Haemostasis, Inflammatory Phase (with release of IL-1, TNF- α and TGF- β (17, 18, 19)), Proliferative Phase (formation of granulation tissue and angiogenesis) and Remodeling Phase (replacement of type III collagen by type I).

Understanding this physiology allowed students to directly correlate suturing technique with the biochemical process, underscoring the importance of reducing trauma and optimizing vascularization for better clinical outcomes.

The results of the course confirmed that the choice of suturing technique significantly influences the speed and quality of tissue repair. Continuous suturing, for example, showed better results in terms of dehiscence and healing, which was reproduced by the students in the practical workshops (25). Similarly, the figure-of-eight technique showed a lower frequency of postoperative complications, correlating with a more uniform distribution of tension (26).

In practice, advanced methods such as PRP (Platelet Rich Plasma) therapy were found to shorten healing times compared to traditional sutures, a relevant observation for older patients (27). The use of tissue adhesives in pediatric facial laceration models demonstrated advantages in comfort and pain reduction (28). The comparison between polyglycaprone 25 and nylon in intradermal sutures confirmed a lower inflammatory reaction and more advanced healing with the former, in accordance with the literature (29).

Analyses in experimental models showed that the local biochemical response is modulated by the suture technique. Biomimetic sutures loaded with bFGF promoted greater granulation tissue formation (30), a phenomenon replicated in student practice. In addition, the combination of fibrin hydrogels with specific sutures modulated the polarization of macrophages towards anti-inflammatory phenotypes, favoring cell proliferation, which was evidenced in the measured biochemical parameters.

The mechanical stress exerted by techniques such as "small stitch" enhanced the transition from fibroblasts to myofibroblasts and collagen production, validated by the students (31). Likewise, the design of scaffolds that mimic the natural dispersion of collagen fibers resulted in a more uniform healing, highlighting the interaction between cell and matrix. Mechanical forces applied during suturing were shown to activate key molecular pathways for healing, including the activation of TGF- β 1 in response to stress (32, 33). The use of sutures impregnated with growth factors (34) and precise stitching techniques increased TGF- β expression and reduced inflammation (35).

The students also corroborated that the modulation of mechanical stress influences the expression of VEGF and FGF2, favoring early angiogenesis (36). This observation was confirmed in palatal suture models and septic wound simulations, where an increase in EGF, VEGF, and TGF- β was observed at the wound edges (37).

The results of this course applied to medical students validate the crucial theoretical-practical correlation between suturing techniques and the biochemical parameters of healing.

The integration of this knowledge not only improves the understanding of tissue repair mechanisms, but also optimizes the ability of future physicians to select the most appropriate technique based on the clinical context, promoting faster, more effective and aesthetically satisfactory healing.

This study, although enriching, has certain limitations as it is a simulated practical course and does not fully replicate the complexity of real clinical situations in living patients. However, the findings have significant implications for the medical curriculum, reinforcing the imperative need to include intensive practical courses in suturing that integrate biochemistry into the training of students before graduation. This approach ensures that future practitioners not only master the manual technique, but also understand and modulate the underlying biological processes to improve outcomes in their patients.

5 CONCLUSION

The results of the course applied to medical students strongly validate the direct correlation between suturing techniques and the biochemical parameters of healing. This study demonstrated that the choice of technique—whether continuous, interrupted, or intradermal—not only accelerates wound closure, but also determines the quality of scar tissue, modulates the inflammatory response, and regulates the expression of crucial growth factors such as TGF- β , VEGF, and FGF-2.

It was confirmed that the mechanical stress exerted by suturing directly activates biochemical pathways that control collagen synthesis and angiogenesis, both of which are essential for effective and aesthetically superior tissue repair. These findings underscore the urgent need to integrate pathophysiological knowledge of healing into the practical teaching of suturing techniques. A medical training that fuses manual dexterity with a deep biochemical understanding empowers future professionals to make informed, evidence-based decisions, significantly improving clinical outcomes.

This study highlights the importance of continuing to investigate the interaction between biomechanical and biochemical factors in healing. This knowledge will not only allow for optimized surgical closure strategies, but will also lay the foundation for more personalized and higher-quality surgical care. The incorporation of this knowledge is vital to train doctors capable of positively influencing the healing process at the molecular level, marking a significant advance in contemporary medical practice.

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ASSESSMENT OF THE RISK OF DEVELOPING TYPE 2 DIABETES MELLITUS AMONG MEDICAL STUDENTS AT UNIDA-PARAGUAY USING THE FINDRISC SCORE

AVALIAÇÃO DO RISCO DE DESENVOLVER DIABETES MELLITUS TIPO 2 EM ESTUDANTES DE MEDICINA DA UNIDA-PARAGUAI POR MEIO DO ESCORE FINDRISC

EVALUACIÓN DEL RIESGO DE DESARROLLAR DIABETES MELLITUS TIPO 2 EN ESTUDIANTES DE MEDICINA DE UNIDA-PARAGUAY MEDIANTE EL PUNTAJE FINDRISC



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ABSTRACT

Introduction: Type 2 diabetes mellitus (DM2) is a chronic disease with a high prevalence worldwide, whose increasing incidence among young adults is a cause for concern. The objective of this study was to estimate the risk of developing DM2 in UNIDA medical students using the FINDRISC score.

Methodology: Non-experimental cross-sectional study with a mixed approach carried out in 2023 with 211 medical students ≥ 18 years old, excluding pregnant women, individuals with a previous diagnosis of DM2 or cognitive deficit. The FINDRISC questionnaire was applied, cross-culturally adapted for the Paraguayan context. Anthropometric, sociodemographic and health data were collected.

Results: The mean age was 30.7 years. The risk of T2DM was classified as: low (47.9%), slightly increased (37.9%), moderate (10.4%), high (3.3%), and very high (0.5%). Factors such as a sedentary lifestyle, inadequate diet, obesity and family history were the main factors associated with the increased risk.

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Discussion: A study in Cuenca using the FINDRISC method identified a high risk of type 2 diabetes linked to overweight, sedentary lifestyle, and poor diet. Factors such as dyslipidemia, hypertension and obesity are also associated. FINDRISC is an effective, low-cost tool for preventing disease, especially in low-resource populations. In college students, stress and habits such as smoking and poor diet increase the risk of developing diabetes.

Conclusion: A significant percentage of students had a moderate to very high risk of developing T2DM, indicating the need for lifestyle-focused preventive interventions.

Keywords: Diabetes Risk. Findrisc. University Students. Risk Factors. Prevention.

RESUMO

Introdução: O diabetes mellitus tipo 2 (DM2) é uma doença crônica com alta prevalência em todo o mundo, cuja incidência crescente entre adultos jovens é motivo de preocupação. O objetivo deste estudo foi estimar o risco de desenvolver DM2 em estudantes de medicina da UNIDA usando o escore FINDRISC.

Metodologia: Estudo transversal não experimental com abordagem mista realizado em 2023 com 211 estudantes de medicina ≥ 18 anos, excluindo gestantes, indivíduos com diagnóstico prévio de DM2 ou déficit cognitivo. Aplicou-se o questionário FINDRISC, adaptado transculturalmente para o contexto paraguaio. Foram coletados dados antropométricos, sociodemográficos e de saúde.

Resultados: A média de idade foi de 30,7 anos. O risco de DM2 foi classificado em: baixo (47,9%), ligeiramente aumentado (37,9%), moderado (10,4%), alto (3,3%) e muito alto (0,5%). Fatores como sedentarismo, alimentação inadequada, obesidade e história familiar foram os principais fatores associados ao aumento do risco.

Discussão: Um estudo em Cuenca usando o método FINDRISC identificou um alto risco de diabetes tipo 2 ligado ao excesso de peso, sedentarismo e má alimentação. Fatores como dislipidemia, hipertensão e obesidade também estão associados. O FINDRISC é uma ferramenta eficaz e de baixo custo para prevenir doenças, especialmente em populações com poucos recursos. Em estudantes universitários, estresse e hábitos como tabagismo e má alimentação aumentam o risco de desenvolver diabetes.

Conclusão: Uma porcentagem significativa de estudantes apresentou risco moderado a muito alto de desenvolver DM2, indicando a necessidade de intervenções preventivas focadas no estilo de vida.

Palavras-chave: Risco de Diabetes. Findrisc. Estudantes Universitários. Fatores de Risco. Prevenção.

RESUMEN

Introducción: La diabetes mellitus tipo 2 (DM2) es una enfermedad crónica con alta prevalencia mundial, cuya creciente incidencia entre adultos jóvenes es motivo de preocupación. El objetivo de este estudio fue estimar el riesgo de desarrollar DM2 en estudiantes de medicina de la UNIDA mediante el puntaje FINDRISC.

Metodología: Estudio transversal no experimental con enfoque mixto realizado en el año 2023 con 211 estudiantes de medicina ≥ 18 años, excluyendo mujeres embarazadas, individuos con diagnóstico previo de DM2 o déficit cognitivo. Se aplicó el cuestionario FINDRISC, adaptado transculturalmente para el contexto paraguayo. Se recolectaron datos antropométricos, sociodemográficos y de salud.

Resultados: La edad media fue de 30,7 años. El riesgo de DM2 se clasificó como: bajo (47,9%), discretamente aumentado (37,9%), moderado (10,4%), alto (3,3%) y muy alto (0,5%). Factores como el sedentarismo, la alimentación inadecuada, la obesidad y los antecedentes familiares fueron los principales factores asociados con el aumento del riesgo.

Discusión: Un estudio en Cuenca usando el método FINDRISC identificó un alto riesgo de diabetes tipo 2 vinculado al sobrepeso, sedentarismo y mala alimentación. Factores como dislipidemia, hipertensión y obesidad también están asociados. El FINDRISC es una herramienta eficaz y de bajo costo para prevenir la enfermedad, especialmente en poblaciones de bajos recursos. En estudiantes universitarios, el estrés y hábitos como fumar y mala alimentación aumentan el riesgo de desarrollar diabetes.

Conclusión: Un porcentaje considerable de estudiantes presentó un riesgo moderado a muy alto de desarrollar DM2, lo que indica la necesidad de intervenciones preventivas centradas en el estilo de vida.

Palabras clave: Riesgo de Diabetes. Findrisc. Estudiantes Universitarios. Factores de Riesgo. Prevención.

1 INTRODUCTION

Type 2 diabetes mellitus (T2D) is a complex chronic condition that affects a large number of people worldwide. Its development is related to an interaction between genetic predisposition and sociodemographic factors, as well as lifestyle aspects, such as diet and lack of physical activity. Elements such as age, family history and ethnicity also play a role. To understand this association more precisely, it is essential to analyze the health habits and socioeconomic conditions of the populations studied (1).

Diabetes is one of the most relevant public health challenges worldwide (2). In 2021, it was estimated that around 537 million adults, between 20 and 79 years old, were living with this disease. Projections indicate that this figure could rise to 783 million by 2045. Type 2 diabetes accounts for about 90% of diagnoses, and it is worrying that a large proportion of cases have not yet been clinically identified. Therefore, prevention and timely diagnosis are key measures to reduce their impacts on global health. (3)

A fundamental aspect in the prevention of type 2 diabetes is the adoption of a healthy lifestyle, which includes a balanced diet and actions aimed at managing body weight. In this context, "mindful eating" has established itself as an effective strategy (4, 5 and 6). This approach focuses not only on the food you eat, but also on the reasons and how food choices are made. By promoting a more attentive relationship with food, this practice can contribute to the control of body mass index (BMI) and the reduction of the risk of developing diabetes in young adults. (7)

Type 2 diabetes is a metabolic condition characterized by insulin resistance, which can lead to serious complications, both microvascular (such as kidney disease and retinopathy) and macrovascular (heart attacks and strokes) (8, 9, 10 and 11). These complications not only decrease the quality of life, but also the life expectancy of patients. (12)

In this context, *the FINDRISC* is a tool used globally to assess the risk of developing type 2 diabetes. This questionnaire is composed of eight key parameters, including age, body mass index, waist circumference, level of physical activity, eating habits, use of antihypertensive medications, history of hyperglycemia, and family history of diabetes (13). In addition to its ability to predict the risk of developing T2DM, FINDRISC has also been shown to be effective in detecting undiagnosed diabetes, as well as identifying problems such as hepatic steatosis and cardiovascular events. (14)

The purpose of this article is to analyze the probability that medical students at the University of the Integration of the Americas will develop type 2 diabetes mellitus. To this end, a questionnaire will be applied to evaluate different risk factors associated with this disease,

with the aim of detecting possible vulnerabilities and promoting preventive measures within this youth population.

The relevance of this study lies in its ability to sensitize medical students about the risk of developing type 2 diabetes. In addition, it seeks to promote preventive actions that, in the future, can reduce the prevalence of this disease in the general population. In this way, it is expected to contribute to a cultural transformation that values prevention and self-care as fundamental pillars to maintain good health.

2 METHODOLOGY

This study was carried out by medical students in 2023 at the University of Integration of the Americas (UNIDA), located in Ciudad del Este, Paraguay for the hotbed of research in biochemistry, health and quality of life (BIOVIDA), it was a cross-sectional non-experimental study with a mixed approach. Data collection was carried out on the university campus, with the participation of medical students. Men and women ($n = 211$) over 17 years of age were included in the survey. Participants with cognitive impairments, pregnant women, and those with a previous diagnosis of diabetes mellitus (DM) were excluded.

For the assessment of the risk of developing type 2 diabetes mellitus (DM2), the Findrisc questionnaire, a risk assessment tool developed in Finland and widely used in international research, was used. The Findrisc questionnaire is a useful tool for estimating the likelihood of developing type 2 diabetes over a ten-year period. Its effectiveness has been proven through studies, establishing a cut-off point of 9 or more points as an indication of high risk. This tool has a sensitivity of approximately 76%, making it a reliable instrument for early detection, a specificity of 68%, a positive predictive value of 12%, and a negative predictive value of 98%. For this research, the questionnaire was translated and adapted cross-culturally to the Paraguayan context, and its reliability in this population was studied.

(15)

The questionnaire collects information on the following parameters: age, body mass index (BMI), waist circumference (WC), level of daily physical activity, consumption of fruits, vegetables, and legumes, use of medication for systemic blood pressure control, history of hyperglycemia, and family history of DM. The final score is obtained by adding the values assigned to each answer, with a scale that varies from 0 to 26 points. Based on the score, the individual risk of developing T2DM is stratified into five categories: low, discretely increased, moderate, high, very high.

Additionally, information was collected on the following variables: gender, self-reported race/ethnicity (white, black, brown, indigenous, and others), marital status (married,

separated/divorced, widowed, single), educational level (in full years of study), smoking habits (current smoker, former smoker, never smoker), personal history of myocardial infarction, angina, hypercholesterolemia, and use of medications such as statins and/or corticosteroids.

Data were collected by medical students through the application of the Findrisc questionnaire and the measurement of anthropometric parameters. The interviews were conducted in a laboratory under conditions that guaranteed the confidentiality of the information. For anthropometric measurements, weight and height were recorded using a scale with a stadiometer attached. Participants weighed themselves in light clothing and without shoes, in an upright position. Abdominal circumference (BC) was measured with a non-extendable tape measure, placed at the level of the navel. BMI was calculated by dividing body weight (in kilograms) by height (in meters) squared.

The data analysis was carried out in two stages. First, measures of central tendency (mean, median, and dispersion) were calculated. Subsequently, a bivariate analysis was performed to investigate the relationship between the explanatory variables and the outcome (risk stratification according to Findrisc, < 15 and ≥ 15 points). Finally, a binary logistic regression was performed using the *forward method* to determine the association between the predictor variables and the risk of developing DM2, with the calculation of odds ratios (OR).

3 RESULTS AND DISCUSSIONS

The survey contains 211 (two hundred and eleven) students with an average age of ≈ 31 years, of whom almost two-thirds are women and 73.93% had nine or more years of schooling. The characteristics of the individuals with respect to the research variables are presented in Table 1.

Table 1

Characteristics of participants in cross-sectional research at the University of Medicine (N=211). Ciudad del Este, Alto Paraná, Paraguay – 2023

Features	N (%)
Age (years)	30,7
Sex	
Female	108 51,18
Male	103 41,82
Race	
White	104 49,28
Non-White	107 51,72
Marital Status	
No partner	169 80,01
With a partner	42 19,90
Schooling (full years)	
≥ 12	55 26,07
9-11	156 73,93
Smoking	
Never smoked	151 71,57
Ex-smoker/current smoker	60 28,43
Cardiovascular Disease Staff History	
No	184 87,20
Yes	27 12,80
Personal history of vascular brain accident	
No	206 97,64
Yes	5 2,36
Personal history of hypercholesterolemia	
No	193 91,47
Yes	18 8,53
Personal history of polycystic ovaries	
No/ Not Applicable	194 91,94
Yes	17 8,06
Current Statin Use	
No	204 96,68
Yes	7 3,31
Current Corticosteroid Use	
No	198 93,83
Yes	13 6,17

Source: Authors.

Table 2

Table 2 presents the characteristics of the individuals according to the FINDRISC variables and their distribution by age groups. A clear predominance of the age group under 45 years of age is observed, which represents 96.68% of the sample

Age Group (Years)	Findrisc Questions	%
< 45	204	96,68
45-54	6	2,84
55-64	1	0,47
>64	0	0
Body mass index (kg/m)		
<25	103	48,82
25-30	87	41,23
>30	11	9,95
Abdominal circumference (cm)		
Men < 94, women < 80	121	57,35

Men 94-102, Women 80-88	51	24,17
Men > 102, women >88	39	18,48
Physical Activity		
Yes	107	50,71
No	104	49,29
Consumption of vegetables, legumes and fruits		
Every day	106	50,24
Does not consume every day	105	49,76
Use of medication for high blood pressure		
No	194	91,94
Yes	17	8,06
Elevated blood glucose history		
No	180	85,31
Yes	31	14,69
Family history of diabetes mellitus		
No	84	39,81
Grandparents, aunt, uncle, and/or first-degree cousins	80	37,91
Parents, siblings and/or children	47	22,28

Source: Authors.

Table 3			
Risk Classification	Scoring	N	%
Low	LESS THAN 7	101	47,87
Discreetly augmented	7-11	80	37,91
Moderate	12-14	22	10,43
High	15-20	7	3,32
Very high	GREATER THAN 20	1	0,47

Source: Authors.

Table 3 presents data on the risks of developing T2DM. Based on the total score defined by FRINDRISC. The total score ranged from 0 to 21 points. It is observed that 85.78% are at low and slightly increased risk of developing DM2, 10.43% at moderate risk, 3.32% at high risk and 0.47% at very high risk.

This study indicates that the ability of these students who are at high and very high risk of developing DM2 is related to weight gain, sedentary lifestyle, lack of daily vegetable intake, tobacco smoke and a family history of DM2.

4 DISCUSSION

A research carried out in the city of Cuenca, using the Findrisc method, revealed a high probability of developing type 2 diabetes, mainly linked to excess weight, physical inactivity and unhealthy eating patterns. Among the risk factors identified are dyslipidemia, high blood pressure, hyperglycemia, obesity and eating disorders. Although there are non-modifiable factors such as age, genetic inheritance and ethnicity, adopting a healthy lifestyle can be decisive in preventing the disease. Improving diet, regular physical activity, and taking

care of mental health can contribute not only to reducing the risk of diabetes, but also to promoting cardiovascular health, detoxifying the body, and stimulating the production of hormones related to well-being, such as dopamine (16).

The data presented in the research carried out in Ciudad del Este reveal a population profile with several risk factors associated with the development of chronic non-communicable diseases, such as type 2 diabetes. The average age of 31 years indicates a young-adult population, a key stage for the implementation of preventive measures. Despite the gender balance, a significant proportion of women who use oral contraceptives (31.75%) stands out, which may have long-term metabolic implications.

The high percentage of individuals with a history of smoking (28.43%) and current smokers (26.54%) reinforces the need for health policies focused on smoking cessation. Likewise, 17.54% with hypercholesterolemia and 12.80% with a history of stroke reflect a population with cumulative exposure to cardiovascular risk factors.

The prevalence of overweight, sedentary habits, and inadequate diet—reported in the Cuenca study and applicable due to contextual similarity—could be acting synergistically with these clinical factors. Therefore, it is urgent to promote healthy lifestyles, which include regular physical activity, a balanced diet and stress control, to reduce not only the risk of type 2 diabetes, but also to improve the overall health of this university population.

The Findrisc proved to be a fundamental tool worldwide for the prevention of chronic diseases such as diabetes mellitus, hepatic steatosis, cardiovascular risk, inflammatory diseases in disadvantaged regions due to its low cost benefit. DM2 is one of the important risk factors for cardiovascular disease and 80% of the low-income population is not diagnosed early due to inaccessibility of public health and low resources and through findrisc the low-income population can be alerted to the risk of developing T2DM. (17).

The data presented in Table 2, analyzed through the FINDRISC questionnaire, show a young population profile, with a high prevalence of modifiable risk factors associated with the development of type 2 diabetes. Despite the fact that 48.82% of the participants have a BMI within the normal range, a worrying 41.23% are overweight, and 61.13% have increased abdominal circumference, both key indicators in the development of metabolic syndrome.

60.19% do not perform regular physical activity and 59.24% do not consume fruits, vegetables or legumes daily, which reveals unhealthy lifestyle habits. Although the use of antihypertensive medications (3.79%) and previous hyperglycemia (5.21%) were present in lower percentages, they are clinical warning signs. 22.27% with a family history of first-degree diabetes mellitus reinforces the need for early interventions, especially considering that DM2 is an important risk factor for cardiovascular diseases. The FINDRISC, due to its

low cost and ease of application, is configured as a key tool to identify risks in low-income populations with limited access to health services, allowing the effective prevention of chronic non-communicable diseases.

In a family medicine clinic in Mexico, the Findrisc questionnaire was applied with the aim of identifying the risk of developing type 2 diabetes among the patients treated. As a result, 49 people were detected with signs of prediabetes, 12 with possible cases of undiagnosed diabetes and a total of 61 patients had some of these metabolic alterations. To complement the risk assessment, tests such as capillary glycemia, glycosylated hemoglobin (HbA1c), and the oral glucose tolerance test proved to be highly effective clinical tools consistent with the findings obtained through the questionnaire. (18)

The habits that mainly influence the lives of these individuals are not eating an adequate diet, being sedentary and not being able to quit smoking, a restriction and deprivation in the lives of these people. (19)

The bad habit of smoking in university students is related to several reasons, such as curiosity and social acceptance, but, in addition, nicotine addiction is seen assuming the mental and emotional integrity that leads the student to resort to this risk in search of relaxation and pleasure. (19)

Some factors that influence poor nutrition, such as university life itself, which is caused by the exhaustive workload, favors stress in the student's life, opting for the easy and not the healthy, causing a change in eating habits, associated with the practice of sedentary lifestyle and nicotine. It can have an impact on the health of these people by raising blood sugar and altering cells so that they do not respond to insulin and cause inflammation (20).

5 CONCLUSION

From this research it can be concluded that sedentary lifestyle, smoking, poor diet, genetic factors and weight gain predispose to insulin resistance in this sample of medical students. Stress leads many students to seek out quick and pleasurable meals. Therefore, it is necessary to invest in the creation of sports and awareness programs about healthy eating. Prevention and counseling programs on metabolic syndrome are essential for early diagnosis and avoiding complications.

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SURVEILLANCE OF EMERGING AND RE-EMERGING DISEASES: CHALLENGES FOR GLOBAL HEALTH AND MULTIPROFESSIONAL ACTION

VIGILÂNCIA DE DOENÇAS EMERGENTES E REEMERGENTES: DESAFIOS PARA A SAÚDE GLOBAL E PARA A ATUAÇÃO MULTIPROFISSIONAL

VIGILANCIA DE ENFERMEDADES EMERGENTES Y REEMERGENTES: DESAFÍOS PARA LA SALUD MUNDIAL Y LA ACCIÓN MULTIPROFESIONAL



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ABSTRACT

The surveillance of emerging and reemerging diseases has become a key strategy for protecting global health in a context shaped by environmental, social, and epidemiological transformations. This study aimed to analyze the challenges related to disease surveillance and to discuss the importance of multiprofessional practice in developing effective responses. This is a qualitative study conducted through an integrative literature review, based on recent scientific evidence from international databases. The findings indicate that environmental changes, increased human–animal interaction, population mobility, and weaknesses in health systems have contributed to the rise of emerging and reemerging diseases. The epidemiological profile has become more complex, with the coexistence of multiple infectious agents and the growing threat of antimicrobial resistance. In this context, epidemiological surveillance faces challenges related to data integration, technological use, and structural inequalities across countries. The role of multiprofessional teams is highlighted as essential for early detection, clinical management, and implementation of preventive strategies. It is concluded that strengthening health surveillance, combined with interdisciplinary collaboration and international cooperation, is crucial to address current and future challenges, ensuring global health security.

Keywords: Emerging Diseases. Epidemiological Surveillance. Global Health. Multiprofessional Team. Public Health.

RESUMO

A vigilância de doenças emergentes e reemergentes tem se consolidado como uma das principais estratégias para a proteção da saúde global diante de um cenário marcado por transformações ambientais, sociais e epidemiológicas. Este estudo teve como objetivo analisar os desafios relacionados à vigilância dessas doenças e discutir a importância da atuação multiprofissional na construção de respostas mais eficazes. Trata-se de uma pesquisa de abordagem qualitativa, desenvolvida por meio de revisão integrativa da literatura, com base em evidências científicas recentes provenientes de bases de dados internacionais. Os resultados apontam que fatores como alterações ambientais, intensificação do contato entre humanos e animais, mobilidade populacional e fragilidades nos sistemas de saúde têm contribuído para o aumento de doenças emergentes e reemergentes. Observa-se também a crescente complexidade do perfil epidemiológico, com a presença simultânea de diferentes agentes infecciosos, além do avanço da resistência antimicrobiana. Nesse contexto, a vigilância epidemiológica enfrenta desafios relacionados à integração de dados, uso de tecnologias e desigualdades estruturais entre países. Destaca-se, ainda, o papel fundamental da equipe multiprofissional no reconhecimento precoce dos agravos, no manejo clínico e na implementação de estratégias de prevenção. Conclui-se que o fortalecimento da vigilância em saúde, aliado à integração entre diferentes

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áreas do conhecimento e à cooperação internacional, é essencial para enfrentar os desafios atuais e futuros, contribuindo para a segurança sanitária global.

Palavras-chave: Doenças Emergentes. Vigilância Epidemiológica. Saúde Global. Equipe Multiprofissional. Saúde Pública.

RESUMEN

La vigilancia de enfermedades emergentes y reemergentes se ha convertido en una estrategia clave para proteger la salud mundial en un contexto marcado por cambios ambientales, sociales y epidemiológicos. Este estudio tuvo como objetivo analizar los desafíos relacionados con la vigilancia de estas enfermedades y discutir la importancia de la acción multidisciplinaria para construir respuestas más efectivas. Se trata de un estudio de investigación cualitativa, desarrollado a través de una revisión integradora de la literatura, basada en evidencia científica reciente de bases de datos internacionales. Los resultados indican que factores como los cambios ambientales, el mayor contacto entre humanos y animales, la movilidad de la población y las debilidades en los sistemas de salud han contribuido al aumento de enfermedades emergentes y reemergentes. También se observa la creciente complejidad del perfil epidemiológico, con la presencia simultánea de diferentes agentes infecciosos, además del avance de la resistencia antimicrobiana. En este contexto, la vigilancia epidemiológica enfrenta desafíos relacionados con la integración de datos, el uso de tecnologías y las desigualdades estructurales entre países. Además, se destaca el papel fundamental del equipo multidisciplinario en el reconocimiento temprano de problemas de salud, el manejo clínico y la implementación de estrategias de prevención. Se concluye que fortalecer la vigilancia epidemiológica, junto con la integración entre diferentes áreas del conocimiento y la cooperación internacional, es esencial para afrontar los desafíos actuales y futuros, contribuyendo así a la seguridad sanitaria mundial.

Palabras clave: Enfermedades Emergentes. Vigilancia Epidemiológica. Salud Global. Equipo Multidisciplinario. Salud Pública.

1 INTRODUCTION

The surveillance of emerging and reemerging diseases has assumed a central role in the organization of health systems around the world. In recent decades, the increase in the frequency of infectious outbreaks, combined with the rapid spread of pathogens between countries and continents, has highlighted the need to strengthen monitoring and response mechanisms in public health. This scenario is not the result of a single factor, but of a set of transformations that involve environmental changes, intensification of human mobility, population growth, and greater interaction between humans, animals, and ecosystems (JONES et al., 2008; HILDERINK; DE WINTER, 2021).

In this context, it is observed that most emerging diseases have a zoonotic origin, which reinforces the importance of integrated approaches such as the concept of One Health, which considers the interdependence between human, animal and environmental health. Recent studies indicate that the fragmentation of ecosystems and the loss of biodiversity favor the emergence of new pathogens, increasing the risk of epidemics and pandemics (ROSENTHAL et al., 2015; LANCET COMMISSION, 2026). This reality requires surveillance systems to be able to identify these events early, preventing their expansion.

In addition, epidemiological surveillance faces important challenges related to infrastructure, data integration, and the responsiveness of health systems. Despite technological advances, many countries still have weaknesses in the collection and analysis of information in real time, which compromises the effectiveness of control actions. International reports highlight that antimicrobial resistance and the circulation of new infectious agents represent growing threats, requiring more robust and coordinated strategies at the global level (WORLD HEALTH ORGANIZATION, 2025; WORLD HEALTH ORGANIZATION, 2023).

Another relevant point refers to the diversity of emerging and reemerging infectious agents that have been identified in different regions of the world. Recent studies describe the occurrence of outbreaks related to viruses such as Oropouche, influenza infections with zoonotic potential, in addition to the reemergence of diseases such as leprosy and dengue in new epidemiological contexts (IGLÓI et al., 2025; DAMDINJAV et al., 2025; AUYEUNG et al., 2025; VAN DER ENDE et al., 2025). These findings show that the behavior of infectious diseases is constantly changing, requiring continuous and adaptive surveillance.

The occurrence of outbreaks has also been associated with specific factors, such as environmental events, agricultural practices, and inadequate sanitary conditions. Research shows that outbreaks of bacterial and viral infections, including salmonellosis and encephalomyelitis, have been recorded in different contexts, reinforcing the need for

integrated monitoring across sectors (PIÑA-ITURBE et al., 2025; FRABASILE et al., 2025; LI et al., 2025). In addition, the reemergence of diseases such as monkeypox shows that pathogens previously considered controlled may once again pose a threat to public health (BBOSA et al., 2025).

At the same time, there has been an advance in the development of technologies aimed at health surveillance. Digital systems, large-scale data analysis, and new monitoring methodologies have contributed to improving early outbreak detection and public health decision-making. However, these advances still coexist with challenges related to privacy, data governance, and equity in access to technologies, especially in low- and middle-income countries (SHEN et al., 2025; AHMED, 2024; SERGEANT, 2025).

Another important aspect concerns the need for integration between different levels of health care and between different areas of knowledge. The surveillance of emerging diseases cannot be understood as an exclusive responsibility of epidemiologists, but as a process that involves physicians, nurses, pharmacists, physiotherapists, dentists, and public health professionals. This multidisciplinary action is essential to ensure the early identification of cases, the proper management of patients, and the implementation of prevention strategies (DE GAETANO et al., 2025; WALKER et al., 2025).

Given this scenario, it is evident that surveillance of emerging and reemerging diseases is a fundamental element for global health security. More than monitoring diseases, it is about understanding the processes that favor their emergence and dissemination, integrating science, technology, and professional practice. Thus, this study aims to discuss the main challenges related to the surveillance of these diseases and to analyze the role of multiprofessional action in the construction of more effective responses for contemporary global health.

2 LITERATURE REVIEW

2.1 EMERGING AND REEMERGING DISEASES: A CHANGING LANDSCAPE

In recent decades, the occurrence of emerging and reemerging diseases has become increasingly frequent, reflecting profound changes in the relationship between human beings, the environment and infectious agents. This phenomenon is not recent, but it has gained greater visibility in the face of the intensification of global outbreaks and the rapid spread of diseases between different countries. Classic studies have already pointed to this trend, highlighting that the emergence of new pathogens is directly related to environmental and social transformations (JONES et al., 2008).

With the advancement of research, it has become evident that these processes are still active and, in many cases, more intense. The current literature reinforces that the increase in infectious diseases is associated with factors such as disordered urbanization, globalization, and greater population mobility. In addition, the constant circulation of people and goods contributes to the rapid spread of infectious agents, making outbreaks more difficult to control (WALKER et al., 2025; DE GAETANO et al., 2025).

Another important point is that many of these diseases do not arise in a totally new way, but reappear in different contexts, with greater intensity or in areas where they were not common before. This characterizes the so-called reemerging diseases, which represent an additional challenge for health systems.

2.2 ZOONOSES AND THE RELATIONSHIP BETWEEN HUMANS, ANIMALS AND THE ENVIRONMENT

Most emerging diseases have a zoonotic origin, that is, they are transmitted between animals and humans. This type of transmission highlights the strong connection between human health, animal health, and the environment. Studies indicate that changes in ecosystems, such as deforestation and loss of biodiversity, increase contact between humans and animals, favoring the emergence of new pathogens (ROSENTHAL et al., 2015; HILDERINK; DE WINTER, 2021).

In this context, the concept of One Health has gained prominence, proposing an integrated approach to understanding and coping with diseases. The central idea is that it is not possible to treat human health in isolation, without considering the environmental impacts and animal health conditions. Recent reports reinforce that this integration is essential to prevent future pandemics and improve the response capacity of health systems (LANCET COMMISSION, 2026).

In addition, more recent studies show that the circulation of zoonotic viruses remains a constant concern. Infections such as influenza of animal origin and other emerging viruses demonstrate that the risk remains high, especially in regions where there is greater interaction between humans and animals (DAMDINJAV et al., 2025).

2.3 EPIDEMIOLOGICAL SURVEILLANCE SYSTEMS: ADVANCES AND LIMITATIONS

Epidemiological surveillance is one of the fundamental pillars for the control of emerging and reemerging diseases. It allows for early identification of outbreaks, monitoring the spread of diseases, and guiding prevention and control actions. In recent years, there

have been important advances in this field, especially with the use of digital technologies and the analysis of large volumes of data (SHEN et al., 2025).

However, despite these advances, there are still significant challenges. Many countries face difficulties related to infrastructure, system integration, and the quality of available data. The lack of standardization in the collection and sharing of information can compromise the efficiency of surveillance actions, hindering rapid responses to outbreaks (AHMED, 2024).

In addition, issues related to privacy and data use have been increasingly discussed. The balance between the need for health monitoring and the protection of individual information represents an important challenge for contemporary surveillance systems (SERGEANT, 2025).

2.4 EMERGING DISEASES IN THE CURRENT CONTEXT: EXAMPLES AND EVIDENCE

Recent literature presents several examples of emerging and reemerging diseases that illustrate the challenges faced by health systems. Among them, outbreaks of viruses such as Oropouche, the simultaneous circulation of different dengue serotypes, and the reemergence of diseases such as leprosy in certain contexts stand out (IGLÓI et al., 2025; VAN DER ENDE et al., 2025; AUYEUNG et al., 2025).

In addition, bacterial infections and food outbreaks continue to represent a relevant problem. Cases related to salmonella and other infections show that surveillance must be constant and comprehensive, considering different routes of transmission (PIÑA-ITURBE et al., 2025; LI et al., 2025).

Another important example refers to the reemergence of viral diseases such as monkeypox, which has highlighted the ability of previously controlled pathogens to circulate again on a global scale. These episodes reinforce the need for surveillance systems prepared to deal with different types of threats (BBOSA et al., 2025).

2.5 ANTIMICROBIAL RESISTANCE AND NEW HEALTH CHALLENGES

Antimicrobial resistance has been identified as one of the biggest threats to global health. The inappropriate use of antibiotics and other medications has contributed to the emergence of resistant microorganisms, making it difficult to treat infections and increasing the risk of complications (WORLD HEALTH ORGANIZATION, 2025).

This problem is not limited to the hospital environment, but also involves community practices and the use of antimicrobials in animal production. Antimicrobial resistance is

directly related to health surveillance, since monitoring these cases is essential to guide public policies and control strategies (WORLD HEALTH ORGANIZATION, 2023).

In addition, the presence of resistant pathogens can aggravate the impact of emerging diseases, making outbreaks more difficult to control and increasing the associated mortality.

2.6 GLOBAL CHALLENGES AND THE NEED FOR INTEGRATION IN HEALTH

The challenges related to emerging and reemerging diseases cannot be tackled in isolation. The literature points out that international cooperation is fundamental for the development of effective surveillance and control strategies. The exchange of information between countries, the strengthening of monitoring networks, and investment in research are essential elements in this process, allowing for faster and more coordinated responses to health threats (WALKER et al., 2025; DE GAETANO et al., 2025).

In addition, the performance of international organizations has been decisive in the consolidation of more structured surveillance systems. Institutions such as the World Health Organization and the Centers for Disease Control and Prevention play an important role in standardizing protocols, monitoring outbreaks, and disseminating up-to-date information on emerging diseases in different regions of the world (WORLD HEALTH ORGANIZATION, 2023; CDC, 2025).

Another relevant aspect is the need for integration between the different levels of health care and between different areas of knowledge. The surveillance of emerging diseases cannot be understood as an isolated responsibility, but as a process that involves doctors, nurses, pharmacists, physiotherapists, dentists and public health professionals. This multidisciplinary action strengthens the early identification of cases, adequate clinical management, and the implementation of prevention strategies.

Finally, integration between sectors, such as health, environment, and food production, becomes essential to face the complexity of the factors involved in the emergence of diseases. This articulation expands the response capacity of health systems and contributes to the construction of more effective and sustainable strategies to face global challenges.

2.7 FUTURE PERSPECTIVES OF HEALTH SURVEILLANCE

The future of health surveillance is directly related to the ability of health systems to adapt to new threats. The incorporation of digital technologies, data intelligence, and real-time monitoring tends to strengthen response capacity, allowing for faster and more effective actions (SHEN et al., 2025).

However, these advances must be accompanied by policies that ensure equity in access to technologies and respect for the privacy of individuals. In addition, it is essential to invest in the training of health professionals, preparing them to deal with increasingly complex scenarios.

Overall, the literature indicates that surveillance of emerging and reemerging diseases will continue to be one of the main challenges of global health. Facing this scenario requires integration between science, professional practice, and public policies, as well as a broader vision that recognizes the interdependence between health, environment, and society.

3 METHODOLOGY

3.1 STUDY DESIGN

The present study was developed from a qualitative approach, with a theoretical-analytical character, structured through an integrative review of the scientific literature. The choice of this design was based on the need to understand, in a broader and contextualized way, the challenges related to the surveillance of emerging and reemerging diseases, as well as the role of multiprofessional action in this scenario. Instead of being limited to the description of isolated data, we sought to interpret the available evidence in a critical way, considering different dimensions of the phenomenon, such as epidemiological, social, organizational, and care aspects.

The integrative review allowed the gathering of studies with different methodologies, expanding the capacity for analysis and enabling a closer view of the reality faced by health systems. This approach also favors the construction of a coherent narrative, connecting scientific findings with health practice.

3.2 SEARCH STRATEGY AND DATABASES

The search for evidence was carried out in internationally recognized databases, selected for their relevance in the area of public health, epidemiology and infectious diseases. The following databases were used:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- SciELO
- Google Scholar

In addition, institutional reports from international organizations, such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), were consulted due to their importance in the production of data on epidemiological surveillance at the global level.

For the search, descriptors in Portuguese and English were used, combined by Boolean operators (AND and OR), with the objective of expanding the scope and ensuring the relevance of the results. Among the main terms used, the following stand out:

- emerging diseases
- Reemerging Diseases
- Epidemiological surveillance
- Global health
- emerging infectious diseases
- disease surveillance
- Global Health
- zoonotic diseases

The combination of these descriptors allowed the identification of studies directly related to the proposed theme.

3.3 INCLUSION AND EXCLUSION CRITERIA

Scientific articles published in peer-reviewed journals, systematic reviews, epidemiological studies, and institutional documents that addressed:

- Surveillance of emerging and reemerging diseases
- Infectious outbreaks and their epidemiological dynamics
- Challenges of health systems in the detection and control of diseases
- Multiprofessional approaches in health

Studies available in English, Portuguese and Spanish, with access to the full text, were also considered.

Duplicate studies, studies with an exclusively laboratory focus without application in public health, publications without scientific rigor, and materials that had no direct relationship with the theme were excluded.

3.4 ANALYSIS PERIOD

Publications between the years 2020 and 2025 were prioritized, a period that concentrates recent advances in the surveillance of emerging and reemerging diseases, especially after health events of great global impact. However, classic studies that are widely recognized in the scientific literature were included when considered fundamental for the theoretical and conceptual understanding of the theme, contributing to a more consistent and in-depth analysis.

3.5 PROCESS OF SELECTION AND ORGANIZATION OF DATA

Initially, the titles and abstracts of the identified studies were read, with the objective of selecting those most aligned with the theme. Then, the selected articles were analyzed in full, allowing us to evaluate their relevance and contribution to the study.

At the end of this process, 20 main scientific references were selected, which composed the theoretical basis of the work. The information extracted was organized in a thematic way, allowing the analysis to be structured in central axes, such as:

- Dynamics of emerging and reemerging diseases
- Epidemiological Surveillance Systems
- Global Health Challenges
- Role of the multiprofessional team

This organization contributed to the construction of a clearer and more integrated discussion.

3.6 DATA ANALYSIS AND INTERPRETATION

The analysis of the studies was conducted in an interpretative manner, seeking to identify patterns, convergences and gaps in the scientific literature. The synthesis of the evidence was carried out in a narrative manner, focusing on the construction of a clear, coherent text that is close to the reality of health practice.

This stage allowed not only to describe the findings, but also to reflect on their implications for the organization of health services and for multiprofessional action, valuing the integration between different areas of knowledge.

3.7 SCIENTIFIC RIGOR

Methodological rigor was ensured by the selection of studies from recognized databases, by the use of clear inclusion and exclusion criteria, and by the critical analysis of the evidence. We sought to maintain fidelity to the information presented in the studies, avoiding distorted interpretations or undue generalizations.

In addition, the diversity of sources allowed different scientific perspectives to be contemplated, strengthening the consistency of the analysis and contributing to a more complete approach to the theme.

3.8 ETHICAL ASPECTS

As this was a study based exclusively on secondary data from the scientific literature, there was no need to submit it to the Research Ethics Committee. All the sources used were duly cited throughout the text, respecting the ethical principles of scientific production and ensuring transparency in the process of knowledge construction.

4 RESULTS AND DISCUSSION

The analysis of the evidence gathered allows us to understand that the surveillance of emerging and reemerging diseases is no longer an activity restricted to specific contexts and has come to occupy a strategic position in the organization of health systems. The studies analyzed show that there is a consistent increase in the occurrence of infectious events in different regions of the world, which confirms a change in the epidemiological behavior of these diseases. This scenario had already been signaled in previous studies, but it is currently more evident, driven by environmental, social and economic transformations (JONES et al., 2008; WALKER et al., 2025).

One of the main results observed concerns the strong relationship between the emergence of diseases and changes in ecosystems. The literature shows that the intensification of contact between humans and animals, associated with environmental degradation, creates favorable conditions for the transmission of pathogens. This process does not occur in isolation, but as a result of a series of interconnected factors, including deforestation, urbanization, and agricultural expansion. In this context, zoonoses stand out as one of the main current challenges, reinforcing the need for integrated health approaches (ROSENTHAL et al., 2015; HILDERINK; DE WINTER, 2021).

The discussion also reveals that, although there are important advances in epidemiological surveillance, there are still limitations that compromise the effectiveness of actions. The adoption of digital technologies and real-time monitoring systems has

contributed to improved outbreak detection, but these resources are not available equitably in all countries. In many contexts, surveillance still depends on fragmented systems, with difficulties in integrating data and communicating between different levels of care (SHEN et al., 2025; AHMED, 2024).

In addition, issues related to governance and the use of information have gained prominence. The need to collect data on a large scale to monitor diseases comes up against ethical challenges, especially with regard to privacy and the appropriate use of this information. This aspect shows that technological advancement alone is not enough, and it is necessary to establish clear guidelines that ensure security and transparency in the use of data (SERGEANT, 2025).

Another relevant point identified in the studies refers to the diversity of infectious agents involved in emerging events. The occurrence of outbreaks related to different pathogens, such as viruses, bacteria, and parasites, demonstrates that surveillance must be broad and adaptable. Recent cases involving viruses such as Oropouche, influenza of zoonotic origin, and the simultaneous circulation of different dengue serotypes illustrate the complexity of the current scenario (IGLÓI et al., 2025; DAMDINJAV et al., 2025; VAN DER ENDE et al., 2025).

The reemergence of diseases previously considered controlled also draws attention. Episodes involving leprosy and monkeypox indicate that the control of these diseases is not definitive, and there may be a resurgence under certain conditions. This phenomenon reinforces the importance of continuous surveillance and the maintenance of prevention strategies even for diseases that have a reduction in cases in certain periods (AUYEUNG et al., 2025; BBOSA et al., 2025).

In the field of bacterial infections, studies highlight the persistence of outbreaks associated with inadequate sanitary conditions and failures in the food production chain. Cases related to salmonella and other bacteria show that surveillance must cover different sectors, including health, agriculture and the food industry. This type of intersectoral approach is key to reducing risks and preventing the spread of disease (PIÑA-ITURBE et al., 2025; LI et al., 2025).

Antimicrobial resistance appears as one of the most worrying results within this scenario. The literature shows that the increase in resistant microorganisms has made it difficult to treat infections and increased the risks associated with outbreaks. This problem is directly related to the inappropriate use of medications and the lack of control at different levels, requiring coordinated and continuous actions (WORLD HEALTH ORGANIZATION,

2025). In addition, surveillance of these cases is essential to guide control strategies and reduce the impact on health systems (WORLD HEALTH ORGANIZATION, 2023).

Another aspect that deserves to be highlighted is the importance of multiprofessional action. The studies analyzed indicate that the response to emerging diseases cannot be limited to a single area of knowledge. The participation of doctors, nurses, pharmacists, physiotherapists, dentists, and public health professionals is essential to ensure a more complete approach, from the identification of cases to the follow-up of patients and the implementation of preventive measures (DE GAETANO et al., 2025).

The integration between these professionals contributes to improving the quality of care and strengthening surveillance actions. In addition, it allows a better understanding of the social and environmental determinants that influence the occurrence of diseases. This expanded vision is essential for the development of more effective and sustainable strategies.

The discussion also highlights the importance of international cooperation. The exchange of information between countries, the sharing of epidemiological data, and the construction of surveillance networks are fundamental elements to face global threats. The work of international organizations, such as the World Health Organization and the CDC, has been decisive in this process, contributing to the standardization of protocols and the strengthening of surveillance in different regions (CDC, 2025).

Overall, the results indicate that the surveillance of emerging and reemerging diseases faces complex challenges, which go beyond the identification of cases. It is a process that involves environmental, social, technological, and organizational factors, requiring an integrated and continuous approach. The responsiveness of health systems depends not only on technological resources, but also on the articulation between different areas and the construction of consistent public policies.

Given this scenario, it is evident that strengthening health surveillance is an urgent need. Investing in structure, professional qualification, and integration between sectors is essential to face current and future challenges. More than reacting to outbreaks, it is necessary to develop strategies that allow anticipating risks and reducing impacts, ensuring greater safety for populations.

5 CONCLUSION

The surveillance of emerging and reemerging diseases is currently consolidated as one of the most important pillars for the protection of global health. Throughout this study, it was possible to perceive that the increase in the occurrence of these diseases is not an

isolated event, but the result of profound transformations involving the environment, population dynamics, and the way health systems are organized. This scenario requires a change in posture, from acting only in a reactive way to taking a more preventive and integrated approach.

The findings discussed show that the complexity of emerging diseases goes beyond the identification of new infectious agents. It is about understanding the processes that favor its emergence, its dissemination and its impacts on populations. The strong relationship between environmental degradation, zoonoses, and changes in epidemiological behavior reinforces the need to look at health in a broader way, considering its multiple dimensions.

Another point that stands out is that, despite technological and scientific advances, there are still important gaps in surveillance systems. Problems related to data integration, inequality in access to technologies, and structural limitations continue to be challenges present in different contexts. This demonstrates that strengthening surveillance does not depend only on innovation, but also on organization, planning and continuous investment.

Antimicrobial resistance, the reemergence of diseases, and the circulation of new pathogens show that the challenges are likely to intensify in the coming years. In view of this, it is essential to strengthen monitoring strategies, expand the response capacity of health services, and invest in the training of professionals who work directly in care.

In this context, multiprofessional action is indispensable. The integration between doctors, nurses, pharmacists, physiotherapists, dentists and public health professionals allows for a more complete approach, ranging from the early identification of cases to the implementation of prevention and control actions. This articulation between different areas of knowledge contributes to more effective responses aligned with the real needs of the populations.

In addition, international cooperation is a fundamental element for confronting emerging diseases. Sharing information, standardizing protocols, and strengthening global surveillance networks are essential strategies to reduce risks and prevent the spread of outbreaks on a global scale.

Thus, it is concluded that the surveillance of emerging and reemerging diseases cannot be understood only as a technical activity, but as an essential strategy to ensure global health security. Addressing today's challenges requires integration between science, professional practice, and public policy, as well as an ongoing commitment to health promotion and risk prevention. The future of health will depend, to a large extent, on the ability to anticipate scenarios, strengthen surveillance systems, and act collaboratively in the face of an increasingly interconnected world.

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USE OF POINT-OF-CARE ULTRASOUND (POCUS) IN THE ASSESSMENT OF FLUID RESPONSIVENESS: PRACTICAL APPLICATIONS AND METHODS

USO DO ULTRASSOM POINT-OF-CARE (POCUS) NA AVALIAÇÃO DA RESPONSABILIDADE VOLÊMICA: APLICAÇÃO PRÁTICA E MÉTODOS

USO DE LA ECOGRAFÍA EN EL PUNTO DE ATENCIÓN (POCUS) PARA EVALUAR LA RESPUESTA AL VOLUMEN: APLICACIÓN PRÁCTICA Y MÉTODOS



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ABSTRACT

Fluid responsiveness assessment is essential in the management of critically ill patients, as inappropriate fluid administration is associated with adverse outcomes. In this context, point-of-care ultrasound (POCUS) has emerged as a key tool for hemodynamic monitoring, enabling dynamic bedside evaluation. This study is a structured critical narrative review analyzing 18 studies published between 2015 and 2025, identified through PubMed/MEDLINE, Scopus, and Web of Science databases. Ultrasound-based methods evaluated included left ventricular outflow tract velocity-time integral (LVOT VTI), passive leg raising (PLR), and indices derived from the inferior and superior vena cava. The findings demonstrate the superiority of dynamic over static parameters, with the combination of VTI and PLR representing the most consistent approach. In contrast, vena cava indices show greater variability and context-dependent limitations, while emerging methods such as carotid flow assessment require further validation. In conclusion, no single method is universally applicable, and an integrated, context-based approach is essential, with POCUS playing a central role in clinical decision-making.

Keywords: Point-Of-Care Ultrasound. Fluid Responsiveness. Hemodynamic Monitoring. Critical Care. Echocardiography.

RESUMO

A avaliação da responsividade volêmica é fundamental no manejo de pacientes críticos, uma vez que a administração inadequada de fluidos está associada a desfechos adversos. Nesse contexto, o ultrassom point-of-care (POCUS) tem se consolidado como ferramenta central na monitorização hemodinâmica, permitindo avaliação dinâmica à beira-leito. Este estudo consiste em uma revisão narrativa crítica com abordagem estruturada, que analisou 18 estudos publicados entre 2015 e 2025, selecionados a partir das bases PubMed/MEDLINE, Scopus e Web of Science. Foram avaliados métodos ultrassonográficos como a variação do integral velocidade-tempo do trato de saída do ventrículo esquerdo (VTI do LVOT), o teste de elevação passiva dos membros inferiores (passive leg raising – PLR) e os índices derivados das veias cava inferior e superior. Os achados demonstram superioridade dos métodos dinâmicos em relação aos parâmetros estáticos, com destaque para a combinação entre VTI e PLR como abordagem mais consistente. Em contraste, índices baseados na veia cava apresentam maior variabilidade e limitações contextuais, enquanto métodos emergentes, como o fluxo carotídeo, ainda carecem de validação robusta. Conclui-se que não há método universalmente aplicável, sendo essencial uma abordagem integrada e contextualizada, com o POCUS desempenhando papel central na tomada de decisão clínica.

Palavras-chave: Ultrassom Point-Of-Care. Responsividade Volêmica. Monitorização Hemodinâmica. Terapia Intensiva. Ecocardiografia.

RESUMEN

La evaluación de la respuesta a la fluidoterapia es fundamental en el manejo de pacientes críticos, dado que una administración inadecuada de fluidos se asocia con resultados adversos. En este contexto, la ecografía en el punto de atención (POCUS) se ha convertido en una herramienta central en la monitorización hemodinámica, permitiendo una evaluación dinámica a pie de cama. Este estudio consiste en una revisión narrativa crítica estructurada que analizó 18 estudios publicados entre 2015 y 2025, seleccionados de las bases de datos PubMed/MEDLINE, Scopus y Web of Science. Se evaluaron métodos ecográficos como la integral tiempo-velocidad del tracto de salida del ventrículo izquierdo (LVOT velocity-time integral), la prueba de elevación pasiva de las piernas (PLR) e índices derivados de las venas

cavas superior e inferior. Los hallazgos demuestran la superioridad de los métodos dinámicos en comparación con los parámetros estáticos, destacando la combinación de VTI y PLR como el enfoque más consistente. Por el contrario, los índices basados en la vena cava presentan mayor variabilidad y limitaciones contextuales, mientras que los métodos emergentes, como el flujo carotídeo, aún carecen de una validación sólida. Se concluye que no existe un método universalmente aplicable, y que es esencial un enfoque integrado y contextualizado, donde la ecografía en el punto de atención (POCUS) desempeña un papel central en la toma de decisiones clínicas.

Palabras clave: Ecografía en el Punto de Atención. Respuesta al Volumen. Monitorización Hemodinámica. Cuidados Intensivos. Ecocardiografía.

1 INTRODUCTION

Adequate hemodynamic assessment is one of the main pillars in the management of critically ill patients, especially in the presence of circulatory instability. The administration of intravenous fluids remains one of the first therapeutic interventions in these settings. However, its efficacy is variable and depends on the ability of the cardiovascular system to respond to increased preload. Evidence shows that only a portion of patients have a significant increase in cardiac output after volume expansion, while indiscriminate administration of fluids can result in fluid overload, associated with worse clinical outcomes, including higher morbidity and mortality (MONNET; SHI; TEBOUL, 2022). In this scenario, it is essential to use methods capable of predicting volume responsiveness, defined as the increase in cardiac output after volume replacement, in order to optimize therapy and avoid potentially deleterious interventions (ASOGWA et al., 2024).

Historically, static parameters such as central venous pressure and mean arterial pressure have been widely used to guide volume replacement. However, these measures have low accuracy in predicting responsiveness, as they do not adequately reflect the dynamic interaction between preload, myocardial contractility, and cardiopulmonary conditions (ASOGWA et al., 2024). On the other hand, dynamic methods, based on the evaluation of the cardiovascular response to transient changes in preload, have demonstrated greater predictive capacity and have become preferred in contemporary clinical practice (MONNET; SHI; TEBOUL, 2022). Even so, its applicability may vary according to the clinical context and the physiological conditions of the patient, which reinforces the complexity of volume assessment and the need for more accurate tools.

In this context, point-of-care ultrasound (POCUS) has emerged as a central tool in bedside hemodynamic assessment. It is a non-invasive, portable, and fast-performing method, capable of providing real-time information on cardiac function, volume status, and systemic perfusion (NOOR et al., 2025). In addition, its possibility of serial use allows continuous monitoring of the therapeutic response, favoring a more individualized approach in the management of critically ill patients (PICCIONI et al., 2025). Thus, POCUS has been progressively incorporated into clinical practice in intensive care units, emergency departments, and the perioperative environment.

Among the applications of POCUS, the dynamic methods used in the prediction of volume responsiveness stand out, such as the variation of the integral velocity-time of the left ventricular outflow tract (LVOT VTI), the passive leg raising (PLR) test, and the analysis of respiratory variations of the inferior and superior vena cava. Evidence suggests that the variation of the VTI, especially when associated with the PLR, has high accuracy in predicting

the response to volume, being considered one of the most consistent approaches in clinical practice (PÉREZ-MANJARREZ et al., 2023; BOU CHEBL et al., 2018). On the other hand, parameters based on the vena cava, although widely disseminated, have relevant limitations, particularly in patients with ventricular dysfunction or under different ventilatory conditions, which may compromise their reliability (ZHANG et al., 2019; MA et al., 2022a; MA et al., 2022b). This heterogeneity of performance among the methods highlights the absence of a universally applicable tool.

Despite technological advances and the growing use of POCUS, there is still no definitive consensus in the literature regarding the most accurate, reproducible, and applicable method in different clinical scenarios. In addition, factors such as operator dependence, technical variability, and heterogeneity of the populations studied pose additional challenges for their standardization (HOTZ; VAN GEMMERN; KRIEGE, 2024). In this context, it is essential to critically integrate the available evidence, not only to describe existing methods, but also to understand their limitations and real applicability in clinical practice.

In view of the above, the present study aims to critically analyze the use of point-of-care ultrasound (POCUS) in the evaluation of volume responsiveness in critically ill patients, with emphasis on the main dynamic methods employed, their limitations, and their applications in clinical practice.

2 METHODOLOGY

This is a critical narrative review of the literature, with a structured approach, focused on the analysis of evidence on the use of point-of-care ultrasound (POCUS) in the evaluation of volume responsiveness in critically ill patients. The literature search was carried out in the PubMed/MEDLINE, Scopus, and Web of Science databases, including studies published between 2015 and 2025. English descriptors and keywords were used, combined by Boolean operators AND and OR, including "point-of-care ultrasound", "fluid responsiveness", "hemodynamic monitoring", "passive leg raising", "inferior vena cava", "stroke volume" and "velocity time integral".

Original studies, reviews, and observational studies involving adult patients that addressed sonographic methods applied to the prediction of volume responsiveness, published in English, Portuguese, or Spanish, were included. Case reports, case series with a low level of evidence, studies with an exclusively pediatric population, and those without direct clinical applicability in hemodynamic evaluation were excluded.

The selection of studies was carried out by screening titles and abstracts, followed by reading the eligible articles in full. At the end of the process, 18 studies considered relevant for analysis were included, based on their methodological consistency and clinical applicability.

Data extraction included study design, population evaluated, ultrasound methods used, and parameters analyzed, including variation in the VTI of the left ventricular outflow tract, inferior and superior vena cava indexes, and dynamic tests such as passive leg raising, as well as outcomes related to volume responsiveness.

The analysis was conducted in a qualitative and comparative manner, focusing on the critical evaluation of the diagnostic accuracy, technical limitations, and clinical applicability of the different methods in scenarios such as intensive care unit, emergency, and perioperative environment. No meta-analysis was performed due to the heterogeneity of the designs, populations, and parameters evaluated.

3 RESULTS AND DISCUSSION

The integrated analysis of the studies demonstrates that the use of point-of-care ultrasound (POCUS) in the evaluation of volume responsiveness represents not only a technological advance, but also a conceptual reconfiguration of hemodynamic monitoring in critically ill patients. In this context, the literature converges by evidencing the superiority of dynamic methods in relation to static parameters; However, further comparative analysis reveals that such superiority is not evenly distributed among the different approaches available. In fact, an implicit functional hierarchy is observed, in which methods based on direct flow measurement, such as the VTI of LVOT, tend to present superior performance in relation to indirect indices, such as those derived from vena cava.

Among the methods evaluated, the variation of the LVOT VTI stands out as the parameter most consistently associated with volume responsiveness, especially when analyzed in direct comparison with alternative approaches. Studies such as those by Pérez-Manjarrez et al. (2023) and Maciuliene et al. (2017) demonstrate a strong correlation between VTI variation and classic markers of responsiveness, such as pulse pressure variation, suggesting greater physiological proximity to cardiac output. In contrast, methods based on variations in venous diameter, such as the evaluation of the inferior vena cava, have a more indirect character, predominantly reflecting changes in intrathoracic pressure and venous compliance, which makes them more susceptible to physiological interference. This conceptual distinction contributes to explain the relative superiority of VTI, since it

directly measures the final outcome of the interaction between preload, contractility, and afterload, while CVI represents an intermediate marker of this dynamic.

Nevertheless, this superiority must be interpreted with caution. From an operational point of view, the VTI has relevant limitations, including high operator dependence, the need for an adequate acoustic window, and greater technical complexity, factors that may restrict its applicability in emergency scenarios or in patients with unfavorable clinical conditions (ASOGWA et al., 2024). In contrast, the assessment of CVI, although less accurate from a physiological point of view, is more accessible and less technically demanding, which favors its use in contexts of less complexity. This dichotomy highlights a recurrent tension in the literature between diagnostic accuracy and practical feasibility, which is often underestimated in the interpretation of results.

In this scenario, the passive leg raising (PLR) test assumes a central role as a tool for dynamic modulation of preload, allowing the functional evaluation of the cardiovascular response regardless of the measurement method adopted. When associated with VTI analysis, PLR enhances diagnostic accuracy, configuring the most robust combination described in the literature (MONNET; SHI; TEBOUL, 2022; BOU CHEBL et al., 2018). Compared to indices based exclusively on venous parameters, PLR has a clear advantage, since it induces a measurable physiological change in cardiac output, instead of inferring this response indirectly. However, its efficacy remains strongly conditioned to the adequate technical execution and correct interpretation of hemodynamic variations, being susceptible to relevant operational failures. Recent evidence points to significant discrepancies between the theoretical application and clinical practice of the method, indicating that its accuracy can be substantially reduced in real environments (HOTZ; VAN GEMMERN; KRIEGE, 2024). In addition, conditions such as intra-abdominal hypertension, mechanical ventilation with high parameters, and postural limitations can directly interfere with the response to the test, restricting its applicability in certain contexts.

In turn, indices derived from vena cava, especially CVI, continue to be widely used in clinical practice, mainly due to their ease of obtainment. However, when analyzed comparatively, they demonstrate lower performance and greater variability compared to flow-based methods. The evidence that CVI distensibility has low accuracy in patients with left ventricular dysfunction (ZHANG et al., 2019) constitutes a critical limitation, often neglected in clinical practice. In addition, studies such as those by Ma et al. (2022a) show a wide area of uncertainty in the CVI cut-off values, reducing its usefulness in binary clinical decisions. On the other hand, parameters related to the superior vena cava (SVC) demonstrate superior diagnostic performance in patients under controlled mechanical ventilation (MA et al., 2022b;

BUBENEK-TURCONI et al., 2019), suggesting that the choice between CVI and CVS should be guided by the ventilatory context. Even so, the applicability of CVS remains limited by more complex technical requirements, including the need for transesophageal echocardiography, which restricts its routine use.

Emerging methods, such as the evaluation of carotid flow and carotid VTI, represent an attempt to overcome technical limitations of conventional methods, particularly in scenarios of difficult echocardiographic access. Although studies such as the one by Dai et al. (2024) indicate promising performance, including with accuracy comparable to the VTI of LVOT in specific populations, the generalizability of these findings remains limited. The predominance of highly selected populations and the absence of validation in more heterogeneous clinical contexts introduce important biases, in addition to the scarcity of direct comparisons with consolidated methods, which prevents more definitive conclusions about their relative position in clinical practice.

In a comprehensive way, the comparative analysis of the methods reinforces that the evaluation of volume responsiveness through POCUS should not be based on a single isolated parameter, but rather on an integrated and contextualized approach. The choice of the optimal method should consider not only diagnostic accuracy, but also factors such as technical feasibility, clinical context, and operator experience. This perspective is supported by recent reviews that emphasize the need for multimodal interpretation of sonographic findings (NOOR et al., 2025; PICCIONI et al., 2025), reflecting the pathophysiological complexity of critically ill patients.

In addition, the robustness of the available evidence is limited by recurrent methodological aspects. The predominance of observational studies, often single-center and with small sample sizes, combined with the lack of standardization in the criteria for defining volume responsiveness, compromises the comparability between the findings. The use of different reference methods for measuring cardiac output, associated with the lack of systematic control of the operating factor, introduces relevant biases that should be considered in the interpretation of the results.

In view of this set of evidence, the combination of the passive lower limb elevation test and the measurement of the LVOT VTI is the most consistent and physiologically based strategy for predicting volume responsiveness. However, this superiority must be interpreted relatively, since its applicability remains conditioned by technical and clinical factors. In this sense, POCUS should be understood as a central tool, but dependent on integration with the clinical context and other hemodynamic variables.

In summary, the literature does not support the existence of a universally superior method, but points to the relative primacy of approaches based on direct flow measurement, especially when associated with dynamic tests such as PLR. The consolidation of POCUS as a standard in the evaluation of volume responsiveness will depend on methodological standardization, validation in heterogeneous populations and systematic qualification of operators, and the advancement of the area is more related to the critical and contextualized integration of the available tools than to the introduction of new isolated parameters.

The present review has limitations that should be considered. This is a critical narrative review, with greater dependence on the authors' judgment in the selection and interpretation of studies, which implies a potential risk of selection bias. In addition, the included studies present relevant heterogeneity in terms of methodological design, populations evaluated, and clinical contexts, which limits the generalization of the findings. The predominance of observational studies and the lack of standardization in the criteria of volume responsiveness make direct comparisons difficult. In addition, no formal assessment of the risk of bias of the included studies was performed, which represents an additional limitation in the interpretation of the results.

4 CONCLUSION

Point-of-care ultrasound (POCUS) has established itself as a central tool in the assessment of volume responsiveness, reflecting the transition to dynamic and functionally oriented approaches in hemodynamic monitoring. Among the available methods, the relative superiority of techniques based on direct flow measurement stands out, especially the variation of the VTI of the LVOT associated with the passive elevation test of the lower limbs, configuring the most consistent strategy from the physiological point of view.

However, this superiority is conditioned by technical and contextual limitations, which maintains the relevance of more accessible methods, such as the evaluation of the inferior vena cava, in specific scenarios, while more complex approaches have operational restrictions. Thus, the current evidence does not support the existence of a universal method, reinforcing the need for an integrated and contextualized evaluation.

The consolidation of POCUS in clinical practice depends, therefore, on methodological standardization, validation in heterogeneous populations, and operator qualification. In this sense, the advancement of the area lies in the critical integration of available tools, focusing on the optimization of decision-making and clinical outcomes.

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USE OF NITROUS OXIDE IN ELDERLY PATIENTS WITH COMORBIDITIES: AN INTEGRATIVE REVIEW

USO DO ÓXIDO NITROSO EM IDOSOS COM COMORBIDADES: REVISÃO INTEGRATIVA

USO DE ÓXIDO NITROSO EN PERSONAS MAYORES CON COMORBILIDADES: UNA REVISIÓN INTEGRADORA



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ABSTRACT

Nitrous oxide (N₂O) is widely used for conscious sedation in outpatient settings, particularly in dentistry, due to its favorable pharmacological profile, characterized by rapid onset of action, easy titration, and predictable recovery. Its use has been consolidated as an effective strategy for anxiety control, improvement of patient cooperation, and facilitation of clinical procedures with greater comfort and safety. In this context, its application in elderly patients with comorbidities represents a relevant alternative, especially in scenarios that require less invasive approaches and greater physiological stability. This study aimed to evaluate the safety and clinical applicability of N₂O for conscious sedation in this population through an integrative literature review. The literature search was conducted in PubMed/MEDLINE, SciELO, and ScienceDirect databases using descriptors related to “nitrous oxide,” “conscious sedation,” “elderly,” and “comorbidities,” and a total of 12 scientific articles were included. The findings indicate that N₂O presents a consistent safety profile, particularly when used in controlled concentrations and under appropriate monitoring, with clinical risks more strongly associated with patients’ baseline conditions rather than the agent itself. Metabolic effects, especially those related to vitamin B12, should be considered in a contextualized manner, particularly in individuals with pre-existing conditions, and do not constitute an absolute limitation to its use. In addition, advantages such as maintenance of spontaneous ventilation, rapid recovery, and broad clinical applicability are highlighted. In conclusion, N₂O represents a viable, safe, and effective strategy for conscious sedation in elderly patients with comorbidities, provided it is used judiciously, with individualized assessment and structured clinical protocols.

Keywords: Nitrous Oxide. Conscious Sedation. Elderly. Comorbidities. Clinical Safety.

RESUMO

O óxido nitroso (N₂O) é amplamente utilizado na sedação consciente em contextos ambulatoriais, especialmente na odontologia, devido ao seu perfil farmacológico favorável, caracterizado por rápido início de ação, fácil titulação e recuperação previsível. Sua

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utilização tem se consolidado como estratégia eficaz para controle da ansiedade, melhora da cooperação do paciente e viabilização de procedimentos clínicos com maior conforto e segurança. Nesse contexto, sua aplicação em pacientes idosos com comorbidades representa uma alternativa relevante, especialmente em cenários que demandam abordagens menos invasivas e maior estabilidade fisiológica. O presente estudo teve como objetivo analisar a segurança e a aplicabilidade clínica do N₂O em sedação consciente nessa população por meio de uma revisão integrativa da literatura. A busca foi realizada nas bases PubMed/MEDLINE, SciELO e ScienceDirect, utilizando descritores relacionados a “nitrous oxide”, “conscious sedation”, “elderly” e “comorbidities”, sendo incluídos 12 artigos científicos. Os resultados evidenciam que o N₂O apresenta perfil de segurança consistente, especialmente quando utilizado em concentrações controladas e sob monitorização adequada, sendo os riscos clínicos mais associados às condições basais dos pacientes do que ao agente isoladamente. Alterações metabólicas, como aquelas relacionadas à vitamina B12, devem ser consideradas de forma contextualizada, particularmente em indivíduos com condições pré-existentes, não configurando, de maneira isolada, uma limitação absoluta ao seu uso. Além disso, destacam-se vantagens como manutenção da ventilação espontânea, rápida recuperação e ampla aplicabilidade clínica. Conclui-se que o N₂O representa uma estratégia viável, segura e eficaz para sedação consciente em idosos com comorbidades, desde que empregado de forma criteriosa, com avaliação individualizada e adoção de protocolos estruturados.

Palavras-chave: Óxido Nitroso. Sedação Consciente. Idosos. Comorbidades. Segurança Clínica.

RESUMEN

El óxido nitroso (N₂O) se utiliza ampliamente en la sedación consciente en entornos ambulatorios, especialmente en odontología, debido a su favorable perfil farmacológico, caracterizado por un rápido inicio de acción, fácil titulación y recuperación predecible. Su uso se ha consolidado como una estrategia eficaz para el control de la ansiedad, una mejor cooperación del paciente y la realización de procedimientos clínicos con mayor comodidad y seguridad. En este contexto, su aplicación en pacientes ancianos con comorbidades representa una alternativa relevante, especialmente en escenarios que requieren enfoques menos invasivos y mayor estabilidad fisiológica. Este estudio tuvo como objetivo analizar la seguridad y la aplicabilidad clínica del N₂O en la sedación consciente en esta población a través de una revisión integradora de la literatura. La búsqueda se realizó en las bases de datos PubMed/MEDLINE, SciELO y ScienceDirect, utilizando descriptores relacionados con "óxido nitroso", "sedación consciente", "ancianos" y "comorbidades", lo que resultó en la inclusión de 12 artículos científicos. Los resultados muestran que el N₂O presenta un perfil de seguridad consistente, especialmente cuando se utiliza en concentraciones controladas y bajo una monitorización adecuada, y que los riesgos clínicos están más asociados a las condiciones basales de los pacientes que al agente en sí. Las alteraciones metabólicas, como las relacionadas con la vitamina B12, deben considerarse en su contexto, particularmente en personas con afecciones preexistentes, y no constituyen, por sí solas, una limitación absoluta para su uso. Además, se destacan ventajas como el mantenimiento de la ventilación espontánea, la rápida recuperación y su amplia aplicabilidad clínica. Se concluye que el N₂O representa una estrategia viable, segura y eficaz para la sedación consciente en pacientes ancianos con comorbidades, siempre que se utilice con criterio, con una evaluación individualizada y la adopción de protocolos estructurados.

Palabras clave: Óxido Nitroso. Sedación Consciente. Ancianos. Comorbidades. Seguridad Clínica.

1 INTRODUCTION

Nitrous oxide (N_2O) remains one of the most widely used agents in clinical practice for conscious sedation, especially in outpatient and dental settings, due to its favorable pharmacological profile, characterized by rapid onset of action, easy titration, and predictable recovery. At subanesthetic concentrations, N_2O promotes effective sedation associated with the preservation of spontaneous ventilation and protective reflexes, characteristics that make it particularly relevant in clinical scenarios that require safety and physiological control, such as in the care of elderly patients.

Population aging has resulted in a significant increase in the demand for clinical procedures in elderly individuals, often with multiple comorbidities. This population presents important physiological changes, including reduced cardiovascular functional reserve, changes in drug metabolism, and greater neurological vulnerability. In this context, the adoption of sedation strategies that combine efficacy, predictability, and safety becomes essential. N_2O stands out as an advantageous alternative, since it has low hemodynamic impact, rapid reversibility, and good tolerability, characteristics that favor its application in patients with greater clinical complexity (PRASAD et al., 2022).

In addition, the use of N_2O in conscious sedation has been associated with improved patient cooperation, reduced anxiety, and greater comfort during procedures, contributing to the feasibility of interventions that might otherwise require more invasive techniques, such as general anesthesia. Evidence from geriatric dentistry and specialized care services indicates that N_2O can expand access to treatment in populations with physical or cognitive limitations, reducing risks associated with more complex interventions (LIM; BOYLE, 2020). The widespread use of this agent in consolidated health systems, such as the United States, reinforces its clinical viability, especially when associated with standardized protocols, adequate professional training, and continuous monitoring.

From a physiological point of view, the effects of N_2O are well characterized, including its interaction with vitamin B12 metabolism and the possible elevation of homocysteine levels (NAGELE et al., 2013; KIASARI et al., 2014). Such mechanisms should be considered in the clinical evaluation, especially in patients with pre-existing conditions, but their relevance should be interpreted in a contextualized way, since there is no consistent evidence of significant clinical impact on short-term exposures, typical of conscious sedation.

Additionally, studies conducted in elderly populations, although often in anesthetic contexts, indicate that the use of N_2O is not associated with a significant increase in neurological complications, such as delirium or cognitive decline (SPRUNG et al., 2019). These findings reinforce the understanding that the agent, when used appropriately, has a

consistent safety profile, and the clinical outcomes are more strongly influenced by the patient's baseline conditions than by the use of N₂O alone.

In view of this scenario, it is relevant to analyze the use of nitrous oxide not only from the perspective of possible limitations, but also considering its potential as an effective and widely applicable therapeutic tool. Thus, the present study aims to perform an integrative review of the literature to evaluate the safety and clinical applicability of N₂O in conscious sedation in elderly patients with comorbidities, highlighting its benefits, its feasibility and its role in contemporary clinical practice.

2 METHODOLOGY

The present study is an integrative literature review, a methodological design that allows the critical synthesis of evidence from different types of studies, maintaining analytical breadth and enabling the integration of relevant data into clinical practice. This approach was adopted considering the complexity and diversity of the available evidence on the use of nitrous oxide (N₂O) in conscious sedation in elderly patients with comorbidities.

The bibliographic search was conducted in the PubMed/MEDLINE, SciELO and ScienceDirect databases, selected for their relevance and scope in the health area. The search strategy combined controlled descriptors (MeSH) and free terms, structured with Boolean operators. An example of the strategy used in PubMed was: ("nitrous oxide" OR "N₂O") AND ("conscious sedation" OR "inhalation sedation") AND ("elderly" OR "older adults" OR "aged") AND ("comorbidity" OR "chronic disease" OR "systemic disease"). Equivalent strategies were adapted for the other databases, respecting their indexing specificities.

Scientific articles published in indexed journals, available in full, that addressed the clinical use of nitrous oxide in contexts applicable to conscious sedation were included. Studies with clinical and observational designs, and reviews were considered eligible, as long as they presented data related to at least one of the following axes: elderly population, presence of comorbidities, or relevant physiological effects of N₂O. Duplicate studies, exclusively pediatric publications, articles without access to the full text, non-scientific reports, and those whose focus did not directly involve the clinical use of N₂O were excluded.

Considering the multifactorial nature of the theme and the need to broaden the understanding of its clinical aspects, indirect evidence was included through previously defined criteria. Studies investigating the use of N₂O in anesthetic settings or in populations that were not exclusively elderly were considered indirect evidence, as long as they presented physiological, metabolic, cardiovascular, or neurological outcomes with potential

applicability to the context of conscious sedation in older adults with comorbidities. The inclusion of this evidence was conditioned on the presence of relevant pathophysiological mechanisms or on the explicit discussion of clinical factors related to the target population.

The selection process of the studies was carried out in three sequential stages: initial screening by titles, evaluation of abstracts and complete reading of eligible texts. In each stage, the previously established inclusion and exclusion criteria were applied. At the end of the process, 12 scientific articles considered relevant to the theme were included, prioritizing those with greater clinical relevance and methodological consistency.

Data analysis was conducted qualitatively, with organization of findings into thematic axes defined based on the study objectives and the recurrence of the outcomes identified in the literature. The main axes included: clinical safety of N₂O, physiological and metabolic effects, implications in patients with comorbidities, and applicability in the context of conscious sedation. The thematic categorization was carried out through comparative analysis of the results of the studies, allowing the identification of consistent patterns, variations between findings, and aspects relevant to clinical practice. This approach enabled a structured and applied synthesis, in line with the objective of evaluating the role of N₂O as a safe and effective strategy in conscious sedation.

3 RESULTS AND DISCUSSION

The analysis of the included studies shows that nitrous oxide has a broadly favourable safety profile when used in conscious sedation settings, especially at controlled concentrations and under adequate monitoring. Systematic reviews have shown a low incidence of serious adverse events associated with the use of N₂O, which in most cases are mild and self-limited (COLLADO et al., 2007). Although some of this evidence derives from heterogeneous populations, the findings consistently contribute to the consolidation of N₂O as a safe and widely used agent in clinical practice.

In the context of elderly patients, studies conducted in anesthetic settings indicate that the use of N₂O is not associated with a significant increase in neurological complications, such as delirium or cognitive decline (LEUNG et al., 2006; SPRUNG et al., 2019). These results, although often derived from general anesthesia settings, offer relevant support for the understanding that N₂O, when used appropriately, does not constitute a significant independent risk factor. Additional evidence indicates that patient-related factors, such as advanced age, presence of neurodegenerative diseases, and systemic comorbidities, play a more decisive role in clinical outcomes than the sedative agent alone (MANIACI et al., 2025).

The physiological and metabolic effects of N₂O, particularly those related to vitamin B12 inactivation and increased homocysteine levels, are well described in the literature (NAGELE et al., 2013; KIASARI et al., 2014). However, the clinical relevance of these effects should be interpreted in light of the context of use, since most studies demonstrate biochemical changes without direct correspondence with significant clinical adverse events, especially in short-term exposures, as occurs in conscious sedation. Thus, such effects should be understood as conditional factors, especially relevant in patients with pre-existing disabilities or specific clinical conditions.

In addition, recent reviews highlight that vitamin deficiency states may act as predisposing factors for complications in anesthetic contexts (MOGHADDAM et al., 2025). In this sense, prior clinical evaluation plays a fundamental role in the identification of potentially susceptible patients. Clinical reports also describe cases of neuropathy associated with long-term exposure to N₂O (EGAN; STEINBERG; ROSE, 2018), reinforcing the importance of considering the duration and context of use, without compromising its use in controlled protocols of conscious sedation.

The presence of comorbidities is a central element in the assessment of clinical risk in elderly patients. Studies indicate that conditions such as cardiovascular, metabolic, and neurological diseases have a greater association with adverse outcomes than the use of anesthetic agents alone (KINUGAWA et al., 2017). In this context, N₂O should be interpreted as part of an integrated clinical approach, in which preoperative assessment, risk stratification, and appropriate monitoring play a decisive role in the safety of the procedure. Evidence from geriatric dentistry demonstrates that the implementation of structured assessment protocols contributes significantly to the reduction of complications and improvement of clinical outcomes (PRASAD et al., 2022).

From the point of view of clinical applicability, N₂O has relevant advantages that justify its wide use in outpatient settings. Among its main benefits are the rapid onset of action, ease of titration, predictable recovery, and maintenance of spontaneous ventilation, characteristics that are particularly important in elderly patients and those with comorbidities. In addition, its use is associated with improved patient cooperation, reduced anxiety, and greater comfort during procedures (LIM; BOYLE, 2020).

Observational studies also indicate a positive impact on clinical and operational parameters, including recovery time and post-procedure stability (OBEIDAT et al., 2021). The experience accumulated in different health systems, especially in countries such as the United States, reinforces the viability of N₂O as a safe and effective strategy, as long as it is

inserted in well-established protocols, with adequate professional training and continuous monitoring.

Thus, although the literature still has limitations regarding the availability of studies specifically targeting the elderly population with comorbidities in the context of conscious sedation, the body of available evidence consistently supports the use of N₂O as a safe, effective, and widely applicable alternative. Its use, when based on well-defined clinical criteria and individualized evaluation, represents a relevant strategy for performing outpatient procedures with greater safety, predictability, and comfort for the patient.

4 CONCLUSION

The present integrative review demonstrates that nitrous oxide has a consistent safety profile and broad applicability in conscious sedation, including in elderly patients with comorbidities. The findings indicate that, when used in appropriate concentrations and under appropriate monitoring, N₂O maintains favorable characteristics, such as fast action, easy titration, predictable recovery, and preservation of spontaneous ventilation, contributing to the performance of procedures with greater safety and comfort.

The physiological effects associated with its use, particularly those related to the metabolism of vitamin B12, should be considered within an individualized clinical context, especially in patients with pre-existing conditions, and do not constitute, in isolation, an absolute limitation to its use. Likewise, the presence of comorbidities should be interpreted as a factor in the modulation of clinical risk, reinforcing the importance of prior evaluation and the adoption of structured protocols.

The wide use of N₂O in different care contexts and its consolidation in health systems with a high level of organization reinforce its viability as a safe and effective strategy in conscious sedation. In this sense, N₂O represents a relevant tool in contemporary clinical practice, especially in populations that demand less invasive and more predictable approaches.

Thus, it is concluded that the use of nitrous oxide in conscious sedation in elderly people with comorbidities is not only feasible, but also clinically advantageous, as long as it is conducted judiciously, based on individualized evaluation and adequate monitoring.

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USE OF DUAL AND TRIPLE INCRETIN AGONISTS (TIRZEPATIDE AND RETATRUTIDE) IN THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS

USO DOS AGONISTAS DUPLOS E TRIPLOS DE INCRETINAS (TIRZEPATIDA E RETATRUTIDA) NO TRATAMENTO DA OBESIDADE E DIABETES TIPO 2

USO DE AGONISTAS DE INCRETINA DOBLES Y TRIPLES (TIRZEPATIDA Y RETARTIDA) EN EL TRATAMIENTO DE LA OBESIDAD Y LA DIABETES TIPO 2



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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) represent major global public health challenges, requiring more effective and integrated therapeutic strategies. In this context, dual and triple incretin agonists have emerged as innovative approaches by targeting multiple metabolic pathways simultaneously. This study aimed to provide a critical and comparative analysis of tirzepatide and retatrutide in the treatment of obesity and T2DM, based on recent scientific evidence. This narrative critical-analytical review was conducted through a structured search in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Cochrane Library, including studies published between 2016 and 2025. A total of 20 studies were included, comprising clinical trials, systematic reviews, meta-analyses, and narrative reviews. The findings indicate that tirzepatide demonstrates well-established efficacy in glycemic control and weight reduction, whereas retatrutide shows greater potential for weight loss, likely related to increased energy expenditure mediated by glucagon receptor activation. However, this apparent superiority is accompanied by a higher incidence of adverse events and limited long-term evidence. The lack of direct head-to-head clinical trials and methodological heterogeneity across studies limit definitive conclusions regarding their comparative effectiveness. Therefore, although dual and triple incretin agonists represent a significant advancement in the management of obesity and T2DM, further long-term and head-to-head comparative studies are required to define their role in clinical practice.

Keywords: Obesity. Type 2 Diabetes Mellitus. Tirzepatide. Retatrutide. Incretin Agonists.

RESUMO

A obesidade e o diabetes mellitus tipo 2 (DM2) constituem importantes desafios de saúde pública global, demandando abordagens terapêuticas mais eficazes e integradas. Nesse contexto, os agonistas duplos e triplos de incretinas emergem como estratégias inovadoras ao atuarem simultaneamente em múltiplas vias metabólicas. O presente estudo teve como objetivo realizar uma análise crítica e comparativa do uso da tirzepatida e da retatrutida no tratamento da obesidade e do DM2, com base em evidências científicas recentes. Trata-se de uma revisão narrativa de caráter crítico-analítico, conduzida por meio de busca estruturada nas bases PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect e Cochrane Library, contemplando estudos publicados entre 2016 e 2025. Foram incluídos 20 estudos, entre ensaios clínicos, revisões sistemáticas, meta-análises e revisões narrativas. Os resultados indicam que a tirzepatida apresenta eficácia consolidada no controle glicêmico e na redução de peso corporal, enquanto a retatrutida demonstra maior potencial para perda ponderal, possivelmente relacionado ao aumento do gasto energético mediado pela ativação do receptor de glucagon. Entretanto, essa aparente superioridade ocorre em paralelo a maior incidência de eventos adversos e à limitada disponibilidade de evidências de longo prazo. A ausência de estudos comparativos diretos e a heterogeneidade metodológica dificultam a definição do posicionamento ideal dessas terapias. Conclui-se que, embora representem um avanço significativo, os agonistas duplos e triplos de incretinas ainda demandam estudos

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adicionais, especialmente de longo prazo e com comparação direta, para consolidação de seu papel na prática clínica.

Palavras-chave: Obesidade. Diabetes Mellitus Tipo 2. Tirzepatida. Retatrutida. Incretinas.

RESUMEN

La obesidad y la diabetes mellitus tipo 2 (DM2) constituyen importantes desafíos para la salud pública mundial, que exigen enfoques terapéuticos más eficaces e integrados. En este contexto, los agonistas de incretinas duales y triples emergen como estrategias innovadoras al actuar simultáneamente sobre múltiples vías metabólicas. Este estudio tuvo como objetivo realizar un análisis crítico y comparativo del uso de tirzepatida y retatrutida en el tratamiento de la obesidad y la DM2, con base en la evidencia científica reciente. Se trata de una revisión narrativa crítico-analítica, realizada mediante una búsqueda estructurada en las bases de datos PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect y Cochrane Library, que abarca estudios publicados entre 2016 y 2025. Se incluyeron veinte estudios, entre ellos ensayos clínicos, revisiones sistemáticas, metaanálisis y revisiones narrativas. Los resultados indican que la tirzepatida tiene una eficacia consolidada en el control glucémico y la reducción del peso corporal, mientras que la retatrutida demuestra un mayor potencial para la pérdida de peso, posiblemente relacionado con un mayor gasto energético mediado por la activación del receptor de glucagón. Sin embargo, esta aparente superioridad se acompaña de una mayor incidencia de efectos adversos y una disponibilidad limitada de evidencia a largo plazo. La ausencia de estudios comparativos directos y la heterogeneidad metodológica dificultan la definición del posicionamiento ideal de estas terapias. Se concluye que, si bien representan un avance significativo, los agonistas de incretinas duales y triples aún requieren más estudios, especialmente estudios a largo plazo con comparación directa, para consolidar su papel en la práctica clínica.

Palabras clave: Obesidad. Diabetes Mellitus Tipo 2. Tirzepatida. Retatrutida. Incretinas.

1 INTRODUCTION

Obesity and type 2 diabetes mellitus (DM2) are multifactorial chronic conditions whose increasing prevalence imposes substantial challenges to health systems, not only because of their epidemiological magnitude, but also because of the complexity of their pathophysiological mechanisms and the limitation of conventional therapeutic strategies to promote sustained metabolic control. The interdependence between insulin resistance, β cell dysfunction, and neuroendocrine changes in appetite reinforces the need for therapeutic approaches that transcend single targets, since traditional interventions often have limited efficacy and low long-term adherence (ULLAH; TAMANNA, 2025; CARUSO et al., 2024).

In this context, incretin-based therapies have emerged as a relevant advance by integrating glycemic regulation and weight control in the same physiological axis. However, although GLP-1 receptor agonists have partially redefined the clinical management of these conditions, accumulating evidence suggests that modulation of this pathway alone may not be sufficient to achieve optimal metabolic outcomes in a significant portion of patients. This limitation has driven the development of multimodal agonists, whose purpose lies in the simultaneous activation of different hormone receptors, with a potential synergistic effect on multiple metabolic axes (BAILEY; FLATT; CONLON, 2024; GOGINENI et al., 2024).

The introduction of double incretin agonists, particularly tirzepatide, represents a milestone in this paradigm by combining the activation of GLP-1 and GIP receptors. Although the clinical results indicate superiority in glycemic parameters and weight reduction compared to conventional therapies, it remains to be debated whether such benefits reflect a qualitative advance in the modulation of the disease or just a quantitative intensification of already known effects. In addition, the heterogeneity of clinical responses and the need for continuous treatment raise questions about the sustainability of these effects in the real world (LEMPESES; LIU; DALAMAGA, 2022; GALLWITZ, 2022; THIRIVEEDI et al., 2025).

The evolution to triple agonists, such as retatrutide, further amplifies this complexity by incorporating glucagon receptor activation, associated with increased energy expenditure and potential intensification of weight loss. Although initial data suggest superior efficacy, especially in obesity-related outcomes, this advantage occurs in parallel with a still-consolidating safety profile and an increase in the incidence of adverse events. Thus, the comparison between double and triple agonists is not restricted to the magnitude of the effects, but involves a critical analysis of the balance between efficacy, safety, and clinical applicability, especially considering the absence of robust long-term data and the limitation of direct comparative studies (GOLDNEY et al., 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025; SINHA; GHOSAL, 2025).

In addition, issues related to the cost, access, and feasibility of incorporating these therapies into health systems remain relevant barriers, particularly in resource-limited contexts. The current literature, although promising, still lacks consensus regarding the optimal positioning of these drugs in therapeutic algorithms, as well as on their sustained effects on harsh clinical outcomes, such as mortality and macrovascular complications. Thus, the incorporation of these technologies should be interpreted with caution, avoiding premature extrapolations of results obtained in controlled clinical trials (YAN; YU; BLAISE, 2025; MELSON et al., 2024).

In view of this scenario, the present study aims to carry out a critical and comparative analysis of the use of double and triple incretin agonists, with emphasis on tirzepatide and retatrutide, evaluating their impacts on the treatment of obesity and DM2 in the light of the available scientific evidence, as well as discussing their limitations, controversies and implications for contemporary clinical practice.

2 METHODOLOGY

This is a **critical-analytical narrative review**, with a qualitative approach, aimed at the synthesis and comparative analysis of the available evidence on the use of double and triple incretin agonists, with emphasis on tirzepatide and retatrutide, in the treatment of obesity and type 2 diabetes mellitus (DM2).

The bibliographic search was carried out in the **PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and Cochrane Library databases**, covering publications in the period from **2016 to 2025**. Controlled descriptors and free terms combined by Boolean operators were used, including: *"tirzepatide"*, *"retatrutide"*, *"dual incretin agonist"*, *"triple incretin agonist"*, *"GLP-1/GIP receptor agonist"*, *"obesity"* and *"type 2 diabetes"*. The strategy was complemented by a manual search in the reference lists of the selected studies.

Original studies, randomized controlled trials, systematic reviews, meta-analyses, and narrative reviews published in peer-reviewed journals addressing the clinical, metabolic, and safety effects of tirzepatide and/or retatrutide were included. Duplicate studies, publications outside the established period, articles without access to full text or reliable abstract, and those without direct relationship to the topic were excluded. Abstracts of congresses were considered in a complementary way.

At the end of the selection process, **20 studies** were included for analysis, most of which were narrative and systematic reviews, as well as meta-analyses and clinical trials relevant to the topic. The selection of studies was carried out through sequential screening of available titles, abstracts, and full texts.

The included articles were analyzed in terms of design, population characteristics, interventions, clinical outcomes (glycemic control, weight loss, and cardiometabolic parameters), and safety profile. Data synthesis was conducted descriptively, with emphasis on the comparison between double and triple incretin agonists.

The analysis considered the heterogeneity of the designs, populations, and outcomes evaluated, as well as the limited availability of direct comparative studies and long-term data. These aspects were incorporated into the interpretation of the findings, with a focus on the consistency and applicability of the evidence.

3 RESULTS AND DISCUSSION

The analysis of the included studies shows that incretin agonists represent a significant advance in the management of obesity and type 2 diabetes mellitus (DM2), although the magnitude and nature of these benefits vary according to the pharmacological profile of the therapies. In this context, tirzepatide, as a dual agonist of GLP-1 and GIP receptors, demonstrates consistent efficacy in reducing glycated hemoglobin (HbA1c), often higher than 2%, consolidating itself as one of the most potent pharmacological interventions for glycemic control currently available (LEMPESIS; LIU; DALAMAGA, 2022; THIRIVEEDI et al., 2025). This performance is reiterated in meta-analyses, in which tirzepatide is superior to GLP-1 agonists alone and other antidiabetic therapies, suggesting that the simultaneous modulation of multiple incretinal pathways may amplify traditional metabolic effects (YAN; YU; BLAISE, 2025; SINHA; GHOSAL, 2025). However, although retatrutide also promotes relevant glycemic improvement, the available data indicate that its differential does not lie primarily in this outcome, but rather in its broader metabolic action, which limits direct comparisons based exclusively on glycemic parameters and suggests a possible dissociation between glycemic control and other metabolic effects (GOLDNEY et al., 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025).

This distinction becomes even more evident when analyzing weight loss, a central aspect in the contemporary approach to obesity. Tirzepatide promotes significant weight reductions, often greater than 15–20%, approaching results observed in bariatric interventions in certain clinical settings (MELSON et al., 2024; MADSBAD; HOLST, 2025). However, the introduction of retatrutide, with its additional action on the glucagon receptor, seems to further enhance this effect, with initial studies showing losses of more than 20%, possibly related to increased energy expenditure in addition to appetite suppression (GOLDNEY et al., 2025; SINHA; GHOSAL, 2025). Still, this apparent superiority of triple agonists should be interpreted with caution, since the data derive mostly from short-term

studies and highly selected populations, which raises doubts about the sustainability of the effects and their reproduction in real clinical practice scenarios.

The comparison between tirzepatide and retatrutide, therefore, transcends the isolated analysis of specific outcomes and requires an integrated assessment between efficacy and safety. While tirzepatide has a more consolidated profile, with well-documented benefits in both glycemic control and weight reduction, retatrutide emerges as a potentially more potent strategy, but still accompanied by greater clinical uncertainty (GALLWITZ, 2022; ZAFFINA et al., 2023; WINKLER et al., 2023). This difference is also reflected in the profile of adverse events, since, although both therapies share predominantly gastrointestinal side effects, evidence suggests a higher frequency of these events with retatrutide, possibly due to the simultaneous activation of multiple hormonal pathways (BAILEY; FLATT; CONLON, 2024; GOGINENI et al., 2024; SINHA; GHOSAL, 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025). This aspect reinforces the need to weigh incremental efficacy and tolerability, especially considering that therapeutic adherence is a critical determinant of success in the treatment of chronic conditions.

In addition, the absence of randomized controlled trials with direct comparison between double and triple agonists limits the ability to establish unequivocal superiority between these approaches. Although indirect analyses suggest greater weight reduction with retatrutide and robust glycemic performance with tirzepatide, these inferences remain conditioned by methodological limitations, including heterogeneity of studies, differences in the populations evaluated, and variability in the outcomes considered (YAN; YU; BLAISE, 2025; SALHAB et al., 2025). In this scenario, the expansion of the therapeutic arsenal does not necessarily translate into clarity in clinical decision-making, but rather into greater complexity in the individualization of treatment.

This scenario is even more challenging when considering factors extrinsic to pharmacological efficacy, such as cost, access, and large-scale applicability. Studies highlight that, despite the significant metabolic benefits, the incorporation of these therapies may be limited by economic and structural barriers, particularly in health systems with restricted resources (CARUSO et al., 2024; ULLAH; TAMANNA, 2025). In addition, the scarcity of long-term data on relevant clinical outcomes, such as mortality and major cardiovascular events, prevents definitive conclusions about the real impact of these interventions on the natural history of the disease (YAN; YU; BLAISE, 2025; MELSON et al., 2024).

Thus, although double and triple incretin agonists represent a significant evolution in the treatment of obesity and DM2, the current literature still does not support a clear

consensus regarding the ideal positioning of these therapies. Tirzepatide is a more consolidated and predictable option, while retatrutide appears as a promising alternative, but still dependent on more robust evidence to validate its clinical superiority. Thus, the contemporary scenario is characterized less by a replacement of therapeutic paradigms and more by an expansion of possibilities, whose effective application will depend on future evidence that clarifies its real comparative advantages and limitations.

4 CONCLUSION

Double and triple incretin agonists represent a relevant advance in the treatment of obesity and type 2 diabetes mellitus, by promoting integrated metabolic effects that include both glycemic control and weight reduction. Tirzepatide, as a representative of dual agonists, presents more consolidated evidence, with consistent efficacy and a relatively well-established safety profile, positioning itself as a robust therapeutic option in current clinical practice. On the other hand, retatrutide, as a triple agonist, demonstrates superior potential, especially with regard to the magnitude of weight loss, although it is still associated with greater uncertainty regarding its safety and long-term applicability.

The comparative analysis between these therapies shows that the apparent superiority of triple agonists does not translate, so far, into clinical consensus, since the incremental benefits observed occur in parallel with important limitations, including a higher incidence of adverse events, scarcity of long-term data, and absence of clinical trials with direct comparison. In this context, the choice between double and triple agonists should be guided by an individualized evaluation, considering not only efficacy, but also factors such as tolerability, patient profile, and feasibility of continuous use.

In addition, aspects related to cost, access, and sustainability of treatment emerge as critical elements for the incorporation of these therapies in different health systems. The current literature, although consistent in terms of metabolic benefits, still does not allow us to clearly establish the impact of these interventions on more relevant clinical outcomes, such as mortality and cardiovascular complications, which limits the definition of their definitive role in therapeutic algorithms.

Thus, multimodal incretin agonists should be understood as part of an expanding therapeutic scenario, in which the increase in available options does not necessarily imply an immediate replacement of existing approaches, but rather greater complexity in clinical decision-making. Future studies, especially direct comparative clinical trials and long-term investigations, will be key to elucidate the relative advantages between double and triple

agonists and consolidate their position in the treatment of obesity and type 2 diabetes mellitus.

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INCIDENCE OF CERVICAL CANCER IN THE STATE OF PARAÍBA IN 2023 AND ITS CORRELATION WITH CYTOPATHOLOGICAL EXAMINATION

INCIDÊNCIA DE CÂNCER DO COLO DO ÚTERO NO ESTADO DA PARAÍBA NO ANO DE 2023 E SUA CORRELAÇÃO COM O EXAME CITOPATOLÓGICO

INCIDENCIA DE CÁNCER DE CUELLO UTERINO EN EL ESTADO DE PARAÍBA EN 2023 Y SU CORRELACIÓN CON EL EXAMEN CITOPATOLÓGICO



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ABSTRACT

Cervical cancer is caused by the Human Papillomavirus (HPV), although it is preventable through vaccination, especially serotypes 16 and 18, due to its virulence. This article aims to outline the epidemiological profile of cervical cancer in 2023 and its prospects. This is an exploratory, retrospective epidemiological study with a quantitative approach. The results were collected from data from INCA (National Cancer Institute), whose reports are issued biennially. A higher incidence was observed in the North and Northeast regions, with Paraíba accounting for 10.5% of cases and the Northeast 13.8% of cases. Cervical cancer detection is related to Pap smear or cytopathological testing, which should reach 100% of women aged 25 to 64, i.e., the most vulnerable population. The study resulted in a coverage rate of 83.23, and, because of its greater screening coverage, it has a lower cervical cancer mortality rate, since detection is linked to early treatment. It can be concluded that cervical cancer is a major public health problem; therefore, healthcare professionals should encourage patients to undergo this screening annually for early detection of HPV-related lesions and cancers.

Keywords: Cervical Cancer. Cytopathological. HPV. Women.

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RESUMO

O câncer de colo de útero é causado pelo Papiloma Vírus Humano (HPV), apesar de prevenível por vacinação, sobretudo os sorotipos 16 e 18, em virtude de sua virulência. O presente artigo tem como objetivo delinear o perfil epidemiológico do câncer do colo do útero no ano de 2023 e suas perspectivas. Trata-se de um estudo exploratório, retrospectivo epidemiológico, numa abordagem quantitativa. Os resultados foram colhidos a partir dos dados do INCA (Instituto Nacional do Câncer), cujo os relatórios são emitidos bienalmente, observou-se uma maior incidência nas regiões norte e nordeste, onde a Paraíba representa 10,5 de prevalência de casos e o nordeste 13,85. A detecção do câncer do colo de útero está relacionada a realização do exame Papanicolau ou citopatológico, que deverá alcançar 100% das mulheres na faixa etária entre 25 a 64 anos, ou seja, a população mais vulnerável. A pesquisa resultou em uma cobertura de 83,23 e, por ter maior cobertura de exames, possui menor coeficiente de mortalidade de Câncer de colo de útero, uma vez que a detecção está relacionada ao tratamento precoce. Pode-se concluir que o câncer de colo do útero é um importante problema de saúde pública, portanto, os profissionais da rede de atenção à saúde devem motivar os pacientes a realização anual deste exame a fim de detecção precoce de lesões e cânceres relacionados ao vírus do HPV.

Palavras-chave: Câncer de Colo do Útero. Citopatológico. HPV. Mulheres.

RESUMEN

El cáncer de cuello uterino es causado por el Virus del Papiloma Humano (VPH), aunque es prevenible mediante vacunación, especialmente los serotipos 16 y 18, debido a su virulencia. Este artículo tiene como objetivo describir el perfil epidemiológico del cáncer de cuello uterino en 2023 y sus perspectivas. Se trata de un estudio epidemiológico exploratorio y retrospectivo, con un enfoque cuantitativo. Los resultados se obtuvieron de datos del INCA (Instituto Nacional del Cáncer), cuyos informes se publican cada dos años. Se observó una mayor incidencia en las regiones Norte y Noreste, donde Paraíba representa una prevalencia del 10,5% de los casos y el Noreste del 13,85%. La detección del cáncer de cuello uterino está relacionada con la realización de la prueba de Papanicolaou o el examen citopatológico, que debería alcanzar al 100% de las mujeres de 25 a 64 años, es decir, la población más vulnerable. La investigación arrojó una cobertura del 83,23%, y debido a esta mayor cobertura de exámenes, se observa una menor tasa de mortalidad por cáncer de cuello uterino, ya que la detección está relacionada con el tratamiento precoz. Se puede concluir que el cáncer de cuello uterino es un problema de salud pública importante; por lo tanto, los profesionales de la salud deben alentar a las pacientes a someterse a este examen anualmente para la detección temprana de lesiones y cánceres relacionados con el virus del VPH.

Palabras clave: Cáncer de Cuello Uterino. Citopatología. VPH. Mujeres.

1 INTRODUCTION

Despite the advances obtained through prevention campaigns and the expansion of actions aimed at comprehensive women's health care within the scope of Primary Health Care (PHC), it is essential to highlight the institutional efforts undertaken to improve public policies aimed at combating cervical cancer in Brazil. In this context, several intersectoral meetings were held with the aim of discussing more effective strategies for prevention, early diagnosis, and management of the disease, culminating in the revision of SAS Ordinance No. 497, of 2016. This review reflected the need to strengthen multiprofessional integration in cervical cancer control actions, recognizing that the approach to this disease requires the articulated action of different health professionals, including physicians, nurses, community agents, psychologists and others in all stages of care.

Cervical cancer has as its main etiological agent the Human Papillomavirus (HPV), whose infection is considered one of the most common among sexually transmitted diseases. Among the numerous subtypes of the virus, serotypes 16 and 18 stand out for being the most oncogenic, being associated with most cases of invasive cervical neoplasms.

This study is justified by the epidemiological and social relevance of cervical cancer and the need to understand its dynamics in the regional context, especially in the state of Paraíba. The investigation aims to describe the incidence of registered cases of cervical cancer in 2023 and to establish its correlation with the coverage of cytopathological tests performed in the female population. Such an analysis is essential to assess the effectiveness of screening and prevention strategies, as well as to identify possible gaps in the supply of and access to primary health care services.

In view of the above, the following guiding question emerges: what is the incidence of cervical cancer cases in the state of Paraíba in the year 2023? This question becomes particularly relevant, considering the strategic role of epidemiological surveillance and Primary Health Care (PHC) in the early detection and control of neoplasms with the greatest impact on women's health. The present study aims to outline the incidence of cervical cancer cases in the state of Paraíba during the year 2023, establishing an updated panorama that enables the understanding of the distribution of the disease in the state territory. Based on this analysis, it is intended to support the decision-making process of health managers, providing qualified information that guides the planning of more effective actions directed to the real needs of the population.

The methodological approach adopted in this study is based on a retrospective epidemiological approach, focused on the analysis of data regarding the incidence of cervical cancer. This approach allows the observation and interpretation of previously recorded

information, enabling the identification of temporal patterns and trends relevant to disease monitoring. Data collection was carried out through consultations with the official databases of the José Alencar Gomes da Silva National Cancer Institute (INCA), a reference body of the Ministry of Health responsible for the consolidation and dissemination of epidemiological information on malignant neoplasms in Brazil. For this study, information from the biennial reports made available by INCA was used, thus configuring the use of secondary sources of data.

The introduction presents an in-depth contextualization of the investigated problem, emphasizing the scientific and social relevance of the theme, as well as the justification that underlies its choice. In this section, the general and specific objectives of the study are outlined, in addition to the exposition of the main methodological approaches and theoretical references that guide the analysis. In sequence, the theoretical foundation includes a critical review of the pertinent literature, addressing the central concepts, recent scientific evidence and epidemiological aspects related to the incidence, spatial distribution and factors associated with cervical cancer, with emphasis on the context of the state of Paraíba. This section aims to support the theoretical argumentation and situate the study in the field of current scientific knowledge. The section referring to methodological procedures describes in detail the study design, the data sources used, the criteria for selecting information and the analysis techniques used, ensuring transparency and reproducibility of the results obtained. Subsequently, the results and the discussion **are presented**, which bring together an interpretative and critical analysis of the data collected, enabling the identification of trends, patterns and implications for public health policies. This stage aims to establish a dialogue between the empirical findings and the existing scientific literature, contributing to the advancement of knowledge on the subject. Finally, the study concludes with the final considerations, which summarize the main conclusions, recognize the limitations of the research and indicate perspectives for future investigations. This section also highlights the practical and theoretical implications of the results, especially with regard to the improvement of cervical cancer prevention, control, and surveillance actions.

This article aims to improve strategies for preventing and reducing morbidity and mortality from cervical cancer, promoting the strengthening of surveillance, alert, and response related to this disease.

2 CONCEPTUAL THEORETICAL FRAMEWORK

Cervical cancer is one of the most relevant global public health problems, due to its high incidence and its social and economic impact, especially in low- and middle-income

countries. The World Health Organization (WHO) recognizes this disease as widely preventable through effective screening and immunization strategies against the Human Papillomavirus (HPV), its main etiological agent. In this sense, the WHO has set as a goal, within the framework of its Global Strategy for the Elimination of Cervical Cancer, the reduction of the incidence rate of the disease to less than 4 cases per 100,000 women per year worldwide, a milestone that, if achieved, will represent the elimination of cervical cancer as a public health problem (Boon et al, 2022).

In the Brazilian context, the scenario is still challenging. According to the José Alencar Gomes da Silva National Cancer Institute (INCA), it is estimated that approximately 17,000 new cases of cervical cancer will emerge per year in the period from 2023 to 2025, corresponding to an incidence rate of about 13.3 cases per 100,000 women. These numbers place this neoplasm among the most frequent types of cancer in the female population, especially in the North and Northeast regions, where there are greater inequalities in access to health services, lower HPV vaccination coverage, and low adherence to cytopathological screening (Brasil, 2024).

The persistence of high rates in the country reflects not only structural and organizational challenges of the health system, but also social determinants, such as conditions of vulnerability, low schooling, and limitations in access to information and prevention services. Thus, understanding the magnitude and distribution of cases is essential for planning public policies, allowing resources to be directed, expanding vaccination coverage, and strengthening screening and early diagnosis actions (Caminha et al, 2022).

Cervical cancer has as its main etiological agent the Human Papillomavirus (HPV), a virus of high prevalence worldwide, responsible for one of the most common sexually transmitted infections (STIs) among men and women. It is estimated that most sexually active individuals will be exposed to HPV at some point in their lives, although in most cases the infection is transient and spontaneously eliminated by the immune system. However, when the infection persists, especially by the subtypes of high oncogenic risk, there is a greater probability of developing precursor lesions and, eventually, cervical cancer. HPV serotypes 16 and 18 are recognized as the main responsible for cases of cervical neoplasia, being detected in about 70% of cervical cancers worldwide. Other genotypes, such as types 31, 33, 45, 52 and 58, also have oncogenic potential, although less frequently (Brasil, 2024).

Cervical cancer prevention can be carried out at different levels. Primary prevention involves vaccination against HPV, an effective and safe strategy, incorporated into the National Immunization Program (PNI) since 2014, with free offer for girls and boys aged 9 to

14 years. The vaccine confers protection against the main oncogenic serotypes and has proven to be essential to reduce the incidence of persistent infections and precursor lesions. In addition to immunization, the consistent use of condoms during sexual intercourse is a complementary measure that contributes to reducing the risk of transmission, although it does not completely eliminate the possibility of infection, given the contact between uncovered areas. Secondary prevention, on the other hand, involves **cytopathological screening (Pap smear)**, which allows the early detection of cervical cell changes before progression to invasive cancer. The periodicity and age range recommended by the Ministry of Health aim to balance the effectiveness of screening and the rational use of health resources (Glehn et al, 2023).

Cervical cancer ranks third among the most incident types of cancer in women in Brazil, surpassed only by breast cancer and colon and rectal cancers. This position highlights the epidemiological and social relevance of this neoplasm, which continues to represent an important challenge for the public health system, especially in regions with lower levels of socioeconomic development and limitations in access to preventive actions (Caminha et al, 2022).

Between 2012 and 2023, a trend of reduction in the incidence and mortality from cervical cancer was observed in the country, reflecting more effective public policies aimed at cytopathological screening and the implementation of vaccination against the Human Papillomavirus (HPV). However, in parallel with this reduction, there was a significant increase, about 46%, in the number of women who underwent outpatient procedures related to the disease within the scope of the Unified Health System (SUS) (Brasil, 2024).

In 2022, outpatient procedures associated with lesions resulting from HPV infection reached approximately 50,000 records, while at the hospital level, approximately 19,000 visits related to the same etiology were recorded. These numbers demonstrate not only the magnitude of the clinical impact of HPV, but also the growing demand for specialized services in the SUS, both for the diagnosis and treatment of intraepithelial lesions and for the management of more advanced cases of cervical neoplasia (Caminha et al, 2022).

The increase in the number of procedures performed can be interpreted from two complementary perspectives: on the one hand, it reflects the advance of screening and surveillance policies, with earlier detection of precursor lesions; on the other hand, it evidences the persistence of regional and socioeconomic inequalities which hinder women's regular access to preventive actions, contributing to the maintenance of a significant contingent of cases diagnosed in more advanced stages (Farrara et al, 2022).

Cervical cancer control actions in Brazil follow standardized protocols, since the high morbidity and mortality rates associated with the disease require organized and effective coping strategies. The need to standardize screening, diagnosis, and treatment practices has led to the formulation of specific and nationwide public policies (Oliveira et al, 2022).

The first structured initiative took place between 1972 and 1975, with the National Cancer Control Program, implemented by the Ministry of Health, which represented a milestone in the organization of actions aimed at prevention and early detection. Subsequently, in 1998, the National Cervical Cancer Control Program, known as the Viva Mulher Program, was instituted, which significantly expanded access to Pap smears and strengthened health education actions aimed at the female population (Brasil, 2024).

In 2011, the Brazilian Guidelines for Cervical Cancer Screening were published, a reference document that systematizes technical recommendations on the priority age group, frequency of exams and conducts in the face of altered results. These guidelines were updated in 2016, based on recent scientific evidence, incorporating advances such as the use of HPV detection testing and integrated surveillance and monitoring strategies (Brasil, 2024).

The organization of integrated actions aimed at the control of cervical cancer, combined with the intensification of activities in Primary Health Care (PHC), considered the main gateway to the Unified Health System (SUS), has proven to be fundamental for the early detection of precursor lesions and for the adequate and timely referral of patients. Through articulated action between professionals from different areas, the implementation of standardized protocols, and the expansion of the coverage of Pap smears, it becomes possible to identify cervical changes in the early stages, significantly increasing the chances of effective treatment and reduction of complications (Ferrara et al, 2022).

However, despite the advances achieved in prevention, screening, and treatment strategies, cervical cancer remains one of the main causes of female morbidity and mortality in Brazil, especially in populations with less access to health services or in regions characterized by socioeconomic inequalities. This scenario shows that, although public policies have promoted improvements in care, structural, organizational, and social challenges persist that limit the full effectiveness of disease control actions (Jardim et al, 2022).

In Brazil, there has been a stationary trend in the mortality coefficient for cervical cancer since 2014, a phenomenon that may be related to demographic and epidemiological factors, such as population aging and the epidemiological and demographic transition. characterized by the increased prevalence of chronic and degenerative diseases replacing

traditional infectious causes. This scenario highlights the complexity of disease control, which involves not only direct health interventions, but also interaction with broader social and structural processes (Madeiro et al, 2022).

It is important to highlight that significant regional disparities persist, both in the coverage of the Pap smear test and in the incidence and mortality coefficients. Such inequalities are closely linked to factors such as access to health services, implementation and effectiveness of public policies for prevention and screening, as well as social determinants, including schooling, income, housing conditions, and geographic location. These elements can directly influence early detection, appropriate referral, and timely treatment of patients, affecting the effectiveness of disease control actions (Maira et al, 2022).

In 2025, the RT-PCR test for the detection of Human Papillomavirus (HPV) DNA was implemented, considered a more sensitive and effective tool in the identification of high-risk infections, compared to traditional cytopathological screening methods. The test was proposed to be performed every five years, presenting not only greater diagnostic accuracy, but also lower operational costs, which favors its large-scale adoption within the scope of the Unified Health System (SUS). The expectation is that, in the medium and long term, RT-PCR will progressively replace the cytopathological test, consolidating itself as the main method of cervical cancer screening. This initiative reduces the achievement of the diagnosis from 25 to 5 days after the test is performed (Pathah et al, 2022).

The preparation of the technical guidelines for the implementation of the test was coordinated by the José Alencar Gomes da Silva National Cancer Institute (INCA) and had the participation of 81 specialists representing five secretariats of the Ministry of Health, as well as the Pan American Health Organization (PAHO). In addition, 37 institutions from all regions of the country, including universities, reference hospitals, specialized medical societies, and civil society organizations, contributed with technical knowledge, scientific evidence, and practical recommendations to ensure the feasibility and effectiveness of the strategy (WHO, 2024).

3 MATERIAL AND METHOD

This is a retrospective, exploratory and cross-sectional study, with a quantitative approach. The objective is to evaluate the incidence of cervical cancer in the state of Paraíba, in 2023, and to analyze its correlation with the coverage of cytopathological tests performed in the same period. The investigation focused on new cases of cervical cancer registered by the National Cancer Institute (INCA), considering that this neoplasm represents a relevant

public health problem, due to its high morbidity and mortality among women (Timoteo et al, 2020).

The data used in this study were obtained from the National Cancer Institute (INCA), the agency responsible for registering and monitoring cervical cancer cases in Brazil, including those referring to the year 2023. INCA publishes biennial reports on cancer registries, constituting an essential source for the evaluation of morbidity and mortality and its trends over time. In addition, it plays a strategic role by providing a centralized platform for the collection, storage, and analysis of epidemiological information related to this neoplasm, contributing to the planning and implementation of public policies aimed at cancer prevention and control (INCA, 2023).

The choice of the National Cancer Institute (INCA) as a data source is justified by its comprehensiveness, reliability, and national and international recognition in epidemiological investigations. The system provides a comprehensive and detailed set of information on cancer cases registered throughout the country, including patient demographic data, clinical and histopathological characteristics of tumors, types of treatment instituted, and respective clinical outcomes (Brasil, 2023).

Thus, the data from the National Cancer Institute (INCA) constitute a solid and comprehensive basis for the analysis of the epidemiological profile of cancer in the period under study. This information enables an in-depth understanding of morbidity patterns and epidemiological trends related to the disease, both in the context of the state of Paraíba and at the national level, supporting the planning and evaluation of actions aimed at the prevention, early diagnosis, and control of cervical cancer (Timoteo et al, 2020).

After the collection stage, the data were organized, treated and later used to calculate the incidence of cervical cancer. The estimate of this incidence was based on official information provided by the National Cancer Institute (INCA), constituting a robust methodological basis for the presentation, interpretation, and discussion of the results. This procedure enabled a thorough analysis of the frequency and spatial distribution of cases registered in the state of Paraíba during the year 2023, contributing significantly to the understanding of the profile and epidemiological behavior of the disease in the period investigated (Roquayrol, 2018).

The data below were obtained from the incidence equation:

Incidence = Number of new cases of the disease/total population at risk x1000.

The calculation of incidence is a fundamental statistical method to measure the proportion of individuals in a given population who develop a specific condition in a defined period. It is an essential epidemiological measure for understanding the dynamics of disease

occurrence, allowing the evaluation of the behavior and magnitude of a disease in the context of public health. Estimating the incidence is, therefore, an indispensable instrument to support the formulation of public policies, the planning of health services, and the evaluation of the effectiveness of the interventions implemented (Roquayrol, 2018).

4 RESULTS

Data collection was carried out based on information made available by the National Cancer Institute (INCA), referring to the year 2023, with a specific focus on the incidence of cervical cancer. These data were carefully extracted and organized in a table, in order to enable a more accurate statistical analysis. After the tabulation stage, the equation previously described was applied to calculate the incidence of cases in the study period. It is important to emphasize that, as it is a secondary data source, the study has some limitations, such as the impossibility of accessing the exact number of registered cases. However, these data allow us to outline the epidemiological profile of the disease, contributing to the evaluation of control and prevention actions aimed at cervical cancer. (INCA, 2023).

This statistical analysis process made it possible to obtain detailed insights into the incidence of cervical cancer in the state of Paraíba in 2023. From the tabulated data, three graphs were prepared that illustrate, in a clear and objective way, the main trends and patterns identified. These visual instruments are essential for understanding variations in the incidence of the disease, allowing the assessment of the trend of cases over the analyzed period, as well as supporting the identification of possible risk factors and the definition of more appropriate control and prevention measures (Sing et al, 2022).

In the context of public health, these results play a fundamental role in the design of intervention and control strategies, especially aimed at the regions and population groups most vulnerable to the disease. The graphical representation of data, in this sense, not only facilitates the interpretation and analysis of results, but also constitutes an effective tool for communicating scientific evidence to health professionals, managers, and public policy makers, favoring more assertive and evidence-based decision-making (Vale et al, 2021).

The following tables present the detailed results obtained from the incidence equations, enabling an accurate analysis of both the occurrence of cervical cancer cases and the profile of the cytopathological tests performed. It is important to highlight that this neoplasm represents a relevant public health problem, being responsible for high morbidity and mortality rates among women. On the other hand, it is a condition that can be largely prevented, as long as effective screening actions, health education, and expanded access

to primary care services are implemented, benefiting the female population in an equitable way (Santos et al, 2023).

The human papillomavirus (HPV) is recognized as the etiological agent responsible for approximately 99% of cervical cancer cases. The Pap smear, widely used in the public health system, stands out for being a simple, low-cost and effective procedure in the early detection of precursor lesions. The implementation and expansion of this test in primary care, aimed at the target population, have contributed significantly to the reduction of the number of advanced cases, representing an important advance in tackling this relevant public health problem (Brasil, 2022).

Cervical cancer screening represents a key strategy for reducing mortality and can effectively save lives. In this context, the commitment of health professionals and public managers is essential to strengthen disease prevention and control actions. Considering that the evolution of cervical cancer occurs slowly and gradually, there is a wide window of opportunity for effective interventions, both in the political sphere, through the formulation and implementation of public policies, and in the care sphere, through the early detection and timely treatment of precursor lesions (Oliveira et al, 2022).

The strengthening of the health care network is an essential element for reducing the incidence and mortality rates for cervical cancer, by promoting comprehensive, continuous and equitable care for women. This consolidation of the network involves the articulation between the different levels of primary, secondary and tertiary care, ensuring timely access to screening, diagnosis, treatment and rehabilitation services. In addition, the improvement of the technical capacity of the teams, the investment in the continuing education of professionals, and the expansion of health surveillance actions are fundamental strategies to ensure the effectiveness of public policies and compliance with the principles of the Unified Health System (SUS), especially those of universality, equity, and comprehensiveness of care (Jardim et al, 2022).

Brazil has intermediate incidence and mortality rates for cervical cancer (CC) compared to other countries, but with marked regional and interstate inequalities. It is observed that the North and Northeast regions concentrate the highest rates of the disease, while the South and Southeast have significantly lower values. This disparity may be directly related to the social determinants of health, since territories with a lower Human Development Index (HDI) tend to have more precarious conditions of access to health services, lower coverage of Pap smear screening, deficiencies in sanitary infrastructure, and educational and socioeconomic inequalities (Meira et al, 2022).

Table 1 presents the distribution of cervical cancer (CC) incidence in the states of the Northeast region during the year 2023, considering both the absolute number of cases and the inference-adjusted values, calculated using the SPSS software. The first column of the graph represents the total number of cases recorded for the year, providing an overview of the volume of new diagnoses. The second column shows the adjusted values after the application of the prevalence equation, allowing a more refined estimate of the incidence. The joint analysis of this information offers a comprehensive understanding of the epidemiological situation, making it possible to identify trends, patterns, and potential regional disparities in CC cases over the study period.

When analyzing the table presented, it can be seen that the state of Paraíba recorded the lowest incidence of cervical cancer cases among the states in the Northeast region in 2023. This result suggests that the prevention, tracking and coping actions of the disease implemented in the state have obtained positive effects. Such measures include expanding the coverage of Pap smears, health education aimed at the female population, awareness campaigns on risk factors, and vaccination against HPV (Brasil, 2023).

Table 1

Distribution of CC incidence in the northeastern states

Northeast	Cases	Detection tee	Incidence
Alagoas	370	20,91	18,54
Bahia	1.160	14,93	11,84
Ceará	1.030	21,49	13,97
Maranhão	800	21,71	21,13
Paraíba	290	13,42	10,5
Pernambuco	770	15,18	12,14
Piauí	360	21,19	15,23
Rio Grande do Norte	280	15,33	12,06
Sergipe	220	17,71	13,85

Source: Ministry of Health

Table 2 shows the percentage of Pap smears performed annually in the states of the Northeast region. When analyzing the data, a trend of progressive increase in the coverage of these tests is observed over the period studied. This growth may be related to different factors, among which the financial incentive promoted by the federal government, the strengthening of public health policies, and the adequate financing of procedures, which enable the expansion of access to screening services (INCA, 2023).

In addition, the expansion of the coverage of the Pap smear test reflects the effort of the state and municipal health networks to implement actions for the prevention and early detection of cervical cancer. The increase in the performance of these tests is a positive

indication that more women are being monitored, enabling the early identification of precursor lesions and, consequently, the reduction of incidence and mortality from the disease. Thus, the analysis of these data is essential to evaluate the effectiveness of screening strategies, identify regional gaps, and support the formulation of more equitable and effective public policies. See table 2.

Table 2

Percentage of tests performed per year in the northeastern states

STATES	2018	2019	2020	2021	2022
ALAGOAS	78,51	79,45	80,64	81,69	83,56
BAHIA	78,81	79,35	80,9	81,62	82,48
CEARÁ	79,35	78,97	80,83	82,35	83,5
MARANHÃO	77,67	78,24	79,94	81,31	82,14
PARAÍBA	78,79	79,59	81,06	82,12	83,23
PERNAMBUCO	78,8	79,25	80,56	80,94	81,43
PIAUI	80,95	80,67	81,97	84,35	85,26
RIO GRANDE DO NORTE	79,02	79,46	80,64	81,8	82,4
SERGIPE	76,03	77,16	79,35	80,53	81,54

Source: Ministry of Health

When analyzing the graph presented, it was observed that the state of Paraíba stands out as the third state with the highest percentage of coverage of cytopathological tests in the region. At the same time, it was recorded that Paraíba has one of the lowest incidences of cervical cancer (CC) among the states analyzed. This relationship suggests a possible correlation between the wide coverage of the tests and the reduction in the incidence of the disease, indicating that the effectiveness of screening and prevention strategies may have contributed to the early detection of precursor lesions of CC and, consequently, to the reduction in the occurrence of advanced cases (Brasil, 2024).

In addition, the high coverage of Pap smears shows the positive impact of public health policies aimed at preventing CC, reinforcing the importance of maintaining and expanding these actions in the state. Such data can serve as a reference for comparative analysis with other states in the region, enabling the identification of good practices and the improvement of strategies to control and cope with this neoplasm.

The state of Maranhão had the highest incidence of cervical cancer (CC) among the states analyzed, despite having registered a coverage of cytopathological tests above 80%. This data indicates that, although early detection through screening is widely performed, other factors may be influencing the high occurrence of the disease. Among these factors, social determinants stand out, which include socioeconomic conditions, limited access to quality health services, educational inequalities, geographic and cultural barriers, as well as lifestyle habits and behavioral factors of the population.

This situation shows that the coverage of tests, although essential, is not sufficient in isolation to reduce the incidence of cervical cancer. It is necessary to consider integrated strategies that combine effective screening with public policies that act on the social determinants of health, promoting health education, population awareness, and improvements in access to and quality of cancer care. Thus, the analysis suggests that coping with cervical cancer requires a multifactorial approach, which goes beyond the simple performance of tests, contemplating preventive, educational and structural actions to effectively reduce the incidence of the disease.

5 DISCUSSION

The high morbidity and mortality rate for cervical cancer (CC) remains an important indicator of public health, being associated with several behavioral and biological risk factors, such as early initiation of sexual life, multiplicity of sexual partners, smoking, low parity, persistent infections by the HPV virus and unfavorable socioeconomic conditions. These elements contribute to the increased vulnerability of the female population to the development of the disease and to the progression of precursor lesions when there is no early detection (Pathah et al, 2022).

However, it is observed that, with the advancement of public health policies aimed at the prevention and screening of CC, such as the expansion of the coverage of Pap smears, the implementation of HPV vaccination programs, and educational campaigns on sexual and reproductive health, morbidity and mortality rates have shown a downward trend. This decrease highlights the effectiveness of integrated prevention and control strategies, reinforcing the importance of continuous investments in health promotion actions, education, and access to quality services, which act in an articulated way on risk factors and social determinants of the disease (Jardim et al et al, 2022).

Table 1 shows that the state of Paraíba had one of the lowest incidence rates of cervical cancer (CC) compared to the other states in the Northeast region, while Maranhão recorded the highest rate among the states analyzed. This discrepancy, even among geographically close states, suggests that several factors can influence the occurrence of the disease, including the management of public health policies, the Human Development Index (HDI), as well as other social and economic determinants, such as access to health services, education, income conditions, and sanitary infrastructure (Boon et al, 2022).

Despite these regional differences, it is possible to observe a positive trend in all states in the region: coverage in the performance of Pap smears increased throughout the time series analyzed, comprising the years 2018 to 2022. This increase reflects the impact of CC

screening and prevention policies, evidencing continuous efforts to expand access to early detection and reduce morbidity and mortality associated with the disease (Wirtz et al, 2022).

The joint analysis of these data reinforces the importance of considering both the effectiveness of screening strategies and social determinants in the formulation of public policies. While the increase in test coverage contributes to the reduction of risk and mortality from CC, the differences observed between the states indicate that complementary measures, aimed at social equity and the improvement of living conditions, are essential for the full effectiveness of preventive health actions (Madeiro et al, 2022).

The differences in the incidence of cervical cancer (CC) between the states are strongly related to social determinants, and it is observed that regions with lower Human Development Index (HDI) tend to have a higher incidence of the disease. This shows that socioeconomic, educational, and access to health services inequalities play a central role in women's vulnerability to CC (Ferrara et al, 2022).

It is observed that the largest number of cases is concentrated in the municipality of João Pessoa and its metropolitan region, which may be directly related to the higher population density of these areas. More populous municipalities tend to have a higher absolute number of cases, both because of the population's greater exposure to risk factors and because of the greater installed capacity of health services, which favors the detection, registration and notification of diseases. In addition, the centralization of referral services in the capital may contribute to the concentration of records, since individuals from other municipalities often seek care in these places (SES/PB, 2024).

In addition, individual factors, such as gender, age group, education level, income, lifestyle habits, and conditions of access to health services, directly influence the probability of late diagnosis, which is one of the main challenges for effective control of the disease. Diagnosis in advanced stages is associated with worse clinical outcomes and higher morbidity and mortality, reinforcing the need for strategic preventive actions (Madeiro et al, 2022).

Thus, making the population aware of the importance of regular Pap smears and the adoption of preventive measures becomes paramount. Educational campaigns, community health programs, and strategies to promote sexual and reproductive health can contribute significantly to early detection, reducing the number of late diagnoses and, consequently, the incidence and mortality associated with CC (Caminha et al, 2022).

The study was carried out with the objective of analyzing the factors associated with late diagnosis of cervical cancer (CC) from the hospital records of women aged between 18 and 99 years, in the period from 2006 to 2015, obtained through the Integrator of Hospital

Cancer Records. To complement the analysis, contextual variables related to socioeconomic aspects and health infrastructure were collected from the Atlas of Human Development, the National Registry of Health Establishments (CNES), and the Outpatient Information System (SIA) (Brasil, 2024).

The results indicated that the prevalence of diagnosis at an advanced stage was 48.4%. Significant associations were identified with several individual and contextual factors. Among the individual factors, older age stood out (PR 1.06; CI 1.01–1.10), black, brown, and indigenous race/skin color (PR 1.04; CI 1.01–1.07), lower levels of education (PR 1.28; CI 1.16–1.40) and absence of a marital partner (PR 1.10; CI 1.07–1.13). Among the factors related to access to and use of health services, referral by public route (PR 1.07; CI 1.03–1.11) and the lowest rate of Pap smears (PR 1.08; CI 1.01–1.14) were also significantly associated with late diagnosis (INCA, 2023).

These findings indicate that diagnosis in advanced stages of CC is related both to individual factors, such as age, education, race, and marital status, and to contextual determinants linked to access to and quality of health services. The identification of these factors reinforces the need for integrated prevention and screening strategies, especially aimed at the most vulnerable population groups, in addition to strengthening public policies that expand access to early detection exams and ensure equity in cancer care (Sing et al, 2022).

Cervical cancer (CC) has a long natural history, characterized by slow development that offers several opportunities for intervention through primary and secondary prevention strategies. Primary prevention primarily involves vaccination against the human papillomavirus (HPV), while secondary prevention focuses on early detection of precursor lesions through cytopathological examinations and HPV testing, allowing intervention before progression to invasive stages of the disease (Pathah et al, 2022).

Recognizing the relevance of cervical cancer as a public health problem, the Pan American Health Organization (PAHO) developed and approved, in 2018, the Plan of Action for the Prevention and Control of Cervical Cancer 2018–2030. This plan proposes an integrated set of actions aimed at eliminating CC as a public health problem by 2030, including targets related to vaccination coverage, expansion of screening, timely treatment of precursor lesions, and ensuring equitable access to health services (WHO, 2022).

The implementation of this plan emphasizes the need for coordinated and continuous strategies that combine public health policies, health education, strengthening of the primary care system, and rigorous monitoring of coverage and effectiveness indicators. The prospect of eliminating CC reinforces the importance of sustainable investments in prevention and

control programs, as well as the articulation between governments, health institutions, and the community to achieve the internationally established goals (Vale et al, 2021).

In prospective estimates, it is estimated that the world will register approximately 121,000 new cases of cervical cancer (CC), which highlights the magnitude of this public health problem and reinforces the urgency of effective preventive and control actions. This scenario projects a growing need for intervention by health managers, who must implement integrated and sustainable strategies to reduce both the incidence and mortality associated with the disease (WHO, 2024).

Such strategies involve the combination of primary prevention policies, such as vaccination against the human papillomavirus (HPV), with secondary prevention actions, including the expansion of screening through cytopathological examinations and HPV tests, in addition to timely access to treatments for precursor lesions and diagnostic cases. In addition, the effectiveness of these actions depends on the articulation between different levels of the health system, continuous monitoring of epidemiological indicators, and the reduction of inequalities in access to health services, ensuring that the most vulnerable population groups are adequately covered (Oliveira et al, 2022).

Thus, the estimate of new cases reinforces the importance of planned public policies, consistent investments in prevention and control programs, and educational strategies aimed at raising awareness of the population about risk factors, the importance of early detection, and adherence to health recommendations, contributing significantly to the reduction of the CC incidence coefficient globally. When considering the regional distribution, it is observed that the regions with the highest human development indexes (HDI) concentrate approximately 70% of the total incidence of cancer in Brazil. However, the occurrence profile of different types of cancer varies significantly according to the level of socioeconomic development (Jardim et al, 2022).

In these more developed regions, cervical cancer (CC) occupies less expressive positions in the incidence ranking: it is the third most frequent type in the Central-West region (16.66 cases per 100 thousand women), the fourth in the South region (14.55 cases per 100 thousand) and the fifth in the Southeast (12.93 cases per 100 thousand). On the other hand, in regions with lower levels of development, such as the North (20.48 cases per 100,000) and the Northeast (17.59 cases per 100,000), the scenario is reversed: CC occupies a prominent position, being the second most common type of cancer among women. This disparity highlights the strong influence of social determinants of health and unequal access to prevention, diagnosis, and treatment services (Wirtz et al, 2022).

The data reinforce that, although Brazil has made significant advances in cervical cancer screening and control programs, regional inequalities persist. Regions with lower socioeconomic indicators still face structural challenges, such as lower coverage of Pap smears, geographical barriers, a shortage of trained professionals, and difficulties in the continuity of care. Thus, it is essential to strengthen public policies for equity in health, with a focus on expanding access to preventive services and reducing regional inequities, in order to promote a more balanced and effective response to the burden of CC in the country (Caminha et al, 2022).

On the other hand, the staging of cervical cancer (CC) is an important indicator of the quality of access and supply of health services made available by the State. The stage at which the disease is diagnosed directly reflects the effectiveness of public policies for prevention, screening, and early diagnosis, as well as the capacity of the care network to ensure coverage, equity, and continuity of care (Glehn et al, 2023).

Diagnoses made in the early stages generally indicate an efficient health system, with good coverage of Pap smears and easy access to primary care services. On the other hand, a high proportion of cases detected in advanced stages reveals structural weaknesses, such as deficiencies in screening, geographic and socioeconomic barriers, failures in timely referral, and limitations in the response capacity of specialized services (Meira et al, 2022).

Thus, the staging of cervical cancer goes beyond clinical data: it is an epidemiological and social marker that expresses regional inequalities and the effectiveness of public cancer control policies. Monitoring this indicator is essential to support the formulation of more precise intervention strategies, aimed at expanding access, strengthening primary care, and improving comprehensive women's health care, contributing to the reduction of morbidity and mortality rates associated with the disease (Ferrara et al, 2022).

Despite the high coverage of Pap smears, ranging from 66.5% to 76.8%, there is a worrying rate of diagnoses of cervical cancer (CC) in advanced stages, whose prevalence reaches approximately 46%. This paradox shows that expanding coverage, although fundamental, is not enough, by itself, to guarantee the effectiveness of screening and early detection of the disease. Several factors can contribute to this scenario, including the low quality of sample collection and analysis, failures in the periodicity of screening, difficulties in accessing follow-up of altered cases, as well as geographical, socioeconomic and cultural barriers that make it difficult for women to adhere to adequate follow-up. In addition, the absence of an effective and integrated monitoring system between the levels of care can compromise the referral and timely treatment of precursor lesions (Sing et al, 2022).

Although the coverage rates are expressive, the persistence of late diagnoses points to the need to reassess the effectiveness of the CC screening program. It is essential to strengthen the quality of actions developed in primary care, improve referral and counter-referral flows, and invest in professional training, as well as in health education strategies that promote greater awareness among the female population about the importance of prevention and periodic return to health services (Pathah et al, 2022).

There is a lack of studies that comprehensively describe the situation of cervical cancer (CC) in the national scenario, especially with regard to the identification and analysis of factors that contribute to the high rates of the disease in the country. This gap in scientific production limits an in-depth understanding of regional inequalities, structural failures in health services, and the influences of social determinants on the incidence and late diagnosis of CC (Madeiro et al, 2022).

The absence of systematic and up-to-date investigations on the subject makes it difficult to formulate more targeted and effective public policies, capable of responding to the specificities of each territory. Among the factors that possibly contribute to the high rates are unequal access to prevention and screening services, insufficient or ineffective coverage of early detection programs, unfavorable socioeconomic conditions, and the lack of educational strategies aimed at promoting women's health (Boon et al, 2022).

Thus, it is essential to encourage multicenter studies and regional epidemiological analyses that can provide robust evidence on the determinants of the persistence of CC in Brazil. Expanding the scientific knowledge base is essential to support public health decision-making, improve prevention and control strategies, and reduce, in an equitable and sustainable way, disease rates throughout the national territory (Caminha et al, 2022).

The understanding of cervical cancer (cervical cancer) can be significantly improved when analyzed from the perspective of social determinants of health. This approach allows us to recognize that the occurrence, diagnosis, and evolution of the disease are not explained only by biological or individual factors, but also by a set of social, economic, cultural, and environmental conditions that directly influence women's vulnerability and access to prevention and treatment services (Jardim et al, 2022).

Among these determinants, the level of education, family income, occupation, housing conditions, access to information and health services, as well as gender inequalities and geographical barriers that hinder the continuity of care, stand out. Such factors have a direct influence on the behavior of seeking preventive care, adherence to cytopathological screening, and the possibility of early diagnosis (Madeiro et al, 2022).

By considering the social determinants of health, it is possible to understand more broadly the context in which CC develops, favoring the development of more equitable and effective public policies. This perspective broadens the focus of care, integrating biomedical and social actions, and reinforces the need for intersectoral strategies that promote social justice, reduce inequities, and strengthen comprehensive women's health care (Caminha et al, 2022).

The Pan American Health Organization (PAHO), in line with the global strategy led by the World Health Organization (WHO), has proposed a set of ambitious goals for the elimination of cervical cancer (CC) as a public health problem by the year 2030. These goals make up the so-called "90-70-90" strategy, which establishes three fundamental axes of action aimed at prevention, early detection and effective treatment of the disease. The first goal refers to the vaccination coverage of at least 90% of girls up to 15 years of age against the human papillomavirus (HPV), the main etiological agent of CC. This measure aims to interrupt the chain of viral transmission and prevent the emergence of precursor lesions (WHO, 2024).

The second goal seeks to ensure that 70% of women undergo high-precision tests for HPV detection or cytopathological tests between 35 and 45 years of age, an age group considered to be at higher risk for developing the disease. This systematic screening strategy allows for the early identification and treatment of cervical changes, significantly reducing progression to invasive cancer (Wirtz et al, 2022).

Finally, the third goal proposes that 90% of women diagnosed with precancerous lesions receive adequate treatment, as well as 90% of invasive cancer cases be properly managed, ensuring comprehensive care, equitable access and continuous follow-up. The adoption and fulfillment of these goals represent a historic milestone in the fight against CC, reinforcing the global commitment to health equity and the reduction of regional inequities. To this end, it is essential to strengthen care networks, train professionals, invest in laboratory infrastructure, and expand educational campaigns that encourage adherence to prevention and screening strategies (Meira et al, 2022).

Considering the national scenario, Brazil presents intermediate values of incidence and mortality from cervical cancer (CC) when compared to the world scenario, reflecting hybrid characteristics of developed and developing countries. This situation highlights the coexistence of technological and structural advances in certain regions with persistent weaknesses in others, mainly related to unequal access to prevention, diagnosis, and treatment services (Oliveira et al, 2022).

According to estimates for the 2020–2022 triennium, an incidence of 15.4 new cases per 100 thousand women was projected, which places the country at an intermediate level of risk. However, there is marked regional heterogeneity: the highest incidence rates are recorded in the North and Central-West regions, with approximately 23.9 cases per 100 thousand women, while the lowest rates occur in the Southeast region, with about 11.3 cases per 100 thousand women (WHO, 2024).

These discrepancies clearly reflect the socioeconomic, demographic, and care inequalities that exist in the national territory. Differences in income, education, health infrastructure, and availability of screening and treatment programs directly influence the risk of illness and death from CC. In addition, such inequalities are manifested not only between the major regions of the country, but also between urban and rural areas, and even between intra-urban territories, where populations in situations of social vulnerability face greater barriers to access preventive health services. This scenario reinforces the need for integrated and territorially sensitive public policies, which consider the regional particularities and socioeconomic conditions of Brazilian women, aiming to reduce inequities and strengthen screening actions, early diagnosis, and timely treatment of cervical cancer (Glehn et al, 2023).

In another study, a coverage of 78.8% was observed in the performance of the Pap smear, an indicator that, at first glance, suggests a satisfactory performance of cervical cancer (CC) screening actions in the country. However, the authors point out that, even in the face of this high coverage, there is still a significant rate of diagnoses in advanced stages of the disease, which shows that expanding access, by itself, is not enough to guarantee the effectiveness of screening (Boon et al, 2022).

The study also emphasizes the influence of other predictors associated with late detection, such as the low quality of the samples collected, irregularity in the periodicity of the tests, failures in the follow-up of women with altered results, in addition to structural and social barriers, such as unequal access to health services, low education and the lack of knowledge about the importance of periodic screening (Pathah et al, 2022).

6 FINAL CONSIDERATIONS

The present study highlights the challenging profile of coping with cervical cancer (CC) in the Brazilian context, revealing that, although there is a gradual trend of reduction in incidence and mortality, the disease still remains an important cause of morbidity and mortality among women, especially in regions marked by social inequalities and less access to health services.

The findings reinforce that the effective control of cervical cancer depends on an articulated set of strategies, ranging from the expansion of HPV vaccination coverage and the qualification of screening and early diagnosis actions, to the strengthening of the oncological care network and the confrontation of the social determinants of health. Thus, it is concluded that, despite the advances observed in recent decades, CC still represents a persistent challenge for the Unified Health System (SUS) and for public health as a whole, requiring integrated, continuous and equitable policies, capable of promoting not only the reduction of epidemiological indicators, but also the improvement of the quality of life of Brazilian women.

The present study has limitations inherent to the use of secondary data sources, since the analysis depends on the quality, completeness, and consistency of the information recorded in surveillance systems and institutional databases. In addition, relevant sociodemographic variables, such as age, marital status, and education level, which could offer a more comprehensive understanding of the factors associated with the incidence and detection of cervical cancer (CC), were not considered.

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ASSOCIATION BETWEEN THE DIETARY INFLAMMATORY INDEX AND PLASMA CYTOKINES IN RECREATIONAL ROAD RUNNERS AND SEDENTARY INDIVIDUALS

ASSOCIAÇÃO ENTRE O ÍNDICE INFLAMATÓRIO DA DIETA E CITOCINAS PLASMÁTICAS EM CORREDORES DE RUA RECREACIONAIS E INDIVÍDUOS SEDENTÁRIOS

ASOCIACIÓN ENTRE EL ÍNDICE INFLAMATORIO DE LA DIETA Y LAS CONCENTRACIONES PLASMÁTICAS DE CITOCINAS EN CORREDORES RECREACIONALES DE CALLE E INDIVIDUOS SEDENTARIOS



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ABSTRACT

Objective: To evaluate the association between the Dietary Inflammatory Index (DII) and plasma cytokine concentrations in recreational road runners and sedentary individuals.

Methods: A cross-sectional study was conducted with adult recreational runners and sedentary individuals. DII, body composition and training variables, and plasma concentrations of inflammatory cytokines were assessed.

Results: Among runners, DII showed a positive association with IL-6 and IL-1 β , even after adjustment for age, sex, and body fat percentage. In the adjusted models, DII remained associated with IL-6 (β = 28.4%; 95%CI: 8.5–51.2; p = 0.006) and IL-1 β (β = 25.6%; 95%CI: 3.1–47.0; p = 0.021). Among sedentary individuals, the correlations observed between DII and IL-10, IL-1 α , and TNF- α did not remain significant after adjustment. Runners showed higher concentrations of IL-6 and IL-1 β , whereas sedentary individuals showed higher body fat percentage and a positive association between DII and adiposity.

Conclusion: The inflammatory potential of the diet was associated with the plasma cytokine profile in recreational runners, but not in sedentary individuals after adjustment. These

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findings suggest distinct inflammatory profiles between groups and indicate that diet quality may be related to the basal inflammatory profile in physically active individuals.

Keywords: Diet. Cytokines. Inflammation. Running. Body Composition.

RESUMO

Objetivo: Avaliar a associação entre o Índice Inflamatório da Dieta (IID) e as concentrações plasmáticas de citocinas em corredores recreacionais de rua e indivíduos sedentários.

Métodos: Estudo transversal conduzido com adultos corredores recreacionais e sedentários. Foram avaliados o IID, variáveis de composição corporal e treinamento e concentrações plasmáticas de citocinas inflamatórias.

Resultados: Entre os corredores, o IID apresentou associação positiva com IL-6 e IL-1 β , mesmo após ajuste por idade, sexo e percentual de gordura corporal. Nos modelos ajustados, o IID manteve associação com IL-6 ($\beta = 28,4\%$; IC95%: 8,5–51,2; $p = 0,006$) e IL-1 β ($\beta = 25,6\%$; IC95%: 3,1–47,0; $p = 0,021$). Entre os sedentários, as correlações observadas entre IID e IL-10, IL-1ra e TNF- α não permaneceram significativas após os ajustes. Os corredores apresentaram maiores concentrações de IL-6 e IL-1 β , enquanto os sedentários apresentaram maior percentual de gordura corporal e associação positiva entre IID e adiposidade.

Conclusão: O potencial inflamatório da dieta associou-se ao perfil de citocinas plasmáticas em corredores recreacionais, mas não em sedentários após os ajustes. Os achados sugerem perfis inflamatórios distintos entre os grupos e indicam que a qualidade da dieta pode estar relacionada ao perfil inflamatório basal em indivíduos fisicamente ativos.

Palavras-chave: Dieta. Citocinas. Inflamação. Corrida. Composição Corporal.

RESUMEN

Objetivo: Evaluar la asociación entre el Índice Inflamatorio de la Dieta (IID) y las concentraciones plasmáticas de citocinas en corredores recreacionales de calle e individuos sedentarios.

Métodos: Se realizó un estudio transversal con adultos corredores recreacionales y sedentarios. Se evaluaron el IID, variables de composición corporal y entrenamiento, y las concentraciones plasmáticas de citocinas inflamatorias.

Resultados: Entre los corredores, el IID mostró asociación positiva con IL-6 e IL-1 β , incluso después del ajuste por edad, sexo y porcentaje de grasa corporal. En los modelos ajustados, el IID mantuvo asociación con IL-6 ($\beta = 28,4\%$; IC95%: 8,5–51,2; $p = 0,006$) e IL-1 β ($\beta = 25,6\%$; IC95%: 3,1–47,0; $p = 0,021$). Entre los sedentarios, las correlaciones observadas entre el IID e IL-10, IL-1ra y TNF- α no permanecieron significativas después de los ajustes. Los corredores presentaron mayores concentraciones de IL-6 e IL-1 β , mientras que los sedentarios mostraron mayor porcentaje de grasa corporal y asociación positiva entre el IID y la adiposidad.

Conclusión: El potencial inflamatorio de la dieta se asoció con el perfil plasmático de citocinas en corredores recreacionales, pero no en individuos sedentarios tras los ajustes. Los hallazgos sugieren perfiles inflamatorios distintos entre los grupos e indican que la calidad de la dieta puede estar relacionada con el perfil inflamatorio basal en individuos físicamente activos.

Palabras clave: Dieta. Citocinas. Inflamación. Carrera. Composición Corporal.

1 INTRODUCTION

Regular physical exercise is widely recognized for its beneficial effects on metabolism and the immune system. In addition to contributing to body weight control and improved insulin sensitivity, physical exercise plays a role in modulating systemic inflammation, reducing the risk of chronic diseases associated with persistent inflammatory states. Physically active individuals tend to present lower concentrations of pro-inflammatory cytokines and greater release of mediators with regulatory functions, which favors immunometabolic balance (Bernhart et al., 2022; Chamberlin et al., 2022; Gleeson, 2013).

In individuals who engage in regular physical exercise, acute inflammatory peaks become progressively attenuated, while physiological adaptations emerge that promote a more regulated immune environment (Chamberlin et al., 2022). The body adjusts inflammatory responses according to the type, load, and intensity of training, reducing basal inflammation and improving communication between the immune and metabolic systems. In this context, diet also influences these responses, since physically active individuals with a balanced diet tend to show lower inflammatory variability and more efficient recovery after physical exertion (Almeida-Neto et al., 2025; Zhou et al., 2025).

Considering the role of diet in the regulation of inflammation, Shivappa et al. (2014) developed the Dietary Inflammatory Index (DII) as a tool to quantitatively assess the inflammatory potential of dietary patterns. Diets with pro-inflammatory characteristics present higher scores, whereas anti-inflammatory dietary patterns exhibit negative scores. Studies have demonstrated a direct association between higher DII scores and increased concentrations of inflammatory cytokines, such as IL-6, IL-1 β , and TNF- α (Hass et al., 2022; Millar et al., 2022; Godala et al., 2025), reinforcing the usefulness of the DII in identifying the impact of diet quality on the modulation of the inflammatory response.

Another relevant factor in inflammatory mechanisms is body composition. Adipose tissue is recognized as an endocrine organ responsible for the synthesis of regulatory hormones and the production of pro-inflammatory cytokines, such as IL-6 and TNF- α . In contrast, muscle mass plays essential roles in metabolic regulation and in the control of inflammatory processes (Doustmohammadian et al., 2024; Zhang et al., 2023). Recent evidence indicates that a higher body fat percentage is associated with higher DII scores and greater concentrations of pro-inflammatory cytokines, whereas individuals with a higher percentage of lean mass present lower DII scores and a more balanced immune profile (Dave et al., 2025; Li et al., 2025). In runners, the interaction between body composition, diet, and training load plays a relevant role in the modulation of inflammation and physical

performance, reinforcing the importance of analyzing these factors in an integrated manner (Shi et al., 2023).

Although the independent impact of physical exercise and inflammatory diet on inflammatory markers has been well described, studies evaluating the direct association between the Dietary Inflammatory Index and plasma cytokines in recreational road runners, a group characterized by substantial heterogeneity in training volume and dietary patterns, remain scarce. Therefore, the present study aimed to evaluate the association between the DII and plasma cytokine concentrations in recreational road runners and sedentary individuals.

2 METHODS

This was an analytical cross-sectional study conducted between September 2022 and March 2024 in the city of Porto Alegre, Rio Grande do Sul, Brazil. The study was conducted in accordance with the principles of the Declaration of Helsinki and Resolution No. 466/12 of the Brazilian National Health Council, and was approved by the Research Ethics Committee involving Human Beings of the Federal University of Health Sciences of Porto Alegre (CAAE: 58330022.6.0000.5345). All volunteers were recruited through social media and sports advisory services, were informed about the objectives and procedures of the study, and signed an informed consent, prior to enrollment.

Participants

The sample consisted of recreational road runners and sedentary individuals aged 18 to 50 years. The runner group included participants who had been participating in road running for at least six months, with a minimum frequency of 150 minutes of physical activity per week, and who performed long-distance running sessions of at least 5 km per session. The sedentary group consisted of individuals who had not engaged in regular physical activity for at least six months and were classified as inactive or insufficiently active according to the short version of the International Physical Activity Questionnaire (IPAQ) (Matsudo et al., 2001).

The exclusion criteria were: (i) body mass index (BMI) ≥ 30 kg/m²; (ii) smoking; (iii) pregnancy; (iv) history of surgery within the six months prior to data collection; (v) presence of acute inflammatory disease, recent infection, or gingival/periodontal disease; (vi) use of anti-inflammatory drugs or corticosteroids; and (vii) occurrence of musculoskeletal injury during the week prior to data collection.

Sociodemographic and anthropometric data collection

Sociodemographic information and training-related parameters were collected using

an online questionnaire. Anthropometric assessment was performed in person by a single trained evaluator, using a digital scale with stadiometer (capacity of 150 kg, precision of 100 g) to measure body weight and height. For body composition assessment, seven skinfolds were measured (chest, midaxillary, triceps, subscapular, suprailiac, abdominal, and medial thigh), all on the right side of the body, using a Cescorf® scientific skinfold caliper (sensitivity of 0.1 mm, reading range of 88 mm), following the recommendations of the International Society for the Advancement of Kinanthropometry (ISAK). Each skinfold was measured in triplicate, and the mean value was used. Body density was estimated using the equations of Jackson and Pollock (1978) for men and Jackson, Pollock, and Ward (1980) for women. Body fat percentage was obtained using Siri's equation (1961), $\%BF = (495/D) - 450$, from which lean mass (kg) and fat mass (kg) values were derived.

Dietary intake assessment and DII calculation

Habitual dietary intake was assessed using a semi-quantitative Food Frequency Questionnaire (FFQ), validated for the Brazilian population and based on the reduced version of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) (Molina et al., 2013). The instrument evaluated the frequency of consumption of 76 food items over the previous 12 months, distributed into seven food groups (bread, cereals, and tubers; fruits; vegetables, legumes, and pulses; meat, eggs, milk, and dairy products; pasta and mixed dishes; sweets; and beverages). Responses were recorded in nine frequency categories, ranging from “never or almost never” to “more than three times a day.” Nutrient content was calculated based on the Brazilian Food Composition Table (TBCA, 2023), and household measures were converted into grams (Fisberg; Villar, 2002).

The DII was calculated according to the method proposed by Shivappa et al. (2014), considering 25 of the 45 food parameters available in the database. The evaluated components included vitamins A, C, D, E, B6, and B12, folic acid, β -carotene, calcium, iron, magnesium, zinc, selenium, niacin, riboflavin, thiamine, protein, carbohydrates, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, cholesterol, and fiber.

Dietary intake values were standardized as z-scores, multiplied by the respective inflammatory effect scores, and summed to generate the total DII score. Positive values indicate a diet with pro-inflammatory characteristics, whereas negative values reflect a diet with anti-inflammatory characteristics.

Plasma collection and cytokine determination by ELISA

A total of 20 mL of venous blood was collected from the cubital vein after 24–48 hours without vigorous exercise and without alcohol intake. No dietary restrictions were imposed before sample collection. Samples were placed in EDTA tubes and centrifuged at 3000 rpm

for 10 minutes to obtain plasma, which was subsequently stored at -80°C until analysis.

Plasma concentrations of IL-6, IL-10, IL-1 β , IL-1ra, IFN- γ , and TNF- α were determined by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions (Peprotech®, USA). Standard curves were prepared using eight calibration points, and readings were performed on an automated optical reader SpectraMax® ($\lambda = 540$ nm), using SoftMax Pro® software for curve fitting and concentration calculations.

The intra-assay coefficient of variation was $< 7.5\%$ and the inter-assay coefficient of variation was $< 10\%$. The detection limits were: IL-6 (24–1500 pg/mL), IL-10 (23–3000 pg/mL), IL-1 β (8–1000 pg/mL), IL-1ra (23–1500 pg/mL), IFN- γ (8–3000 pg/mL), and TNF- α (8–2000 pg/mL).

Sample size calculation

Sample size calculation was performed using GPower software version 3.1.3 (Franz Faul, Universität Kiel, Germany). The sample size was estimated considering the difference in plasma interleukin-6 (IL-6) levels between physically active and sedentary individuals, a marker widely used in studies on low-grade inflammation related to physical exercise and diet (Haß U, et al., 2022). Based on evidence from the literature indicating moderate to large differences in baseline IL-6 levels between groups with different levels of physical activity, a significance level of 5% and statistical power of 80% were adopted. A minimum of 25 participants per group was estimated. Considering possible sample losses, the final planned sample size was approximately 30 participants in each group.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro–Wilk test. Variables with normal distribution were expressed as mean $\pm$ standard deviation (SD) and compared between groups using Student's t-test. For variables with non-normal distribution, the Mann–Whitney U test was applied.

Correlations between the DII score and plasma cytokines (IL-6, IL-10, IL-1 β , IL-1ra, IFN- γ , and TNF- α) were evaluated using Spearman's correlation coefficient, with analyses stratified by group (runners and sedentary individuals).

The association between DII and training volume was analyzed after stratifying weekly mileage and weekly training time into tertiles, representing three levels of training load: low (≤ 33.3 rd percentile), moderate (33.3rd–66.6th percentile), and high (> 66.6 th percentile). Comparisons between tertiles were performed using the nonparametric Kruskal–Wallis analysis of variance.

Multiple linear regression models were applied to investigate the independent effect of DII on plasma cytokines, using natural logarithmic transformation of the dependent

variables [$\ln(\text{cytokine})$]. The models were adjusted for age, sex, and body fat percentage, and were conducted separately for each group (runners and sedentary individuals). The results were expressed as β coefficient (percentage change per +1 point in DII), 95% confidence interval (95% CI), p-value, and adjusted R^2 . The statistical significance level adopted was $p < 0.05$. All statistical analyses were performed using SPSS software, version 25.

3 RESULTS

The sample consisted of 80 participants, including 55 recreational runners and 25 sedentary individuals. As shown in Table 1, runners were significantly older on average (35.96 ± 7.51 years) compared with sedentary individuals (26.12 ± 5.06 years; $p < 0.001$). Regarding body composition, runners had a lower body fat percentage ($p < 0.001$) and higher lean mass ($p = 0.027$) than sedentary individuals. In addition, the DII score was significantly lower among runners (-0.04 ± 1.09) than among sedentary individuals (0.84 ± 1.39 ; $p = 0.011$), indicating a more anti-inflammatory dietary pattern in the physically active group. Regarding cytokines, Table 1 shows that runners had higher plasma concentrations of IL-6 (12.21 ± 5.91 pg/mL vs. 6.97 ± 0.93 pg/mL; $p < 0.001$) and IL-1 β (17.88 ± 11.38 pg/mL vs. 8.42 ± 5.53 pg/mL; $p < 0.001$). Sedentary individuals, in contrast, had higher levels of IL-10 (19.87 ± 1.73 pg/mL vs. 12.34 ± 5.24 pg/mL; $p < 0.001$) and IL-1ra (112.70 ± 60.72 pg/mL vs. 37.17 ± 15.69 pg/mL; $p < 0.001$).

The correlations between DII and plasma cytokines, presented in Table 2, showed distinct patterns between the groups. Among runners, DII was positively correlated with IL-6 ($r = 0.44$; $p = 0.009$) and IL-1 β ($r = 0.35$; $p = 0.028$). Among sedentary individuals, positive correlations were observed between DII and IL-10 ($r = 0.39$; $p = 0.044$), IL-1ra ($r = 0.42$; $p = 0.031$), and TNF- α ($r = 0.41$; $p = 0.036$).

As shown in Table 3, DII was positively correlated with body fat percentage in the sedentary group ($r = 0.472$; $p = 0.017$). In contrast, no significant associations were observed between DII and any body composition variable in the runner group.

For the analysis of the association between DII and training volume, weekly mileage (km/week) and weekly training time were stratified into tertiles and are presented in Table 4. Mean weekly mileage was 41.8 ± 23.2 km, while total weekly training time was 346.1 ± 197.2 minutes. An inverse trend was observed between weekly mileage and DII ($p = 0.061$), and a significant difference was found according to training time per session ($p = 0.042$).

All individual DII components were correlated with plasma cytokines. Table 5 presents those that showed statistically significant correlations. Among runners, a negative correlation

was observed between omega-3 intake and IL-6 ($r = -0.45$; $p = 0.018$), and between fiber intake and IL-1 β ($r = -0.38$; $p = 0.041$). In addition, saturated fat intake showed a negative correlation with IL-10 ($r = -0.43$; $p = 0.027$). Among sedentary individuals, trans fat intake showed a positive correlation with IL-6 ($r = 0.46$; $p = 0.022$), while polyunsaturated fat intake was positively correlated with IL-10 ($r = 0.44$; $p = 0.029$).

The multiple linear regression models (Figure 1) indicated that, among runners, DII remained positively and independently associated with IL-6 levels ($\beta = 28.4\%$; 95% CI: 8.5 to 51.2; $p = 0.006$) and IL-1 β levels ($\beta = 25.6\%$; 95% CI: 3.1 to 47.0; $p = 0.021$), even after adjustment for age, sex, and body fat percentage. Among sedentary individuals, no cytokine showed a significant association with DII.

Table 1

Participant characteristics regarding body composition, total DII score, and plasma cytokines in road runners and sedentary individuals

Variable	Runners (mean $\pm$ SD) n=55	Sedentary individuals (mean $\pm$ SD) n=25	p-value
Age (years)	35,96 $\pm$ 7,51	26,12 $\pm$ 5,06	< 0,001
BMI (kg/m ²)	23,71 $\pm$ 2,91	24,45 $\pm$ 4,65	0,467
Body Fat (%)	15,96 $\pm$ 7,12	26,97 $\pm$ 8,80	< 0,001
Lean mass (kg)	58,53 $\pm$ 11,89	45,61 $\pm$ 7,08	0,027
Fat mass (kg)	10,88 $\pm$ 4,92	17 $\pm$ 9,15	< 0,001
DII (total score)	-0,04 $\pm$ 1,09	0,84 $\pm$ 1,39	0,011
IL-6 (pg/mL)	12,21 $\pm$ 5,91	6,97 $\pm$ 0,93	< 0,001
IL1-ra (pg/mL)	37,17 $\pm$ 15,69	112,70 $\pm$ 60,72	< 0,001
IL-10 (pg/mL)	12,34 $\pm$ 5,24	19,87 $\pm$ 7,13	< 0,001
IL-1 β (pg/mL)	17,88 $\pm$ 11,38	8,42 $\pm$ 5,53	< 0,001
IFN- γ (pg/mL)	15,67 $\pm$ 7,49	18,15 $\pm$ 7,42	0,188
TNF- α (pg/mL)	224,97 $\pm$ 232,49	188,49 $\pm$ 217,65	0,548

Legend: Student's t-test was used for variables with normal distribution, and the Mann–Whitney U test was used for variables with non-normal distribution. BMI: body mass index; DII: Dietary Inflammatory Index; IL-6: interleukin-6; IL-10: interleukin-10; IL-1 β : interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IFN- γ : interferon-gamma; TNF- α : tumor necrosis factor-alpha. Source: authors.

Table 2

Correlation between DII and plasma cytokines in road runners and sedentary individuals.

Cytokine	Runners r (Spearman) n=55	p-value	Sedentary individuals r (Spearman) n=25	p-value
IL-6 (pg/mL)	0,44	0,009	0,26	0,241

IL-10 (pg/mL)	-0,18	0,218	0,39	0,044
IL-1 β (pg/mL)	0,35	0,028	0,21	0,314
IL-1ra (pg/mL)	0,19	0,203	0,42	0,031
IFN- γ (pg/mL)	0,13	0,331	0,22	0,284
TNF- α (pg/mL)	0,12	0,351	0,41	0,036

Legend: IL-6: interleukin-6; IL-10: interleukin-10; IL-1 β : interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IFN- γ : interferon-gamma; TNF- α : tumor necrosis factor-alpha. Source: authors.

Table 3

Correlation between DII and body composition variables in road runners and sedentary individuals.

Group	Body composition variable	r (Spearman)	p-value
Runners n=55	BMI	0,298	0,058
	Body Fat (%)	0,110	0,492
	Fat mass (kg)	0,146	0,363
	Lean mass (kg)	0,044	0,786
Sedentary individuals n=25	BMI	0,275	0,183
	Body Fat (%)	0,472	0,017
	Fat mass (kg)	0,321	0,118
	Lean mass (kg)	-0,100	0,636

Legend: BMI: body mass index. Source: authors.

Table 4

DII scores according to tertiles of training parameters among road runners.

Training parameters Category		Mean $\pm$ SD	Mean $\pm$ SD DII	n	p-value
Distance (km/week)	Low	24,3 $\pm$ 5,8	-0,12 $\pm$ 0,98	19	0,061
	Moderate	42,5 $\pm$ 6,7	0,55 $\pm$ 1,23	10	
	High	65,7 $\pm$ 8,4	-0,63 $\pm$ 0,96	10	
Time (minutes/week)	Low	200,5 $\pm$ 54,2	0,43 $\pm$ 0,95	16	0,042
	Moderate	340,7 $\pm$ 61,5	-0,22 $\pm$ 1,09	10	
	High	510,3 $\pm$ 80,6	-0,61 $\pm$ 1,13	12	

Legend: km: kilometers; SD: standard deviation; DII: Dietary Inflammatory Index. Source: authors.

Table 5

Correlation between dietary components of the DII and plasma cytokines in road runners and Sedentary individuals

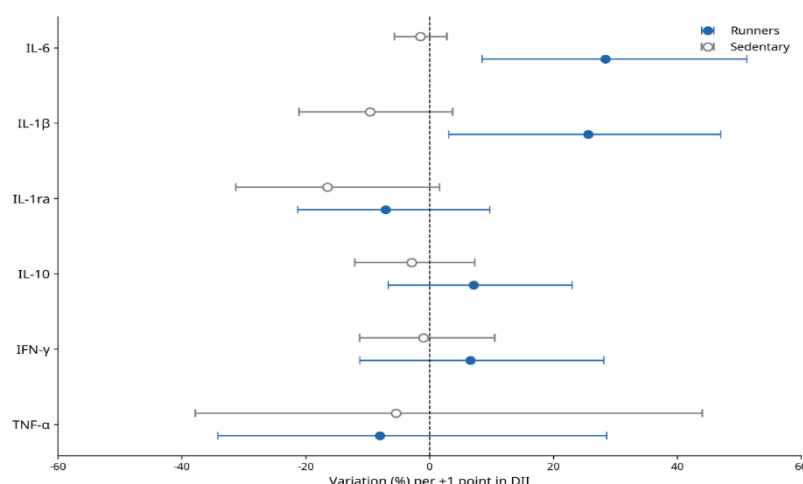
	Nutrient (DII)	Cytokine	ρ (Spearman)	p-value
Runners n=55	Ômega-3	IL-6	-0.45	0,018
	Fiber	IL-1 β	-0.38	0,041

Sedentary individuals n=25	Saturated fat	IL-10	-0.43	0,027
	Vitamin C	IL-1ra	0.42	0,031
	Trans fat	IL-6	0.46	0,022
	Ômega-6	TNF- α	0.41	0,036
	Polyunsaturated fats	IL-10	0.44	0,029

Legend: IL-6: interleukin-6; IL-10: interleukin-10; IL-1 β : interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IFN- γ : interferon-gamma; TNF- α : tumor necrosis factor-alpha; DII: Dietary Inflammatory Index. Source: authors.

Figure 1

Effect of DII on cytokines (adjusted models)



Legend: IL-6: interleukin-6; IL-10: interleukin-10; IL-1 β : interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IFN- γ : interferon-gamma; TNF- α : tumor necrosis factor-alpha; DII: Dietary Inflammatory Index. Source: authors.

4 DISCUSSION

This study investigated the association between DII and plasma cytokine levels in road runners and sedentary individuals, considering aspects of body composition and physical training. The main finding was the positive association between the Dietary Inflammatory Index (DII) and plasma concentrations of IL-6 and IL-1 β among recreational runners. This association was observed both in the correlation analyses and in the models adjusted for age, sex, and body fat percentage, indicating that the inflammatory potential of the diet was related to the profile of these cytokines even after controlling for relevant confounding factors. Among sedentary individuals, correlations were observed between DII and IL-10, IL-1ra, and TNF- α ; however, these associations did not remain after adjustment, suggesting different behavior between the groups.

Runners presented higher concentrations of IL-6 and IL-1 β compared with sedentary individuals, despite having a lower DII score and lower body fat percentage. This result should be interpreted with caution. In individuals who exercise regularly, especially in endurance modalities, higher basal concentrations of some cytokines do not necessarily

indicate pathological inflammation and may reflect physiological adaptations to chronic training. IL-6, for example, acts as a myokine released by skeletal muscle in response to repeated contraction, with metabolic and immunoregulatory functions already described in the literature (Gleeson et al., 2011; Reihmane; Dela, 2014). In this context, the association between IL-6, IL-1 β , and DII only among runners suggests that, in this group, diet quality was related to variation in the basal inflammatory profile even in the presence of regular training.

This finding indicates that exercise alone does not eliminate the influence of diet on inflammatory biomarkers. The higher levels of IL-6 and IL-1 β observed among runners may be related to repeated exposure to acute inflammatory stimuli induced by training (Chamberlin et al., 2022; Via et al., 2024). At the same time, the positive association between DII and these cytokines indicates that a more pro-inflammatory dietary pattern may coexist with regular running practice and be associated with a less favorable inflammatory profile. This interpretation is consistent with findings in athletes and runners linking poorer dietary intake quality to higher concentrations of inflammatory markers (Almeida-Neto et al., 2025; Passos et al., 2019). It is also consistent with studies associating anti-inflammatory dietary patterns with lower concentrations of IL-6 and IL-1 β , in addition to higher concentrations of IL-10 (Ndiema, 2023; Shin et al., 2020; Pietrzak et al., 2023; Kęska et al., 2022). Even among physically active individuals, diet seems to contribute to the organization of the basal inflammatory profile.

Among sedentary individuals, the pattern was different. This group presented higher concentrations of IL-10 and IL-1ra, cytokines traditionally associated with regulatory responses. As the associations between DII and cytokines did not remain significant in the adjusted models, the relationship between diet and inflammation in this group appears to depend more on other characteristics, especially body adiposity. Since sedentary individuals also had a higher body fat percentage, it is plausible that the inflammatory environment was influenced by broader metabolic and body composition factors, and not only by the inflammatory potential of the diet. This interpretation is in line with studies showing a relationship between greater adiposity, higher dietary inflammatory scores, and a worse systemic inflammatory profile (Shivappa et al., 2015; Hass et al., 2022; Millar et al., 2022; Godala et al., 2025; Camargo-Ramos et al., 2017; Phillips et al., 2017; Wang et al., 2025).

Among sedentary individuals, the positive association between DII and body fat percentage suggests that diets with greater inflammatory potential coexisted with higher adiposity, a condition linked to the production of inflammatory mediators and immunometabolic dysfunction. Among runners, no significant correlations were observed

between DII and body composition variables. This result may reflect the lower adiposity of this group and, possibly, the modulating effect of regular exercise on adipose tissue and cytokine secretion (Dave et al., 2025; Doustmohammadian, et al., 2024; Zhang et al., 2023; Li et al., 2025; Shi et al., 2023). As this was a cross-sectional study, it is not possible to establish the direction of these associations.

Regarding training variables, a significant difference in DII was observed according to weekly training time, whereas weekly mileage showed only a trend in the same direction. This result suggests that runners who are more engaged in training may present a less inflammatory dietary pattern. This hypothesis is plausible and may reflect greater awareness of healthy lifestyle habits and greater attention to diet among individuals more engaged in sports practice (Muros et al., 2021; Carey et al., 2024). It may also reflect behavioral differences among recreational practitioners, in whom eating habits and nutritional knowledge seem to vary according to the degree of involvement with the modality (Kosendiak et al., 2023; Dion et al., 2024).

The analysis of the individual DII components added a complementary perspective. Among runners, omega-3 intake was negatively correlated with IL-6, and fiber intake was negatively correlated with IL-1 β . These findings are biologically plausible and reinforce the role of nutrients with recognized anti-inflammatory potential in the regulation of the immune response (Shin et al., 2020; Akbari-Fakhrabadi et al., 2024; Badenhorst et al., 2016). Among sedentary individuals, trans fat intake showed a positive correlation with IL-6, whereas omega-6 intake was positively correlated with TNF- α . These results follow the expected direction for dietary components associated with a more pro-inflammatory profile. The association between polyunsaturated fats and IL-10 should be interpreted with caution, but it is biologically plausible based on experimental and mechanistic evidence describing increased IL-10 and anti-inflammatory effects for certain polyunsaturated fatty acids, especially those from the n-3 series (Bradley et al., 2008; Rocha et al., 2017).

The results do not allow this pattern, by itself, to be interpreted as greater pathological inflammation in runners. The findings point to distinct inflammatory profiles, probably influenced by different mechanisms. Among runners, the combination of chronic training and diet quality seems to be more relevant to variation in IL-6 and IL-1 β . Among sedentary individuals, higher body adiposity may have had a greater influence on the organization of this inflammatory profile. This interpretation seems more consistent with the multifactorial nature of the inflammatory response to exercise, in which training load, timing of sample collection, body composition, and individual characteristics influence the interpretation of biomarkers (Barros et al., 2017).

Among the study limitations, it should be noted that the cross-sectional design prevents causal inferences. The use of only a single blood collection does not allow the temporal variability of cytokines to be assessed. Sampling was performed after 24 to 48 hours without vigorous exercise, an interval that may still be heterogeneous for markers sensitive to recent training, since exercise-induced inflammatory changes may return to baseline within about 24 hours in many protocols, but may also persist longer depending on the intensity, duration, and characteristics of the effort (Alves et al., 2022; Proschinger et al., 2023). There was also no standardization of pre-collection dietary intake, which may have increased the variability of plasma concentrations. In addition, DII was calculated using 25 of the 45 original components, which may reduce the comprehensiveness of the estimate of the inflammatory potential of the diet. Differences between the groups in age and body composition, together with the smaller sample size among sedentary individuals, also require caution in the direct comparison of inflammatory profiles. Even so, the study shows that, among recreational runners, DII was independently associated with IL-6 and IL-1 β in a group that remains little explored in this context.

5 CONCLUSION

In this study, the inflammatory potential of the diet was associated with IL-6 and IL-1 β in recreational runners, but not in sedentary individuals after adjustment. The results show distinct inflammatory profiles between the groups and indicate that, in physically active individuals, diet quality may be related to the basal inflammatory profile. The cross-sectional design and the single blood collection require caution in interpreting the findings. Even so, the data highlight the importance of considering diet quality in the evaluation of inflammatory biomarkers in recreational runners and support the need for longitudinal studies with greater control of training and dietary variables.

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WHEN TERRITORY DETERMINES CARE: THE UNEQUAL DISTRIBUTION OF HEALTH PROFESSIONALS AND ITS DIRECT IMPACTS ON LIFE AND DEATH IN REMOTE REGIONS

QUANDO O TERRITÓRIO DETERMINA O CUIDADO: A DISTRIBUIÇÃO DESIGUAL DE PROFISSIONAIS DE SAÚDE E SEUS IMPACTOS DIRETOS NA VIDA E NA MORTE EM REGIÕES REMOTAS

CUANDO EL TERRITORIO DETERMINA EL CUIDADO: LA DISTRIBUCIÓN DESIGUAL DE PROFESIONALES DE LA SALUD Y SUS IMPACTOS DIRECTOS EN LA VIDA Y LA MUERTE EN REGIONES REMOTAS



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ABSTRACT

This study analyzes how excessive exposure to crime-related news in the media impacts the social perception of criminal severity and modulates institutionalized penal responses. The exploratory bibliographic research examines specialized literature addressing the relationships between media, the social construction of criminal reality, and penal responses. The findings reveal that the trivialization of crime by the media operates through mechanisms of narrative selectivity, sensationalism, and the simplification of structural complexities, which reshape public perceptions of crime. The study identifies a central paradox: trivialization simultaneously trivializes and radicalizes perceptions of crime, generating desensitization that coexists with intensified demands for harsher penal responses. The analysis demonstrates that trivialization does not remain confined to the symbolic domain but penetrates penal institutions, compromising fundamental guarantees of impartiality. The implications for the legitimacy of democratic penal systems are profound, suggesting the need to base decisions on penal severity on rational analyses of effectiveness, rather than on reactions to media pressures that distort criminal realities.

Keywords: Trivialization of Crime. Media and Criminal Justice. Social Perception of Crime. Institutionalized Penal Responses.

RESUMO

Este estudo analisa como a exposição excessiva a notícias de crimes pela mídia impacta a percepção social da gravidade criminal e modula respostas penais institucionalizadas. A pesquisa bibliográfica exploratória examina literatura especializada que aborda relações

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entre mídia, construção social da realidade criminal e respostas penais. Os achados revelam que banalização da criminalidade pela mídia opera através de mecanismos de seletividade narrativa, sensacionalismo e simplificação de complexidades estruturais que remodulam percepções públicas sobre crime. O estudo identifica paradoxo central: a banalização simultaneamente trivializa e radicaliza percepções sobre crime, gerando dessensibilização que coexiste com demandas intensificadas por respostas penais severas. A análise demonstra que banalização não permanece confinada ao domínio simbólico, mas penetra instituições penais, comprometendo garantias fundamentais de imparcialidade. As implicações para legitimidade de sistemas penais democráticos são profundas, sugerindo necessidade de fundamentar decisões sobre severidade penal em análises racionais sobre efetividade, não em reações a pressões midiáticas que distorcem realidades criminais.

Palavras-chave: Banalização da Criminalidade. Mídia e Justiça Penal. Percepção Social do Crime. Respostas Penais Institucionalizadas.

RESUMEN

Este estudio analiza cómo la exposición excesiva a noticias sobre delitos en los medios impacta la percepción social de la gravedad criminal y modula las respuestas penales institucionalizadas. La investigación bibliográfica exploratoria examina literatura especializada que aborda las relaciones entre los medios, la construcción social de la realidad criminal y las respuestas penales. Los hallazgos revelan que la banalización de la criminalidad por parte de los medios opera a través de mecanismos de selectividad narrativa, sensacionalismo y simplificación de las complejidades estructurales, que reconfiguran las percepciones públicas sobre el delito. El estudio identifica una paradoja central: la banalización simultáneamente trivializa y radicaliza las percepciones sobre el crimen, generando una desensibilización que coexiste con demandas intensificadas por respuestas penales más severas. El análisis demuestra que la banalización no permanece confinada al ámbito simbólico, sino que penetra en las instituciones penales, comprometiendo garantías fundamentales de imparcialidad. Las implicaciones para la legitimidad de los sistemas penales democráticos son profundas, sugiriendo la necesidad de fundamentar las decisiones sobre la severidad penal en análisis racionales de efectividad, y no en reacciones a presiones mediáticas que distorsionan las realidades criminales.

Palabras clave: Banalización de la Criminalidad. Medios y Justicia Penal. Percepción Social del Delito. Respuestas Penales Institucionalizadas.

1 INTRODUCTION

The geography of health is not a mere statistical abstraction. It determines, with brutal precision, who lives and who dies. When a heart attack occurs in a metropolis, the patient has intensive care units minutes away; When it occurs in a remote region, death is often inevitable, not for lack of medical knowledge, but for lack of doctors. The unequal distribution of health professionals is one of the most persistent and least visible problems of contemporary health systems, particularly in developing countries where territorial disparities reflect and amplify structural socioeconomic inequalities.

The research problem that guides this study emerges from a disturbing finding: while cities concentrate doctors, nurses, and specialists in proportions that often exceed local needs, remote regions face chronic shortages of health professionals, creating care gaps that translate into avoidable mortality. Assis et al. (2024, p. 4474) document that "spatial patterns of maternal mortality due to abortion in Brazil reveal a concentration of deaths in regions where the provision of primary care is deficient". This finding is not merely epidemiological; It is an indictment of the system that allows the geographic location of birth to determine the probability of maternal survival.

The relevance of this study lies in multiple dimensions. First, the shortage of health professionals in remote regions is not an isolated technical problem, but an expression of structural flaws in human resource allocation policies. Second, the impacts of this unequal distribution transcend abstract public health indicators; directly affect the life and death of vulnerable populations. Third, understanding the mechanisms by which the territory determines care is a prerequisite for formulating public policies that break this cycle of inequality. Basu et al. (2021, p. 923) argue that "alleviating primary care shortages in the United States would produce significant gains in life expectancy, particularly in historically marginalized communities."

The question that guides this research asks: how does the unequal distribution of health professionals between urban and remote territories produce differentiated impacts on mortality and morbidity of populations? What mechanisms explain the persistence of this inequality despite decades of public policies? What are the ethical and political implications of allowing geography to determine access to life-saving care? Cao et al. (2025, p. 2) argue that "inequality in the supply of physicians significantly impacts mortality, with profound implications for global health and health equity."

The overall objective of this study is to analyze the unequal distribution of health workers between urban and remote regions, examining its direct impacts on the lives and deaths of vulnerable populations. The specific objectives include: (1) mapping the patterns

of geographic distribution of health professionals, identifying care gaps in remote regions; (2) to analyze the mechanisms by which this territorial inequality produces differences in mortality and morbidity indicators; (3) to examine existing public policies and their limitations in reducing this disparity; (4) to identify structural barriers that perpetuate the concentration of professionals in urban centers; (5) to propose guidelines for human resource allocation policies that promote territorial equity in health.

The structure of this article is organized as follows. The introduction contextualizes the research problem, justifies its relevance and presents the objectives that guide the investigation. The theoretical framework presents fundamental concepts about equity in health, geographic distribution of human resources and social determinants of health, dialoguing with contemporary theoretical perspectives. The methodology describes the exploratory bibliographic approach adopted, specifying procedures for selection and analysis of literature. The results and discussion section synthesizes findings from the literature, comparing perspectives and indicating implications for public policies. The final considerations resume objectives, synthesize contributions, recognize limitations, and suggest paths for future investigations that deepen the understanding of this vital issue for public health.

2 THEORETICAL FRAMEWORK

Equity in health is a multidimensional concept that transcends simple equality of access. While equality presupposes the equal supply of resources to all, equity recognizes that different populations have different needs and, therefore, demand different allocations of resources to achieve equivalent results. When a remote region has a population density ten times lower than a metropolis, offering the same number of doctors to both is not equitable; it is the perpetuation of inequality. Carreiro (2023, p. 18) argues that "the medical labor market reveals a concentration of professionals in urban centers, reflecting market dynamics that privilege profitability over population need".

The geographical distribution of human resources in health is not a natural or inevitable phenomenon. It results from political decisions, economic incentives, and power structures that have historically favored urban centers. Doctors, nurses and specialists focus on where there are better working conditions, higher pay, opportunities for specialization and access to technological infrastructure. Remote regions, in turn, offer professional isolation, often lower pay and precarious infrastructure, creating a vicious cycle where the initial shortage of professionals discourages new professionals from settling. Castro and Léda

(2021, p. 558) argue that "health regulations and market regulations often disfavor the equitable distribution of resources, concentrating them in already privileged regions".

The social determinants of health provide a theoretical framework for understanding how structural factors, in addition to direct access to medical services, influence health and mortality. Poverty, education, housing, sanitation and access to food are determinants that are often concentrated in remote regions, creating a context where the shortage of health professionals is not an isolated problem, but an expression of broader territorial inequality. Gessi et al. (2021, p. 450) state that "health and its development are intrinsically linked, with regions facing economic vulnerability simultaneously presenting health vulnerability".

Maternal mortality is a particularly sensitive indicator for the distribution of health professionals. Obstetric complications that would be easily treatable in urban contexts become fatal in remote regions where there are no obstetricians, anesthesiologists, or intensive care units. Assis et al. (2024, p. 4474) document that "spatial patterns of maternal mortality due to abortion in Brazil reveal a concentration of deaths in regions where the provision of primary care is deficient". This finding is not merely statistical; It represents women who died not because of a lack of medical knowledge, but because of a lack of access to professionals who have that knowledge.

Life expectancy works as a synthesis of multiple health factors, reflecting both the quality and quantity of life that a population can expect. When the distribution of health workers is unequal, life expectancy diverges dramatically across territories. Basu et al. (2021, p. 923) demonstrate that "alleviating primary care shortages in the United States would produce significant gains in life expectancy, particularly in historically marginalized communities." This finding, although based on a North American context, has universal validity: where there are health professionals, there is life; where there is scarcity, there is premature death.

The issue of the migration of health professionals from remote regions to urban centers is a phenomenon that amplifies inequalities. Professionals trained in remote regions often migrate to cities in search of better conditions, creating a brain drain that leaves these regions even more deprived. This process is not the individual fault of professionals who seek to improve their lives; It is a structural failure of systems that do not create sufficient incentives for retention. Lima et al. (2022, p. 2) argue that "temporal trends and spatial distribution of diseases reveal patterns that reflect inequalities in the provision of health services".

The COVID-19 pandemic has exposed with brutal clarity the consequences of the unequal distribution of health workers. Remote regions have faced collapse of health

systems not only due to a lack of beds or ventilators, but due to a lack of professionals to operate them. Mouta et al. (2023, p. 19698) document that "intensive care units in Brazil have uneven availability, with remote regions facing chronic shortages in the face of pandemic demands". This experience revealed that public health is not merely a technical issue, but a matter of territorial justice.

Primary health care models are a strategy internationally recognized as fundamental to reduce inequalities. When health professionals are present in remote communities, even if they have basic training, they are able to prevent diseases, identify problems early and refer complex cases to specialized centers. However, the implementation of primary care in remote regions faces structural challenges: lack of infrastructure, difficulty in recruiting and retaining professionals, and insufficient funding. Pinheiro et al. (2024, p. e6993) note that "analysis of the spatial distribution of hospitalizations for severe acute respiratory syndrome reveals disparities that reflect inequalities in the provision of primary care".

The ethical question that emerges from this reality is disturbing: Is it acceptable for geographic location of birth to determine the likelihood of survival? That death is not only possible, but probable, simply because someone was born far from urban centers? These questions are not rhetorical; These are issues that should guide public policies. The unequal distribution of health workers is not a technical problem that can be solved with more training or technology; It is a political problem that requires a willingness to redistribute resources, to recognize that health is a fundamental human right, not a commodity to be allocated according to market logic.

3 METHODOLOGY

This research adopts a qualitative approach of an exploratory nature, based on a systematic review of scientific literature published between 2018 and 2025. The choice of bibliographic methodology is justified by the need to map the state of the art on the geographic distribution of health professionals and its impacts on mortality and morbidity. Martins, Costa, and Curi (2023, p. 15) argue that "the unequal distribution of resources across Brazilian municipalities reflects political choices that perpetuate territorial disparities". This perspective guides the selection of sources and analysis of the data collected, ensuring that the review transcends the compilation of information.

The population of this research comprises scientific articles, dissertations, theses and technical reports published in indexed databases, including PubMed, Scopus, Web of Science, LILACS and SciELO. The sample was constituted through intentional sampling, selecting 94 documents that met the inclusion criteria: (1) publication between 2018 and

2025; (2) explicit approach to the geographical distribution of health professionals; (3) focus on remote, rural or peripheral regions; (4) discussion of impacts on mortality, morbidity, or access to care; (5) Availability of full text in Portuguese or English. Studies that dealt only with technology without considering territorial context, research with more than seven years of publication, and documents that did not present adequate methodological rigor were excluded.

The data collection procedures involved a systematic search using combined descriptors: "geographic distribution AND health professionals", "scarcity AND doctors AND remote regions", "equity AND health AND territory", "mortality AND access AND primary care". McDonald et al. (2025, p. 4) argue that "the interlinkage between availability of health workers and socioeconomic status in rural and remote areas reveals patterns of structural inequality." This observation guided the inclusion of studies that considered socioeconomic dimensions, particularly research carried out in contexts of vulnerability.

Data analysis proceeded in three sequential stages. First, an exploratory reading of the titles and abstracts was carried out, identifying potentially relevant documents. Subsequently, an analytical reading of the full text was performed, extracting information about: (1) research objectives; (2) methodology used; (3) main findings on the distribution of professionals; (4) documented impacts on mortality or morbidity; (5) conclusions and recommendations; (6) Limitations identified. Finally, a thematic synthesis was carried out, grouping findings into analytical categories: patterns of geographic distribution, mechanisms of inequality, impacts on health indicators, existing public policies, and structural barriers.

Mouta et al. (2023, p. 19698) highlight that "the unequal availability of intensive care units in Brazil reflects disparities that have intensified during health crises". This understanding underpinned the interpretation of the data, seeking to identify not only the distribution of resources, but also how this distribution translates into concrete differences in life and death. Pinheiro et al. (2024, p. e6993) observe that "analysis of the spatial distribution of hospitalizations reveals patterns that reflect inequalities in the provision of primary care".

Ethical aspects were considered throughout the research. Although this is a literature review that does not involve primary data collection with human participants, the citation standards were strictly respected, avoiding plagiarism and ensuring adequate attribution of authorship. The selection of sources sought to represent diverse perspectives, including studies that present criticisms of existing public policies, ensuring a balanced and unbiased analysis. Soares, García, and Carbonell (2023, p. 1) argue that "territorial inequalities in the financing of education and health policies reflect policy choices that can be transformed."

Methodological limitations include: (1) restriction on publications in Portuguese and English, potentially excluding relevant contributions in other languages; (2) focus on academic literature, leaving aside reports from non-governmental organizations or public policy documents; (3) search period limited to seven years, although sufficient to capture recent trends; (4) possible publication bias, where studies with positive results tend to be more published than studies that did not find significant effects. Souza et al. (2022, p. 2138) observe that "the organization and provision of care in response to health crises reveals structural gaps in the distribution of professionals". Despite these limitations, the methodology adopted allows for a comprehensive and reasoned analysis of the theme.

Table 1

Academic References and Their Contributions to Research

Author	Title	Year	Contributions
CASTRO, M. R. de; LÉDA, P. H. O.	Sanitary regulations and geographic distribution in the manufacture of herbal medicines in Brazil	2021	It analyzes how health regulations influence the geographical location of the production of herbal medicines, evidencing relationships between regulation, territory and health industry.
GESSI, N. L. et al.	Health and its relationship with development: a look at the contribution of health to regional development	2021	It discusses health as a vector of regional development, relating the supply of services, health indicators and territorial socioeconomic dynamics.
SCHUMANN, C. et al.	Housing of the Minha Casa Minha Vida Program (PMCMV): study of locations in relation to risk areas and permanent preservation in the city of Porto Alegre	2021	It investigates the location of PMCMV housing in areas of risk and permanent preservation, pointing out socio-environmental impacts and urban inequalities.
BASU, S. et al.	Estimated Effect on Life Expectancy of Primary Care Shortage Alleviation in the United States	2021	It estimates the impact of the expansion of primary care on life expectancy, evidencing the strategic role of family physicians in reducing mortality.
CASTRO, M. R. de; LÉDA, P. H. O.	Sanitary regulations and geographic distribution in the manufacture of herbal medicines in Brazil	2021	(already described above – reinforces the interface between health policies, the pharmaceutical industry and the territorial organization of health production).
SOUZA, T. S. et al.	Organization and provision of physiotherapy assistance in response to the COVID-19 pandemic in Brazil	2022	It describes the structuring and expansion of physiotherapy during the COVID-19 pandemic, highlighting challenges in the provision of services and in the organization of care networks.
LIMA, L. V. de et al.	Temporal trend, distribution, and spatial autocorrelation of leprosy in Brazil: an ecological study, 2011 to 2021	2022	It analyzes trends and spatial patterns of leprosy, identifying areas of greater risk and supporting the planning of surveillance and control actions.
SANTOS, P. P. G. V. dos; OLIVEIRA, R. A. D. de; ALBUQUERQUE, M. V. de	Inequalities in hospital supply in the context of the Covid-19 pandemic in Brazil: an integrative review	2022	It systematizes evidence on inequalities in hospital supply during the pandemic, highlighting regional asymmetries in the availability of beds and specialized services.

CARREIRO, G. da S.	The medical labor market in Maranhão: internalization of medical courses, trained professionals and the constitution of a private health market	2023	It examines the internalization of medical courses and professionals in Maranhão and its effects on the configuration of a private health market in the state.
MARTINS, L. G. V.; COSTA, M. A.; CURI, R. L. C.	The unequal distribution of revenue collection among Brazilian municipalities	2023	It analyzes asymmetries in the collection of municipal revenues, relating fiscal inequalities to unequal financing capacities for public policies, including health.
MOUTA, A. A. N. et al.	Intensive Care Unit in Brazil: an analysis of the availability of beds in the face of the new Coronavirus pandemic, a narrative review	2023	It discusses the distribution and availability of ICU beds during the COVID-19 pandemic, highlighting regional imbalances and installed capacity challenges.
SOARES, M. M.; GARCÍA, E. M.; CARBONELL, J. R.-H.	Territorial inequalities in the financing of education and health policies in Spain and Brazil	2023	It compares the two countries in terms of territorial asymmetries in health and education financing, contributing to the debate on federative equity.
ASSIS, B. R. de; SANTOS, C. L. D. dos; BARROS, S. S.; LAGES, D. N.	Spatial patterns of maternal mortality due to abortion in Brazil (2014-2023)	2024	It maps and analyzes spatial patterns of maternal mortality due to abortion, highlighting the most vulnerable regions and subsidizing reproductive health policies.
PINHEIRO, R. B. C. et al.	Analysis of the spatial distribution of hospitalization rates for Severe Acute Respiratory Syndrome and mortality for COVID-19 in Paraíba, 2020-2022	2024	It explores the spatial distribution of hospitalizations and deaths from SARS/COVID-19 in Paraíba, identifying critical areas and intrastate inequalities.
CAO, M. et al.	Assessing the Impact of Inequality in the Supply of Physicians on Mortality in China: Global Health Implications	2025	It evaluates how the unequal distribution of physicians influences mortality in China, bringing implications for human resource planning in health on a global scale.
MCDONALD, E. et al.	Interlinkage between availability of health workers and socioeconomic status in rural and remote areas of Australia	2025	It analyzes the relationship between the availability of health professionals and socioeconomic status in rural/remote areas, contributing to the debate on equitable access in contexts of low population density.

Source: Author's elaboration (2026)

The table above organizes, in a temporal perspective, a set of national and international studies that articulate the distribution of services, health professionals, social determinants and health outcomes. This systematization facilitates the visualization of the evolution of knowledge about territorial inequalities, care provision and its impacts on morbidity and mortality, in addition to supporting comparisons between different contexts (Brazil and other countries) and guiding the planning of more equitable and evidence-based public policies.

4 RESULTS AND DISCUSSION

The analysis of the literature revealed consistent patterns of concentration of health professionals in urban centers, with dramatic care gaps in remote regions. Studies document that while metropolises have a density of doctors greater than 3 per thousand inhabitants, remote regions often have less than 0.5 per thousand inhabitants, creating a disparity of up to six times. Santos, Oliveira, and Albuquerque (2022, p. 328) observe that "inequalities in hospital supply in the context of the COVID-19 pandemic in Brazil revealed a concentration of resources in urban centers, leaving remote regions vulnerable to health collapses". This finding is not merely statistical; translates into differential mortality between territories.

The mechanisms that perpetuate this unequal distribution operate on multiple levels. Economically, health professionals migrate to where there are better salaries, technological infrastructure and opportunities for specialization. Socially, remote regions face professional isolation, difficulty in accessing continuing education, and limitations to family life. Politically, investments in health are often concentrated in urban centers where larger populations generate visible demand. Schoueri et al. (2025, p. 2) demonstrate that "physician distribution and income inequality are significantly correlated with lung cancer mortality in Brazil, suggesting that access to early diagnosis varies according to geography and income."

The impacts of this unequal distribution are manifested in alarming health indicators. Maternal mortality in remote regions is often five to ten times higher than in urban centers. Infant mortality follows a similar pattern. Infectious diseases that would be easily treatable in urban contexts become fatal in remote regions. Schumann et al. (2021, p. e00203) argue that "housing and infrastructure in peripheral regions often lack access to adequate health services, creating a context where housing vulnerability intersects with health vulnerability". This intersectionality reveals that the problem is not isolated; it is systemic.

Life expectancy works as a synthesis of multiple factors. Remote regions have a life expectancy 5 to 15 years lower than that of urban centers, a difference that cannot be attributed only to genetic or behavioral factors. Soares, García, and Carbonell (2023, p. 1) argue that "territorial inequalities in the financing of education and health policies in Spain and Brazil reflect political choices that perpetuate historical disparities." This finding points to a fundamental political issue: the unequal distribution is not accidental, but the result of decisions about resource allocation.

The COVID-19 pandemic has exposed with brutal clarity the consequences of this distribution. Remote regions have faced collapse of health systems not only due to a lack of beds or ventilators, but due to a lack of professionals to operate them. Souza et al. (2022, p. 2138) document that "organization and provision of physical therapy assistance in response

to the pandemic revealed disparities in the availability of professionals between urban and remote regions". This experience demonstrated that public health is not merely a technical issue, but a matter of territorial justice.

Existing public policies to reduce this disparity are insufficient. Financial incentive programs for professionals working in remote regions often offer modest additional compensation, insufficient to compensate for professional isolation and infrastructure limitations. Training programs for health professionals in remote regions face retention challenges; Locally trained professionals often migrate to urban centers as soon as they complete their training. McDonald et al. (2025, p. 4) argue that "interlinkage between availability of health workers and socioeconomic status in rural and remote areas of Australia reveals that financial incentives alone are insufficient for retention".

The issue of primary health care emerges as a potentially transformative strategy. When health professionals are present in remote communities, even with basic training, they are able to prevent diseases, identify problems early and refer complex cases. However, the implementation of primary care in remote regions faces structural challenges: lack of infrastructure, difficulty in recruitment and retention, insufficient funding. Pinheiro et al. (2024, p. e6993) note that "analysis of the spatial distribution of hospitalizations for severe acute respiratory syndrome reveals that regions with lower primary care supply have significantly higher hospitalization rates".

The migration of health professionals from remote regions to urban centers is a phenomenon that amplifies inequalities. Professionals trained in remote regions often migrate to cities in search of better conditions, creating a brain drain that leaves these regions even more deprived. This process is not the individual fault of professionals; It is a structural failure of systems that do not create sufficient incentives for retention. Martins, Costa, and Curi (2023, p. 15) argue that "unequal distribution of resources across Brazilian municipalities reflects political choices that perpetuate territorial disparities".

The ethical question that emerges from this reality is disturbing: Is it acceptable that geographic location of birth determines probability of survival? That death is not only possible, but probable, simply because someone was born far from urban centers? These questions are not rhetorical; These are issues that should guide public policies. The unequal distribution of health workers is not a technical problem that can be solved with more training or technology; It is a political problem that requires a willingness to redistribute resources, to recognize that health is a fundamental human right, not a commodity to be allocated according to market logic.

5 FINAL CONSIDERATIONS

This study analyzed the unequal distribution of health workers between urban and remote territories, examining its direct impacts on the life and death of vulnerable populations. The general objective was to understand the mechanisms by which geography determines care, recognizing that the geographic location of birth should not be a determining factor for survival. The question that guided the investigation asked how this unequal distribution produces differentiated impacts on mortality and morbidity, what mechanisms explain its persistence, and what are the ethical implications of allowing the territory to determine who lives and who dies.

The synthesis of the findings in the literature reveals that the concentration of health professionals in urban centers is not a natural or inevitable phenomenon, but the result of political decisions, economic incentives and power structures that have historically privileged metropolises. While cities have a density of doctors greater than 3 per thousand inhabitants, remote regions often have less than 0.5 per thousand inhabitants, creating a disparity of up to six times. This inequality does not remain abstract; It translates into differential mortality between territories, where women die in births that would be easily treatable in urban contexts, children succumb to preventable infectious diseases, and life expectancy diverges dramatically according to geographic location.

The mechanisms that perpetuate this unequal distribution operate at multiple levels simultaneously. Economically, health professionals migrate to where there are better salaries, technological infrastructure and opportunities for specialization, creating a vicious cycle where initial scarcity discourages new professionals from settling in. Socially, remote regions face professional isolation, difficulty in accessing continuing education and limitations to family life, making them unattractive destinations for professionals in training. Politically, investments in health are often concentrated in urban centers where larger populations generate visible demand and where political elites reside, creating a feedback loop that reinforces preexisting inequalities.

The persistence of this unequal distribution despite decades of public policies reveals structural flaws in how health systems allocate human resources. Financial incentive programs for professionals working in remote regions often offer modest additional compensation, insufficient to compensate for professional isolation and infrastructure limitations. Training programs for health professionals in remote regions face retention challenges; Locally trained professionals often migrate to urban centers as soon as they complete their training, creating brain drain that leaves these regions even more deprived.

This dynamic suggests that the solution does not lie in isolated incentives, but in a structural transformation of how society conceives the allocation of resources in health.

The impacts of this unequal distribution are manifested in alarming health indicators that cannot be ignored. Maternal mortality in remote regions is often five to ten times higher than in urban centers, representing women who died not because of lack of medical knowledge, but because of lack of access to professionals who have this knowledge. Infant mortality follows a similar pattern, with children in remote regions facing a significantly higher risk of death than children in urban centers. Infectious diseases that would be easily treatable in urban contexts become fatal in remote regions where there are no adequate antibiotics, no staff to diagnose or no infrastructure to treat.

Life expectancy works as a synthesis of multiple health factors, reflecting both the quality and quantity of life that a population can expect. Remote regions have a life expectancy 5 to 15 years lower than that of urban centers, a difference that cannot be attributed only to genetic or behavioral factors. This disparity reveals that the problem is not isolated in health; It is systemic, reflecting inequalities in education, housing, sanitation, and access to food that are often concentrated in remote regions. The intersectionality between territorial vulnerability, socioeconomic vulnerability, and health vulnerability creates a context where premature death is not the exception, but the norm.

The COVID-19 pandemic has exposed with brutal clarity the consequences of this unequal distribution of health professionals. Remote regions have faced the collapse of health systems not only because of a lack of beds or ventilators, but because of a lack of professionals to operate them, to diagnose them, to guide treatment. This experience has shown that public health is not a merely technical issue that can be solved with more equipment; It is a matter of territorial justice that requires the human presence of trained professionals. The pandemic has also revealed that health crises amplify preexisting inequalities, transforming chronic disparities into acute catastrophes where mass death becomes possible not due to lack of knowledge, but due to lack of access.

Existing public policies to reduce this disparity are insufficient when analyzed in depth. Financial incentive programs for professionals working in remote regions often offer modest additional compensation, insufficient to compensate for professional isolation, infrastructure limitations, and family life difficulties. Health worker training programs in remote regions face retention challenges that cannot be solved with more training alone; require transformation of working conditions, infrastructure and career prospects. This finding suggests that fragmented policies, focused on an isolated aspect of the problem, fail to break cycles of inequality that operate at multiple levels simultaneously.

The issue of primary health care emerges as a potentially transformative strategy, although it is often insufficiently implemented. When health professionals are present in remote communities, even with basic training, they are able to prevent diseases, identify problems early and refer complex cases to specialized centers. However, the implementation of primary care in remote regions faces structural challenges that cannot be ignored: lack of basic infrastructure, difficulty in recruiting and retaining professionals, insufficient funding, and professional isolation that discourages permanence. These challenges are not secondary; are central to understanding why primary care, although recognized as a fundamental strategy, remains underimplemented in remote regions.

The migration of health professionals from remote regions to urban centers is a phenomenon that continuously amplifies inequalities. Professionals trained in remote regions often migrate to cities in search of better conditions, creating a brain drain that leaves these regions even more deprived. This process is not the individual fault of professionals who seek to improve their lives; It is a structural failure of systems that do not create sufficient incentives for retention. The question that arises is whether it is ethical to allow professionals trained with public resources to migrate to urban centers, leaving communities that have invested in their training even more vulnerable.

The ethical question that emerges from this reality is disturbing and cannot be avoided: is it acceptable that geographic location of birth determines probability of survival? That death is not only possible, but probable, simply because someone was born far from urban centers? That women die in childbirth that would be easily treatable in urban contexts? Which children succumb to preventable infectious diseases? These questions are not rhetorical; These are issues that should guide public policies and decisions on resource allocation. The unequal distribution of health workers is not a technical problem that can be solved with more training or technology; It is a political problem that requires a willingness to redistribute resources, to recognize that health is a fundamental human right, not a commodity to be allocated according to market logic.

The contributions of this study are situated in multiple dimensions that transcend academia. First, it offers a comprehensive overview of the state of the art on the geographic distribution of health professionals and its impacts on mortality and morbidity, identifying convergences and divergences in the contemporary literature. Second, it articulates often separate perspectives: technical, pedagogical, ethical, and political impacts, demonstrating that adequate understanding of unequal distribution requires an integrated approach that recognizes the complexity of the problem. Third, it problematizes simplistic narratives that present technical solutions as sufficient to solve a problem that is fundamentally political.

Fourth, it provides the basis for informed public policies that seek to integrate territorial equity in health in a responsible and structural way.

The limitations of this research deserve explicit and honest recognition. The restriction on publications in Portuguese and English potentially excludes relevant contributions in other languages that could offer different perspectives. The focus on academic literature leaves aside reports from non-governmental organizations, public policy documents, and practical knowledge from health professionals and remote communities that experience this reality on a daily basis. The search period limited to seven years, while sufficient to capture recent trends, may set aside historical perspectives that contextualize contemporary debates. There is possible publication bias, where studies with positive results tend to be more published than studies that did not find significant effects of interventions.

The prospects for future research point in multiple directions that deserve in-depth investigation. Longitudinal studies that follow health professionals throughout their careers would provide more robust evidence on factors that determine permanence or migration from remote regions. Research that specifically focuses on the experiences of health workers in remote regions would help to understand the real barriers they face and possible solutions. Investigations into comparative public policies between countries would provide insights into approaches that can reduce territorial inequalities. Studies that examine ethical and justice implications in depth would contribute to the development of normative frameworks that guide the allocation of resources in health.

The integration of territorial equity in health is not an isolated technical issue, but a civilizational challenge that touches the heart of how we conceive justice, human rights, and collective responsibility. When implemented in a reflexive way, with attention to the ethical, political, and structural dimensions, the redistribution of health professionals expands life possibilities for remote populations, allowing geographic location to cease to be a death sentence. When neglected, as it has been historically, it perpetuates cycles of inequality that make premature death the norm for vulnerable populations. The question that arises is not whether to redistribute health professionals, but how to do so in a way that recognizes the fundamental right of all people to life-saving care, regardless of where they are born.

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BLOOD PRESSURE PROFILE IN UNIVERSITY STUDENTS WHO PRACTICE SPORTS VERSUS SEDENTARY INDIVIDUALS

PERFIL TENSIONAL EM INDIVÍDUOS UNIVERSITÁRIOS QUE PRATICAM DESPORTO VERSUS SEDENTÁRIOS

PERFIL DE PRESIÓN ARTERIAL EN ESTUDIANTES UNIVERSITARIOS QUE PRACTICAN DEPORTE EN COMPARACIÓN CON PERSONAS SEDENTARIAS



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ABSTRACT

Hypertension is a clinical condition that has been increasing significantly in recent years, both in the elderly population and in young adults. It is characterized by a persistent elevation of blood pressure and is considered hypertension when systolic blood pressure values are equal to or greater than 140 mmHg and/or diastolic blood pressure values are equal to or greater than 90 mmHg. Hypertension is one of the main risk factors for the development of cardiovascular diseases, and is therefore of great importance.

Keywords: Risk Factors. Obesity. Dietary Habits. Physical Exercise. Hypertension.

RESUMO

A hipertensão arterial é uma condição clínica que tem vindo a aumentar significativamente nos últimos anos tanto na população mais idosa, como nos jovens adultos. Caracteriza-se por uma elevação persistente da pressão arterial sendo considerada hipertensão quando os valores da pressão arterial sistólica são iguais ou superiores a 140 mmHg e/ou os da pressão arterial diastólica iguais ou superiores a 90 mmHg. A hipertensão arterial constitui um dos principais fatores de risco para o desenvolvimento de doenças cardiovasculares, tendo uma grande importância.

Palavras-chave: Fatores de Risco. Obesidade. Hábitos Alimentares. Exercício Físico. Hipertensão Arterial.

RESUMEN

La hipertensión es una afección clínica que ha aumentado significativamente en los últimos años, tanto en la población anciana como en los adultos jóvenes. Se caracteriza por una elevación persistente de la presión arterial y se considera hipertensión cuando los valores de presión arterial sistólica son iguales o superiores a 140 mmHg y/o los valores de presión

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arterial diastólica son iguales o superiores a 90 mmHg. La hipertensión es uno de los principales factores de riesgo para el desarrollo de enfermedades cardiovasculares y, por lo tanto, reviste gran importancia.

Palabras clave: Factores de Riesgo. Obesidad. Hábitos Alimentarios. Ejercicio Físico. Hipertensión.

1 INTRODUCTION

The incidence and mortality rates of cardiovascular disease (CVD) are declining in many countries in Europe, but it is still a major cause of morbidity and mortality. The World Health Organization (WHO) estimates that by 2030, more than 23 million people will die from CVD (1).

CVD is associated with multiple risk factors, which can be divided into modifiable and non-modifiable, the greater the aggregation or accumulation of factors in an individual, the greater the risk of developing CVD (2).

The most important way to prevent CVD is to promote a healthy lifestyle throughout life, with emphasis on regular physical activity, healthy eating, smoking cessation and moderate alcohol intake. The absence of this lifestyle associated with the presence of cardiovascular risk factors in young stages of life, such as adolescence, influences health in adult life (1).

Obesity and overweight are considered one of the main epidemics of the 21st century, influenced by unhealthy lifestyles. Excess body fat is a chronic condition associated with several health problems, and its main cause is an inadequate diet, characterized by excessive consumption of calories, saturated fatty acids, sugar and processed foods, as well as low intake of fruits and vegetables. In addition, physical inactivity and sedentary lifestyle contribute significantly to the problem (3,4).

According to the National Institute of Health Doutor Ricardo Jorge, in Portugal there is a high prevalence of risk factors for brain and cardiovascular diseases and a low rate of their control, especially of HTN and diabetes mellitus. These data highlight the need for strategies to screen the general population for CVD risk factors and promote healthy lifestyle measures and health literacy in Portugal (5).

The prevention of CVD continues to be a major challenge, requiring the implementation of lifestyle changes, primary and secondary prevention measures, as well as appropriate therapies and early diagnosis. To this end, it is essential to conduct studies to understand the aggregation of cardiovascular risk factors in the young population. This study aims to evaluate the prevalence of risk factors for hypertension in university students, comparing regular practitioners of physical activity with non-practitioners.

2 OBJECTIVE

To evaluate the prevalence of risk factors for hypertension in university students, comparing regular practitioners of physical activity with non-practitioners.

3 METHODOLOGY

This is a cross-sectional study with a mixed approach (quantitative and qualitative). Data collection took place during the month of December 2024. The participation of individuals was voluntary, ensuring the freedom to decide on their inclusion in the study and the possibility of withdrawing at any time, even after signing the informed consent. An individual questionnaire was applied to the target population to obtain demographic data and risk factors; then, weight and height and abdominal circumference were measured.

Qualitative variables included race (black or Caucasian), sex, dietary patterns (frequency of fast food and fruit/vegetable consumption, salt consumption), subjective perception of sleep, and regular physical activity. For the latter, two subgroups were defined: participants who perform ≥ 150 minutes of exercise per week and those who practice < 150 minutes. Among the quantitative variables, age, weight, height, BMI, blood pressure, and waist circumference were assessed.

To collect the weight, the individuals wore light clothing and were barefoot, using a properly tested and calibrated scale. Height was recorded with the aid of a stadiometer, in which the participant stood with the heels and head aligned, looking forward. Following these measurements, BMI was calculated by dividing the weight by the square of the height. To assess the abdominal perimeter, a tape measure positioned between the top of the hip bone and the last rib was used, ensuring that the participant had no clothing in that territory.

Blood pressure was assessed using the auscultatory method using an aneroid sphygmomanometer, tested and calibrated. Before each measurement, the participants sat for 5 minutes to ensure the stability and comfort expected for the evaluation, as recommended by the 2024 European Society Cardiology guidelines(6). During this process, appropriate conditions were respected, such as a calm environment, absence of previous consumption of stimulants, tobacco or exercise in the previous 30 minutes. The measurement was performed in both arms, with a maximum interval of two minutes and maintaining an adequate posture, sitting with back and arms supported.

After data collection, the variables were evaluated in order to test the hypotheses previously outlined. The statistical analysis included a descriptive approach for the qualitative variables and the calculation of the mean, standard deviation and percentages for the quantitative variables. For research and organization purposes, a database was created by the research team in Microsoft Excel ®. For the statistical analysis, the statistical data analysis and processing program SPSS Statistics ® (Statistical Product and Service Solutions) version 25 was used.

The normality of the data was tested according to the Kolmogorov-Smirnov test, applying parametric and non-parametric tests. Finally, parametric tests were used for a normal sample distribution or non-parametric tests for an abnormal sample distribution, for a 95% confidence interval and a p-value ≤ 0.05 .

The research team declares that there is no conflict of interest and undertakes to protect the participants involved in this project. The research was previously approved by the Ethics Committee of the Polytechnic Institute of Castelo Branco, under code no. 174/CE-IPCB/2024. All data collected were treated anonymously and confidentially, being coded by numbers or letters, in accordance with the principles established in the Declaration of Helsinki. The information obtained was used exclusively for academic and scientific purposes, and was not intended for any commercial or profitable use.

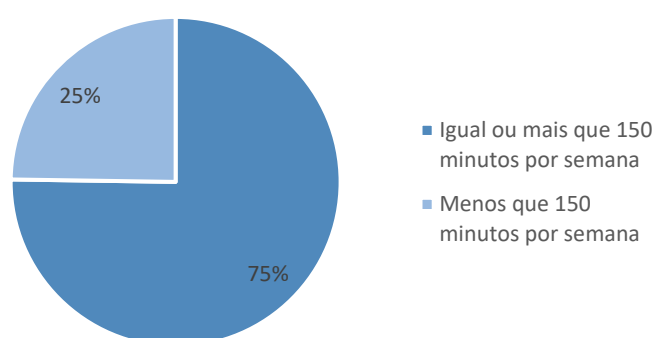
4 DEVELOPMENT

4.1 SAMPLE CHARACTERIZATION

The study sample consists of 105 exclusively male individuals, of which 79 belong to the group that practices 150 minutes or more of sports activity per week, designated as the group of regular sports practitioners (RD) and 26 who practice less than 150 minutes per week, being classified as non-regular sports practitioners (RDN) (Figure 1).

Figure 1

Distribution of individuals by NDR and RD



Source: Authors.

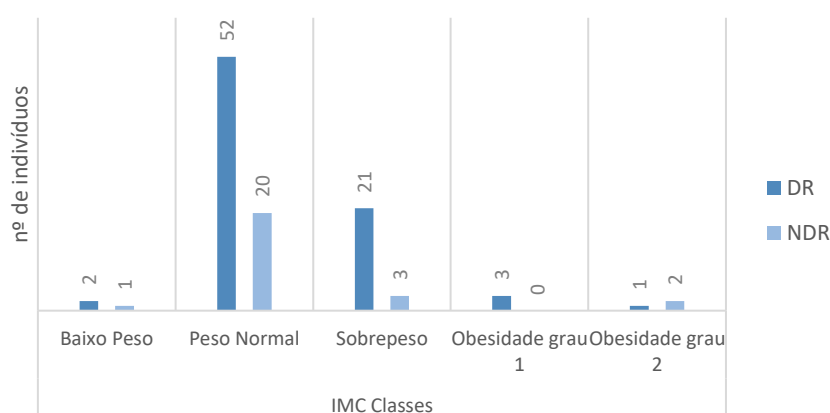
The age of the individuals varies between 18 and 27 years, with a mean of 20.22 ± 2.00 years, with the most prevalent age group being 19 years (22.9%). Regarding body weight, the average is 71.76 kg, with extreme values ranging from 48 kg to 120 kg. Regarding height, the average observed is 174.51 cm. Regarding the distribution of race, the sample is

composed of Caucasian and black individuals, with a total of 103 Caucasian and 2 black individuals.

Regarding abdominal circumference, 16 individuals (15.2%) had increased values. Regarding body mass index (BMI), there was a higher prevalence of overweight among individuals in the RD group (20%) compared to the NDR group (2.9%). Regarding grade 1 obesity, only cases were identified in the RD group. On the other hand, grade 2 obesity is more prevalent among individuals in the NDR group.

Figure 2

Distribution of BMI classes by NDR and RD individuals



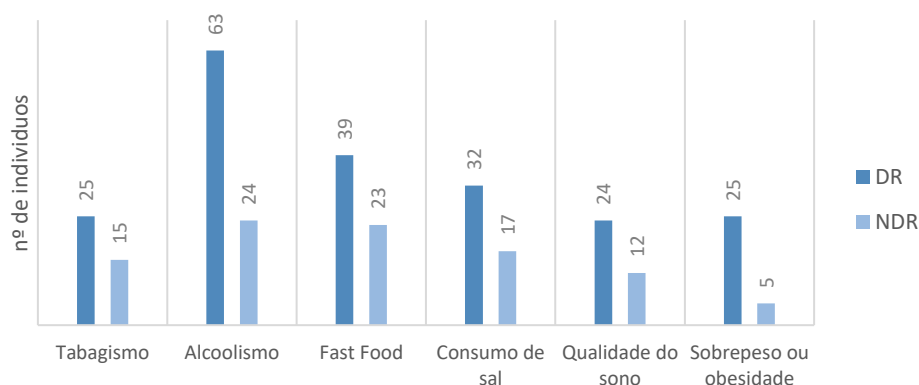
Source: Authors.

Regarding family history of cardiovascular diseases, 32.4% of the sample had a family history, 21.9% of whom belonged to the RD group and 10.5% to the RDN group.

4.2 RISK FACTORS

Figure 3

Distribution of risk factors by the RD and NDR groups



Source: Authors.

When analyzing all risk factors, it can be seen that alcoholism is the most prevalent, both in the group of regular sports practitioners (RD) (60%) and in the group of non-regular practitioners (RDN) (22.9%), followed by the consumption of fast food and excessive salt intake.

4.3 SMOKING

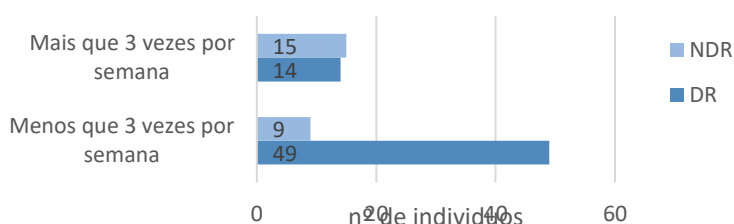
With regard to smoking, a higher number of smokers was observed among individuals in the RD group (23.8%) compared to those in the NDR group (14.3%). The mean duration of tobacco consumption is 3.13 ± 2.00 years, with an average daily smoking history of 9.37 ± 6.25 cigarettes per day. When asked whether entering higher education influenced the initiation of tobacco consumption, 21% of the individuals in the RD group answered affirmatively, while in the NDR group this percentage was only 13.3%. However, no statistically significant association was identified between sports practice and smoking initiation after entering higher education ($p = 0.545$).

4.4 ALCOHOL HABITS

Regarding the consumption of alcoholic beverages, the data show that the RD group has a higher prevalence of consumption, with 60% of the individuals. However, regarding regularity, the individuals in the RDN demonstrate a more frequent consumption. About 14.3% consume alcohol more than three times a week, while among the RD this percentage is only 13.3%. When asked whether entering higher education influenced adherence to alcohol consumption, 18.1% of the RDN and 33.3% of the RD answered affirmatively. There was a statistically significant association between sports practice and alcohol consumption ($p = 0.015$), weekly frequency ($p = 0.001$) and initiation after entering higher education ($p = 0.011$). Less active individuals consume alcohol more frequently.

Figure 4

Regularity of alcohol intake between the NR and NDR groups



Source: Authors.

4.5 FEEDING

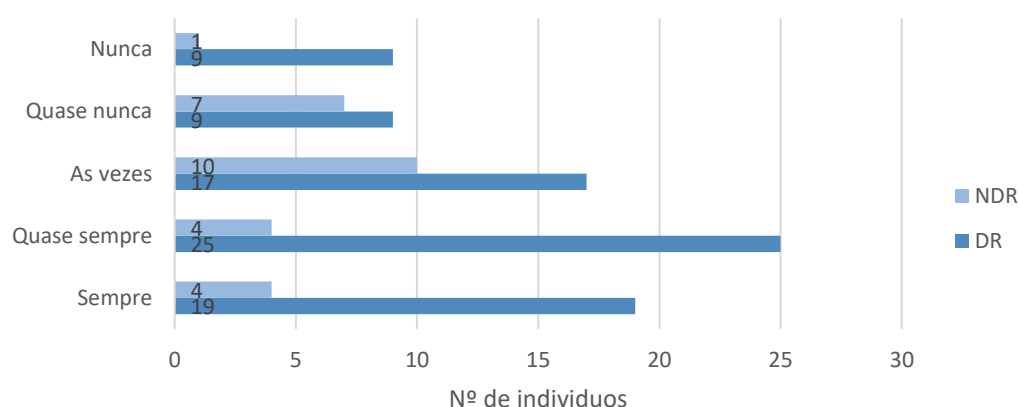
Regarding eating habits, the frequency of fast food consumption was analyzed. Considering the answers "sometimes", "almost always" and "always", it was observed that RD individuals register a higher percentage of *fast food* consumption (37.1%), compared to RDN individuals (21.9%). Although the percentage of fast food consumption is apparently higher in the most active group, statistical tests showed that individuals with less sports practice significantly have a higher frequency of consumption of this type of food ($p = 0.006$).

Regarding salt intake, 30.5% of the RD reported excessive consumption, while among the RDN this percentage was 16.2%. No significant association was found between sports practice and salt consumption ($p = 0.165$).

With regard to vegetable consumption, RD individuals show healthier eating practices, with 54.3% indicating regular consumption, a value higher than that recorded in the RDN. However, the relationship between vegetable consumption and sports practice was not statistically significant ($p = 0.552$). Similarly, with regard to the preparation of their own meals, 58.1% of the RD stated that they cooked their own meals, contrasting with 17.1% of the RDN (Figure 5). The relationship between sports practice and meal preparation showed a trend towards significance ($p = 0.060$), suggesting that more active individuals may be more predisposed to prepare their own food.

Figure 5

Regularity of the preparation of the meals themselves in the DR and NDR



Source: Authors.

Regarding the quality of the diet, most individuals considered that they had improved their eating habits. However, 32.3% of the participants in the RD group and 5.7% in the NDR group reported a worsening in relation to the last year. There was a significant association

between sports practice and the perception of food quality in relation to the previous year ($p = 0.019$), as well as with the self-perception of having a healthy diet ($p = 0.002$).

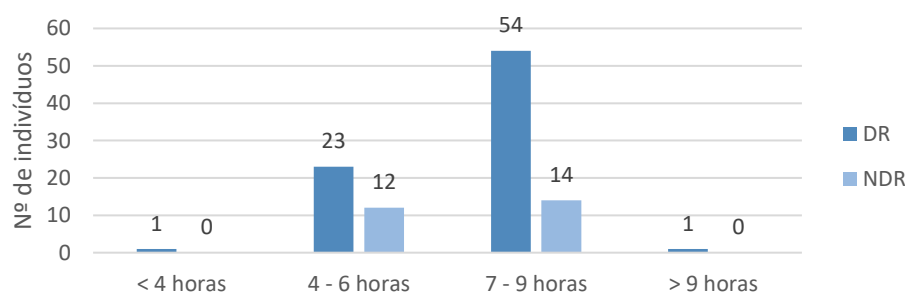
4.6 SLEEP HYGIENE

Regarding sleep quality, RD individuals reported sleeping more hours, with 51.4% reporting sleeping between 7 and 9 hours per night. However, it is observed that 11.4% of NDRs and 21.9% of RDDs sleep only between 4 and 6 hours per night (Figure 8). The relationship between the number of hours of sleep and sports practice was not statistically significant ($p = 0.392$).

Even so, there is a higher percentage of RD individuals who consider that the quality of their sleep has decreased in relation to the last year (21.9%), while 10.5% of NDR individuals. When asked if they considered themselves to have enough time to sleep, 41% of individuals answered negatively. A marginally significant association was identified between sports practice and the feeling of getting enough sleep ($p = 0.045$), with the most active individuals being more likely to consider that they get enough sleep.

Figure 6

Distribution of hours of daily sleep by DR and NDR individuals



4.7 BLOOD PRESSURE

Regarding systolic blood pressure (SBP), individuals in the RD group have a higher prevalence of Grade 1 hypertension (HTN) (32.4%) compared to the NDR group (9.5%). The same is true for Grade 2 HTN, with 6.7% in RD and 2.9% in NDR. No with regard to diastolic blood pressure (DBP), the prevalence of Grade 1 HTN is higher in the NDR group (6.7%) compared to the RD group (3.8%). In the case of Grade 2 HTN, only one case was recorded, belonging to the NDR group (Table 1).

When analyzing the relationship between the variable systolic blood pressure (SBP) and the two groups under study, no statistically significant differences were found. On the

other hand, when diastolic blood pressure (DBP) was related to the same groups, statistically significant differences were found, according to the *Kruskal-Wallis test* ($p < 0.005$).

Table 1

Relationship of DBP and SBP levels in the two groups

	P	Hi	H	H	H	Nor	Eleva	H	H	H
	AS	gh	TA	TA	TA	mal DBP	ted	TA	TA	TA
	Norm	norma	Grade	Grade	Grade		normal	Grade	Grade	Grade
	al	I SBP	1	2	3		DBP	1	2	3
No. of DR Individuals	8	30	34	7	0	31	43	4	0	1
No. of NDR Individuals	1	12	10	3	0	5	13	7	1	0

Legend: SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure. Source: Authors.

5 DISCUSSION

The practice of physical activity is recognized as essential for health and human development, regardless of the modality practiced. However, there is an increase in sedentary lifestyle in modern societies — especially among university students — which reduces the need for physical exertion and negatively impacts general health (7). The systematic review "health benefits of physical activity and fitness in school-aged children and youth" indicates that physically active individuals have better cardiorespiratory and muscular fitness, adequate body composition, higher bone density, and lower rates of anxiety and depression. Additionally, inactivity in youth is associated with increased risk of chronic diseases and reduced life expectancy (8).

The transition to higher education is often accompanied by significant changes in students' routines, particularly due to distance from family and home community. This period is marked by an increase in autonomy and responsibility, which can make it difficult to maintain a balanced and healthy lifestyle (9).

The present study, carried out at the School of Education (ESE), included 105 male individuals. The mean body weight was 71.76 kg and the mean height was 174.51 cm, values that are in line with those obtained in the IPB study in Bragança, where the mean weight was 72.2 kg and the mean height was 173.8 cm (10). Regarding abdominal perimeter, 15.2% of

the individuals had increased values, a percentage higher than the prevalence of 5.8% reported in another national study (11).

Regarding BMI, a higher prevalence of overweight was observed among individuals in the RD group (20%) compared to the NDR group (2.9%). This result may be justified, in our study, by the high number of participants in the RD group. This finding contradicts the results of Motevalli et al., which indicate a significantly lower BMI among physically active individuals, although the literature also presents studies with inconclusive results regarding this association (12,13).

Regarding family history of cardiovascular diseases, 32.4% of the sample had a family history, a value considerably higher than that observed in previous studies (14.15), with 21.9% belonging to the RD group and 10.5% to the NDR group.

Among the main risk factors associated with hypertension identified in this study, alcohol consumption, fast food consumption, and excessive salt intake stood out. Alcohol consumption is the most prevalent, both in the RD (60%) and in the RDN (22.9%) groups. This data differs from the results of Cicekli, according to which physical inactivity was the most common risk factor, with a prevalence of 89.2% (16).

Regarding smoking, the prevalence of smokers was higher in the RD group with 23.8%, compared to the NDR, which registered 14.3%. These data contrast with most of the literature, which generally associates sports practice with lower rates of substance consumption. This paradox may reflect a sports culture where physical performance is not necessarily linked to healthy choices outside the competitive context. In some contexts, excessive emphasis on victory and performance can devalue ethical principles and healthy behaviors, leading to practices such as the use of harmful substances or unsportsmanlike attitudes. Thus, sports culture, when focused only on performance, can neglect fundamental values such as respect, integrity, and the overall well-being of athletes (17). In the total sample, a prevalence of 38.1% of smokers was observed in the total sample, a value significantly higher than that reported by André M. et al., who indicated only 12.6%. However, the highest proportion of smokers is among the RD group (23.8%), in line with the data from the same study, which also reported a higher prevalence among RD (18).

Regarding alcohol consumption, 60% of RDDs reported consuming alcoholic beverages, in contrast to 22% of NDRs. Although most participants indicated that entering higher education did not significantly influence the initiation of consumption, it was observed that NDRs reported a higher frequency of consumption (more than three times a week).

The prevalence of alcohol consumption among RDs (60%) is lower than that reported by another study, which indicated 80.4% (18). However, the trend of higher consumption

among RDs continues. On the other hand, a different study points out that college athletes are less likely to have frequent alcohol consumption. These data suggest that social factors, such as the academic environment and university parties, may have a significant impact on alcohol consumption patterns among higher education students (19). In addition, the majority of participants in both groups indicated that entry into higher education did not significantly influence the onset of alcohol consumption, suggesting that other factors, such as the social environment, may have a greater impact.

Inadequate diet is widely recognized as one of the main risk factors for obesity and, therefore, should be a central focus in health promotion strategies aimed at the university population (9,20,21). In this study, the frequency of fast food consumption was analyzed, considering the answers "sometimes", "almost always" and "always": 37.1% of the RD reported consuming fast food frequently, compared to 21.9% of the RDN. Although these values may seem contradictory, the statistical tests revealed a significant association between less sports practice and higher frequency of fast food consumption ($p = 0.006$), confirming the trend of less healthy eating behaviors among inactive individuals.

Regarding salt consumption, 46.7% of the individuals reported adding more than one dessert spoon of salt to their meals, a value similar to that identified by Zobo et al.(22), in which 41.5% of the participants reported the same habit. Despite this, no statistically significant association was observed between sports practice and salt consumption, which may indicate that this eating behavior is influenced by factors other than physical activity.

Regarding the consumption of legumes and vegetables, 58.1% of the RD stated that they cooked their own meals, in contrast to only 17.1% of the RDN. Overall, 75.1% of the participants indicated that they prepared their own meals, corroborating the findings of Dias Fernandes J. et al., who highlight a positive association between physical activity and healthy eating habits, including higher vegetable intake (23). This data was reinforced by another study, in which 80.5% of the individuals reported cooking their own meals (24), suggesting that food autonomy can be a protective factor in the university context.

The self-assessment of diet quality revealed that, although most indicated an improvement in eating habits, 32.3% of RD and 5.7% of NDR reported a worsening compared to the last year. When asked if they considered themselves to have a healthy diet, 81.9% of participants answered affirmatively. According to the WHO (25), lifestyle and diet changes can prevent up to 50% of diabetes cases and 40% of cancer cases. In addition, poor diet quality is associated with the development of several chronic diseases, such as cardiovascular disease, type 2 diabetes, and certain types of cancer.

Research on sleep health revealed that 51.4% of RDs sleep between 7 to 9 hours per night. However, 33.3% of participants in the total sample sleep only between 4 to 6 hours per night, indicating a pattern of partial sleep deprivation. This pattern is consistent with data from the systematic review *What is Known About Students and Sleep*, which reported an average of 6.95 hours of sleep per night among college students (26).

Although there was no statistically significant association between the number of hours slept and the level of sports practice, there was a marginal association with the subjective perception of getting enough sleep ($p = 0.045$), suggesting that perceived well-being may be higher among the most active, even if the duration of objective sleep does not differ significantly. In addition, a higher percentage of RD indicated that the quality of their sleep decreased in the last year, and 41% of participants said they did not have enough time to rest.

With regard to SBP, it was found that individuals in the RD group have a significantly higher prevalence of Grade 1 hypertension (HTN) (32.4%) compared to RDN (9.5%), this fact may be justified by factors that have been explored, such as the exaggerated response of blood pressure to physical exercise, the type of exercise practiced, anthropometric factors or the use of substances and supplements(27–29). The same was observed in Grade 2 HTN, with 6.7% among RD and 2.9% among RDN. These results are in line with the study "Sports activities at a young age decrease hypertension risk—The J-Fit+ study" (23), which suggests that sports practice from youth has a preventive role in blood pressure control, so it would be beneficial for students, guidelines for university health programs, with the promotion of regular physical activity, education and awareness, as well as monitoring and evaluation (30).

In a previous study (15), it was observed that individuals classified as physically inactive had significantly higher levels of SBP and DBP ($p < 0.05$). In the present study, although the prevalence of systolic HTN was higher among RDs, it was the NDRs that presented higher levels of diastolic HTN in the Grade 1 and 2 classifications, with statistically significant differences between the groups according to the Kruskal-Wallis test ($p < 0.005$).

Finally, a study conducted by João Lopes observed that athletes showed a more pronounced reduction in DBP after low-intensity exercise (50% of heart rate reserve), compared to non-athletes — especially in the 1st, 5th, and 6th hours post-exercise. These results reinforce the hypothesis that regular physical activity contributes positively to the regulation of diastolic blood pressure (31).

In the present study, limitations were identified, such as the sample being composed exclusively of students from a single higher education institution, which limits the

generalization of the results to other university populations or young adults in different socioeconomic and cultural contexts. Factors such as the emotional state of the participants and the technique used can influence the results. The evaluation of the participants' lifestyle and eating patterns was carried out through subjective questionnaires, without defined standard doses, which can compromise the accuracy of the information collected. The use of validated instruments, such as the Food Frequency Questionnaire developed by the Harvard T.H. Chan School of Public Health, would have been beneficial for a more rigorous assessment of the participants' eating habits(32).

In addition, an unequal distribution was observed between the two groups under study, with a predominance of regular practitioners of physical activity, which may limit the comparison between the groups. For future investigations, it is important to minimize the subjectivity inherent in the data collection in the study, it is recommended to standardize food portions and implement consistent schedules for blood pressure assessment. These measures aim to reduce variabilities associated with external factors, such as circadian rhythm and the measurement environment, promoting greater precision and reliability in the results obtained.

6 FINAL CONSIDERATIONS

In future investigations, it is essential to ensure a balanced distribution among groups of participants to avoid selection bias, ensuring data comparability. In addition, the use of validated and objectively measurable instruments for collecting data on students' lifestyles is essential to reduce subjectivity and increase the accuracy of results. Finally, it is necessary to expand scientific research focused on the often neglected university age group to support effective preventive interventions that promote healthy lifestyles and prevent chronic diseases in this population.

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GENETIC LITERACY IN ADOLESCENTS WITH GENETIC DISORDERS: A BIOPSYCHOSOCIAL AND CLINICAL APPROACH

ALFABETIZAÇÃO GENÉTICA EM ADOLESCENTES COM TRANSTORNOS GENÉTICOS: UMA ABORDAGEM BIOPSISSOCIAL E CLÍNICA

ALFABETIZACIÓN GENÉTICA EN ADOLESCENTES CON TRASTORNOS GENÉTICOS: UN ENFOQUE BIOPSISSOCIAL Y CLÍNICO



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ABSTRACT

Genetic literacy constitutes an essential component in contemporary medicine, particularly in the management of adolescents with genetic disorders. This population group faces complex challenges encompassing biomedical, psychological, and social dimensions. The aim of this chapter is to analyze the role of genetic literacy in adolescents with genetic diseases, its relationship with psychological adaptation, and its clinical implications. The components of genetic literacy, associated factors, empirical evidence, and the role of genetic counseling are reviewed. Evidence suggests that, although levels of genetic literacy are often low, adolescents may present adequate levels of psychological adaptation, indicating the influence of psychosocial factors. An integrative biopsychosocial model is proposed to optimize clinical and educational interventions.

Keywords: Genetic Literacy. Adolescents. Genetic Diseases. Psychological Adaptation. Genetic Counseling.

RESUMO

A alfabetização genética constitui um componente essencial na medicina contemporânea, particularmente no manejo de adolescentes com transtornos genéticos. Esse grupo

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populacional enfrenta desafios complexos que abrangem dimensões biomédicas, psicológicas e sociais. O objetivo deste capítulo é analisar o papel da alfabetização genética em adolescentes com doenças genéticas, sua relação com a adaptação psicológica e suas implicações clínicas. São revisados os componentes da alfabetização genética, fatores associados, evidências empíricas e o papel do aconselhamento genético. As evidências sugerem que, embora os níveis de alfabetização genética sejam frequentemente baixos, os adolescentes podem apresentar níveis adequados de adaptação psicológica, o que indica a influência de fatores psicossociais. Propõe-se um modelo integrador biopsicossocial que permita otimizar intervenções clínicas e educacionais.

Palavras-chave: Alfabetização Genética. Adolescentes. Doenças Genéticas. Adaptação Psicológica. Aconselhamento Genético.

RESUMEN

La alfabetización genética constituye un componente esencial en la medicina contemporánea, particularmente en el manejo de adolescentes con trastornos genéticos. Este grupo poblacional enfrenta desafíos complejos que abarcan dimensiones biomédicas, psicológicas y sociales. El objetivo de este capítulo es analizar el papel de la alfabetización genética en adolescentes con enfermedades genéticas, su relación con la adaptación psicológica y sus implicaciones clínicas. Se revisan los componentes de la alfabetización genética, factores asociados, evidencia empírica y el rol del asesoramiento genético. La evidencia sugiere que, aunque los niveles de alfabetización genética suelen ser bajos, los adolescentes pueden presentar adecuados niveles de adaptación psicológica, lo que indica la influencia de factores psicossociales. Se propone un modelo integrador biopsicosocial que permita optimizar intervenciones clínicas y educativas.

Palabras clave: Alfabetización Genética. Adolescentes. Enfermedades Genéticas. Adaptación Psicológica. Asesoramiento Genético.

1 INTRODUCTION

The advancement of medical genetics has profoundly transformed the understanding, diagnosis, and management of multiple diseases. However, this progress has generated a growing need for patients to understand complex genetic concepts in order to actively participate in decision-making about their health (Abrams et al., 2015; Hurle et al., 2013).

In this context, genetic literacy emerges as a fundamental tool, especially in vulnerable populations such as adolescents with genetic disorders. Adolescence represents a critical stage of development characterized by the construction of identity, the search for autonomy, and the consolidation of cognitive and social skills (Alderson, 2007; McGill et al., 2019).. The coexistence of these characteristics with a chronic genetic condition introduces additional challenges that impact both psychological well-being and adherence to treatment (Wakefield et al., 2016).

Various studies have indicated that adolescents with genetic diseases constitute a risk group for emotional alterations, including anxiety, depression and difficulties in social integration. However, a remarkable resilience has also been observed in many of these patients (Forrest et al., 2010).

This chapter aims to comprehensively analyze genetic literacy in adolescents with genetic disorders, exploring its relationship with psychological adaptation and its relevance in clinical practice.

2 CONCEPTS OF GENETIC LITERACY

Genetic literacy is defined as an individual's ability to obtain, understand, and use genetic information to make informed decisions about their health (Hurle et al., 2013; Lea et al., 2011).

This concept is structured in four main dimensions (Abrams et al., 2015) :(FIG. 1)

2.1 FAMILIARITY

Degree of exposure and comfort with concepts such as genes, chromosomes, mutations, and inheritance.

2.2 COMPREHENSION

Ability to interpret genetic information and establish relationships between concepts.

2.3 GENETIC ARITHMETIC

Ability to understand probabilities, risks, and inheritance patterns (Kaphingst et al., 2012).

Genetic literacy is a subcomponent of health literacy, but it is more complex due to the abstract and probabilistic nature of genetic information (Nutbeam, 2000).

3 ADOLESCENCE AND GENETIC DISORDERS

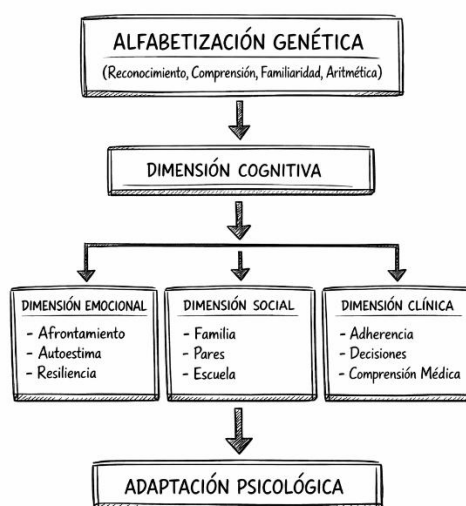
Adolescence is a transitional stage characterized by biological, psychological, and social changes. In this period, individuals develop their identity, autonomy, and decision-making skills (Alderson, 2007).

When a teen has a genetic disorder, multiple stressors are added:

- Chronicity of the disease
- Frequent medical checkups
- Functional limitations
- Social stigmatization
- Uncertainty about the forecast (Biesecker & Peters, 2001)

Figure 1

Conceptual model. Biopsychosocial model of genetic literacy in adolescents



Modelo integrador que ilustra la interacción entre alfabetización genética y factores psicosociales en la adaptación de adolescentes con trastornos genéticos.

Ability to identify basic genetic terms used in clinical practice.

3.1 PSYCHOLOGICAL IMPACT

Teens with genetic diseases may experience:

- Anxiety and depression
- Low self-esteem
- Alterations in body image
- Difficulties in social relationships
- Fear related to future reproduction

These manifestations have been widely documented in the literature, highlighting the emotional impact of genetic knowledge and the associated uncertainty (Wakefield et al., 2016; McGill et al., 2019).

3.2 SOCIAL DIMENSION

Social impact includes:

- Peer integration issues
- Long-term family dependency
- Limitations on school and recreational activities

The family and social environment plays a determining role in the adolescent's adaptation, acting as a protective or risk factor depending on the quality of the support received (Forrest et al., 2010; Bronfenbrenner, 1989).

Despite these challenges, many adolescents maintain similar life aspirations to their peers, highlighting the importance of interventions that promote their autonomy. (FIG.2)

4 LEVELS OF GENETIC LITERACY IN ADOLESCENTS

The available evidence indicates that adolescents with genetic disorders generally have low levels of genetic literacy (Haga et al., 2013; Kaphingst et al., 2012).

Among the most relevant findings:

- Low recognition of specialized terms
- Partial understanding of complex concepts
- Difficulties in interpreting probabilities
- Better performance on everyday concepts such as "heredity"

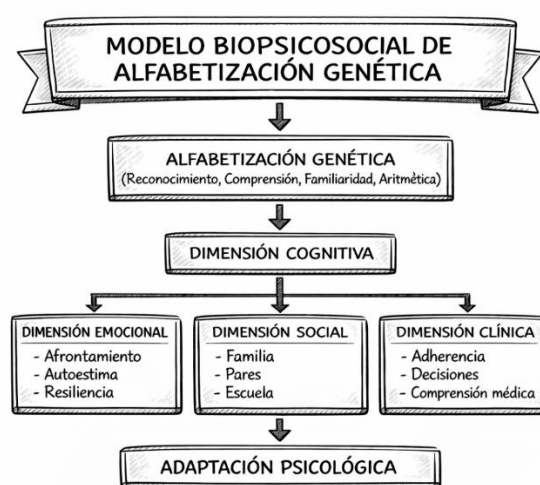
These results suggest that genetic knowledge in adolescents is:

- Fragmented
- Superficial

- Dependent on educational level (Lea et al., 2011)

Figure 2

The figure represents a biopsychosocial model of genetic literacy, where genetic knowledge acts as the starting point of the process. This is channeled through the cognitive dimension, which in turn influences three key areas: emotional (coping, self-esteem, resilience), social (family, peers, school) and clinical (adherence, decision-making, medical understanding). The interaction of these dimensions converges in psychological adaptation, showing that genetic understanding is not only informative, but also decisive in the integral adjustment of the patient



5 PSYCHOLOGICAL ADAPTATION

Psychological adaptation is defined as the degree to which an individual manages to adjust emotionally and cognitively to a chronic condition (Wakefield et al., 2016).

This construct includes:

- Effective coping
- Self-esteem
- Social integration
- Existential well-being

5.1 KEY FINDINGS

Studies have shown that:

- Adolescents may have adequate levels of psychological adjustment
- There is a significant capacity for resilience
- Social support plays a determining role (Forrest et al., 2010; Wakefield et al., 2016)

5.2 RELATIONSHIP TO GENETIC LITERACY

A particularly relevant finding is that:

There is not always a direct relationship between genetic literacy and psychological adaptation (McGill et al., 2019).

This suggests that:

- Knowledge is not the only determinant of well-being
- Emotional and social factors have a significant weight (Bronfenbrenner, 1989)

6 FACTORS ASSOCIATED WITH GENETIC LITERACY

Genetic literacy is influenced by multiple variables (Abrams et al., 2015).

6.1 EDUCATIONAL LEVEL

There is a direct relationship between schooling and genetic understanding (Lea et al., 2011).

6.2 FAMILY ENVIRONMENT

The educational level of the parents significantly influences the adolescent's understanding (Forrest et al., 2010).

6.3 ACCESS TO INFORMATION

The quality of doctor-patient communication is key (Kaphingst et al., 2016).

6.4 COMPLEXITY OF DIAGNOSIS

More complex diseases generate greater difficulty in understanding (Haga et al., 2013).

7 ROLE OF GENETIC COUNSELING

Genetic counseling is a fundamental process in the management of patients with genetic diseases (Resta et al., 2006).

7.1 DEFINITION

It is an educational and psychosocial process that:

- Explain the nature of the disease
- Facilitates decision-making
- Promotes psychological adaptation (Biesecker, 2001)

7.2 MAIN FUNCTIONS

- Translating complex information into understandable language
- Assess patient understanding
- Reduce anxiety and uncertainty
- Support reproductive decisions (Resta et al., 2006)

7.3 IN ADOLESCENTS

In this population, counseling should:

- Adapt to the cognitive level
- Include emotional support
- Promoting progressive autonomy (Alderson, 2007)

8 CLINICAL IMPLICATIONS

Genetic literacy has important applications in medical practice (Lea et al., 2011):

8.1 CLINICAL COMMUNICATION

- Use of clear language
- Understanding Check
- Visual and didactic support (Kaphingst et al., 2016)

8.2 THERAPEUTIC ADHERENCE

- Greater understanding → better adhesion
- Reduction of errors in disease management (Haga et al., 2013).

8.3 PUBLIC HEALTH

- Incorporation of genetics in school education
- Health literacy programs (Nutbeam, 2000)

9 BIOPSYCHOSOCIAL INTEGRATIVE MODEL

A conceptual model based on three dimensions is proposed (Bronfenbrenner, 1989):

9.1 COGNITIVE DIMENSION

- Genetic Literacy

9.2 EMOTIONAL DIMENSION

- Psychological adaptation
- Coping Strategies

9.3 Social dimension

- Family Support
- Peer network
- Educational context

Integrative hypothesis

Psychological adjustment in adolescents with genetic disorders depends more on psychosocial factors than on the level of genetic literacy alone (Wakefield et al., 2016).

10 LIMITATIONS IN CURRENT RESEARCH

- Scarcity of studies in the adolescent population (McGill et al., 2019)
- Predominance of cross-sectional designs
- Lack of specific tools for adolescents
- Limited evidence in Latin American contexts (Penchaszadeh, 2000)

11 FUTURE LINES OF RESEARCH

- Longitudinal studies
- Development of educational interventions
- Assessing the Impact of Genetic Counseling
- Integration of digital tools (O'Connor et al., 2016)

12 CONCLUSIONS

Genetic literacy is an essential component in the comprehensive management of adolescents with genetic disorders (Hurle et al., 2013). Although levels of knowledge are usually limited, adolescents may present an adequate psychological adaptation, which shows the importance of psychosocial factors (Wakefield et al., 2016).

The approach to this population must be comprehensive, incorporating educational strategies, emotional support and adequate genetic counseling. The implementation of biopsychosocial models will optimize clinical results and improve the quality of life of these patients.

13 GENETIC LITERACY IN ADOLESCENT GYNECOLOGY

Adolescent gynecology represents a particularly relevant clinical setting for genetic literacy, given that many decisions at this stage are directly related to reproductive health (Committee on Adolescent Health Care, 2017).

- Pubertal development
- Ovarian function
- Future fertility
- Risk of genetic transmission
- Sexual and reproductive health

In adolescents with genetic disorders, these dimensions become more complex, since genetic information directly influences intimate, identity, and reproductive decisions.

13.1 GENETIC DISORDERS OF GYNECOLOGICAL RELEVANCE

The most relevant conditions include:

- Disorders of Sexual Differentiation (DSD)
- Primary ovarian insufficiency (e.g. Turner syndrome)
- Sex chromosomal abnormalities (e.g., Klinefelter syndrome in mosaic variants)
- Hereditary diseases with reproductive impact (cystic fibrosis, dystrophies, etc.)
- Carriers of X-linked diseases

These conditions require genetic understanding to address fertility and hereditary risk (McCullough & Chervenak, 2008). As well as:

- Reproductive Options
- Medical interventions (e.g., fertility preservation)

14 GENETIC LITERACY AND REPRODUCTIVE HEALTH

One of the most critical aspects is the adolescent's ability to understand reproductive implications (Chen & Goodson, 2007).

14.1 EARLY REPRODUCTIVE DECISION-MAKING

Although reproduction may seem distant, in adolescents with genetic diseases, questions arise such as:

- Can I have children?
- Will my disease be transmitted?
- What options are there to prevent transmission?

Here, genetic literacy has a direct impact on:

- Understanding genetic risk
- Perception of control
- Anticipatory anxiety (Wakefield et al., 2016)

14.2 REPRODUCTIVE TECHNOLOGIES AND GENETIC UNDERSTANDING

Genetic knowledge is key to understanding options such as:

- Preimplantation genetic diagnosis
- Prenatal diagnosis
- Reproductive counseling (Lyerly et al., 2009)

Without adequate literacy, these options can:

- Being misunderstood
- Generating false expectations
- Increase anxiety

15 ETHICAL DIMENSION IN ADOLESCENTS

Genetic literacy in gynecology is deeply linked to ethical dilemmas (Ross et al., 2013).

15.1 AUTONOMY VS. GUARDIANSHIP

In adolescents there is a tension between:

- Right to information
- Decision-making capacity
- Role of parents/guardians

The level of genetic literacy conditions the real ability to exercise autonomy (Alderson, 2007).

15.2 RIGHT NOT TO KNOW

Some teens may prefer:

- Avoid knowing genetic risks
- Postponing decisions

This poses challenges in:

- Late-onset diseases (Biesecker, 2001).
- Serious Hereditary Conditions

16 CLINICAL COMMUNICATION IN GENETIC GYNECOLOGY

Communication in this context must be highly specialized in adolescents (Kaphingst et al., 2016).

16.1 COMMON BARRIERS

- Excessive technical language
- Information overload
- Failure to adapt to cognitive development (Lea et al., 2011)
- Biomedical approach without an emotional component

16.2 ADVANCED STRATEGIES

- Use of analogies (e.g., "genetic instruction manual")
- Visual Models (Simplified Pedigree)
- Teach-back technique
- Tiered communication (Kaphingst et al., 2016)

17 DIGITAL GENETIC LITERACY

Adolescents actively seek information in digital environments (Stellefson et al., 2011).

17.1 RISKS

- Disinformation
- Misinterpretation
- Internet-induced anxiety (O'Connor et al., 2016)

17.2 OPPORTUNITIES

- Educational apps
- Interactive Platforms
- Genetic inheritance simulators (Stellefson et al., 2013)

This opens a key line for innovative interventions.

18 LATIN AMERICAN PERSPECTIVE

This is a key point to increase editorial impact, since genetic literacy in Latin America presents structural and sociocultural particularities that influence its development and implementation (Penchaszadeh, 2000).

18.1 STRUCTURAL GAPS

In Latin America:

- Low access to genetic counseling
- Limited training in clinical genetics
- Inequality in health education

These limitations have been widely documented and reflect an unequal distribution of genetic resources and services in the region (Castillo-Fernandez et al., 2019; Paz-y-Miño et al., 2015).

18.2 SOCIOCULTURAL CONTEXT

Cultural factors influence:

- Perception of genetic diseases
- Reproductive decisions
- Stigma

Cultural beliefs can condition the interpretation of genetic disease, generating barriers in the acceptance of the diagnosis and in the search for care (Biesecker & Peters, 2001; Penhaszadeh, 2001).

18.3 RELEVANCE TO ECUADOR

In contexts such as Ecuador:

- Access to genetics is limited
- Health education is heterogeneous
- The family role is highly decisive

These characteristics reflect the structural and sociocultural inequalities that directly impact genetic literacy (Paz-y-Miño et al., 2015).

19 EXTENDED BIOPSYCHOSOCIAL MODEL WITH A GYNECOLOGICAL APPROACH

An expansion of the integrative model based on an ecological approach is proposed (Bronfenbrenner, 1989).

An expansion of your model is proposed:

19.1 COGNITIVE DIMENSION

- Genetic Literacy
- Reproductive understanding (Hurle et al., 2013)

19.2 EMOTIONAL DIMENSION

- Reproductive anxiety
- Body and sexual identity (Wakefield et al., 2016)

19.3 SOCIAL DIMENSION

- Family Support
- Cultural norms
- Access to health (Forrest et al., 2010)

19.4 CLINICAL DIMENSION

- Medical Interventions
- Gynecological follow-up
- Genetic counseling (Resta et al., 2006)

Extended hypothesis

Reproductive decision-making in adolescents with genetic disorders depends on the interaction between genetic literacy, emotional maturity, and sociocultural context. (McGill et al., 2019).

20 PRACTICAL IMPLICATIONS IN GYNECOLOGY

20.1 CLINICAL CONSULTATION

- Integrating genetics into gynecological history
- Assess patient understanding
- Include anticipatory counseling (Committee on Adolescent Health Care, 2017)

20.2 PATIENT EDUCATION

- Material adapted by age
- Using Visual Tools
- Progressive education (Kaphingst et al., 2016)

20.3 HEALTH POLICIES

- Incorporating Genetics into Adolescent Health Programs
- Strengthen genetic counseling
- Continuing Medical Education (World Health Organization, 2002)

21 CLINICAL INTERVENTION PROPOSAL

A structured model based on educational and psychosocial interventions is proposed (Lea et al., 2011).

4-phase model:

1. Evaluation

- Level of genetic literacy
- Emotional state (Wakefield et al., 2016)

2. Personalized education

- Adapted language
- Visual material (Kaphingst et al., 2016)

3. Psychosocial support

- Clinical Psychology
- Family work (Forrest et al., 2010)

4. Longitudinal Tracking

- Periodic re-evaluation
- Information adjustment (O'Connor et al., 2016)

22 EXTENDED CONCLUSION

Genetic literacy in adolescents with genetic disorders, particularly in the gynecological setting, is a fundamental axis in modern medicine (Hurle et al., 2013). Its impact transcends biomedical knowledge, influencing identity, mental health, and reproductive decisions (Wakefield et al., 2016).

The clinical approach must evolve towards integrative models that consider not only the transmission of information, but also the emotional, social and cultural context of the adolescent (Bronfenbrenner, 1989).

Genetic Literacy in Latin American Adolescents

1. Introduction

Genetic literacy in Latin American adolescents represents an emerging challenge in public health and clinical medicine. Despite the rapid advancement of medical genetics, its integration into clinical practice and health education remains limited in Latin America, generating a gap between scientific knowledge and its application in the general population (Abrams et al., 2015; Hurle et al., 2013).

Adolescents are a particularly vulnerable group, given that they are in a stage of cognitive and psychosocial transition, which influences their ability to understand complex

genetic information and participate in decision-making related to their health (McGill et al., 2019).

2. Structural context in Latin America

2.1 Access to Genetics Services

In Latin America, access to clinical genetics services is limited and heterogeneous. The distribution of geneticists is uneven and services are often concentrated in highly complex urban centers (Penchaszadeh, 2000; Castillo-Fernández et al., 2019).

In countries such as Ecuador, this situation is aggravated by:

- Limitations in the health system
- Lack of integration of genetic counseling in primary care
- Economic and geographical barriers

This conditions late or non-existent access to adequate genetic information (Paz-y-Miño et al., 2015)

2.2 Genetics and health education

Formal education in genetics in Latin America has important limitations. Educational programs tend to focus on theoretical concepts, with little clinical application and little integration into health literacy (Dougherty et al., 2011).

This translates into:

- Superficial understanding of genetic concepts
- Difficulties in interpreting hereditary risks
- Limitations in informed decision-making (Lea et al., 2011).

3. Sociocultural factors

3.1 Family influence

In Latin American contexts, the family plays a central role in health decision-making. Adolescents rely heavily on their parents for the interpretation and management of genetic information (Forrest et al., 2010).

This can generate:

- Information Filtering
- Limitation of adolescent autonomy
- Biased interpretations of medical information

3.2 Beliefs and stigmatization

Several studies have shown that cultural beliefs influence the perception of genetic diseases, associating them in some cases with destiny, punishment or social stigma (Biesecker & Peters, 2001).

These beliefs can lead to:

- Denial of diagnosis
- Delay in seeking care
- Social isolation

4. Genetic literacy and the digital environment

Latin American adolescents have high access to the internet, but do not necessarily possess critical digital literacy skills (Stellefson et al., 2011).

This involves risks such as:

- Disinformation
- Misinterpretation of genetic information
- Self-Diagnosis Related Anxiety

However, the digital environment also represents an opportunity to implement innovative educational interventions (O'Connor et al., 2016).

5. Evidence in Latin American adolescents

The evidence in the region is limited, but it consists of noting:

- Low levels of genetic literacy
- Fragmented understanding of concepts
- Dependence on health professionals for decision-making (Haga et al., 2013; Kaphingst et al., 2012)

Despite this, it has been observed that:

- Many adolescents have adequate psychological adaptation
- Family support is a key protective factor (Wakefield et al., 2016).

6. Implications in adolescent gynecology

Genetic literacy acquires special relevance in adolescent gynecology, where it directly influences reproductive health and future decision-making. (FIG. 3)

6.1 Reproductive health

Understanding genetic concepts is essential to:

- Assess risk of hereditary transmission
- Planning for motherhood
- Understand conditions that affect fertility (Committee on Adolescent Health Care, 2017).

For example, adolescents with Turner syndrome require specific genetic education to understand their reproductive prognosis.

6.2 Teenage pregnancy

In adolescent pregnancy contexts, genetic literacy is often limited, restricting access to:

- Prenatal diagnosis
- Genetic counseling
- Informed decisions (Chen & Goodson, 2007).

6.3 Role of the gynecologist

In Latin America, the gynecologist frequently assumes genetic counseling functions due to the shortage of specialists, which highlights the need for training in genetic communication (Resta et al., 2006).

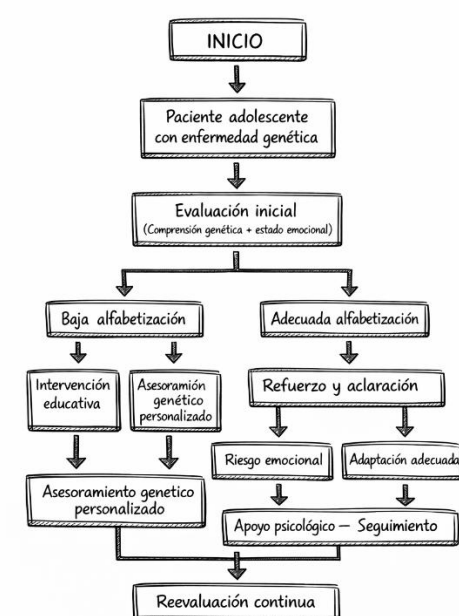
7. Model adapted to Latin America

An integrative model is proposed that includes:

- Individual level: genetic literacy and cognitive development
- Family level: parental education and communication dynamics
- Health level: access to services and quality of care
- Sociocultural level: beliefs, stigma and social norms (Bronfenbrenner, 1989).

Figure 3

Clinical flowchart. Approach to genetic literacy in adolescents



Flujograma de intervención clínica para mejorar la alfabetización genética y la adaptación psicológica en adolescentes.

8. Intervention strategies

8.1 Clinical level

- Use of clear language
- Understanding Check

- Progressive education (Kaphingst et al., 2016)

8.2 Educational level

- Integrating Genetics into School Curricula
- Health literacy programs (Nutbeam, 2000)

8.3 Digital level

- Validated educational platforms
- Technology-based interventions (Stellefson et al., 2013)

8.4 Level of public policies

- Strengthening Genetics Services
- Inclusion of genetic counseling in primary care (World Health Organization, 2002)

9. Conclusions

Genetic literacy in Latin American adolescents is limited and influenced by structural, educational, and sociocultural factors. However, it represents a key opportunity to improve the quality of health care, particularly in the gynecological setting (Hurle et al., 2013).

The development of strategies adapted to the regional context will strengthen the autonomy of the adolescent, optimize decision-making and reduce health inequities.

Ethical Issues in Adolescent Genetic Literacy

1. Introduction

Genetic literacy in adolescents raises important ethical implications related to autonomy, confidentiality, informed decision-making, and the psychological impact of genetic knowledge (McBride et al., 2010; Bunnik et al., 2013). These considerations are especially relevant in this population, given that adolescents are in a process of cognitive and emotional development that conditions their ability to understand complex information and make autonomous decisions (Ross et al., 2013).

2. Autonomy and decision-making capacity

2.1 Progressive autonomy

The principle of autonomy in adolescents must be understood as a dynamic and progressive process. As the individual matures, he or she acquires a greater capacity to understand genetic information and participate in decisions related to his or her health (Alderson, 2007).

However, in Latin American clinical practice, decision-making is usually mediated by parents or guardians, which can limit the active participation of the adolescent in his or her own care process.

2.2 Informed consent

Informed consent in genetics presents particular complexities due to the probabilistic nature of the information and its family implications. In adolescents, it is recommended to obtain the patient's assent, accompanied by the consent of the parents or guardians, adapting the information to the child's level of cognitive development (McCullough & Chervenak, 2008).

3. Right to know and right not to know

One of the most relevant ethical dilemmas in genetics is the balance between the right to know and the right not to know genetic information. This conflict is particularly important in late-onset diseases or with no available treatment (Biesecker, 2001).

In adolescents, the disclosure of genetic information can generate anxiety, affect the construction of identity and modify the perception of the future, so it is recommended to individualize the communication of these results.

4. Genetic confidentiality and privacy

Genetic information is unique because of its predictive and familial nature. This poses ethical challenges when a patient's outcomes have implications for other family members (Offit et al., 2004).

The health professional must balance patient confidentiality with the potential benefit of informing at-risk family members, always maintaining an approach focused on respect for individual rights.

5. Psychological impact and the principle of non-maleficence

Access to genetic information can have significant psychological effects, including anxiety, guilt, or stigmatization. In adolescents, these effects may be more intense due to their stage of development (Wakefield et al., 2016).

The principle of non-maleficence obliges professionals to minimize these risks, through empathetic communication, psychological support and continuous evaluation of the emotional impact.

6. Justice and equity in access

From the principle of justice, it is essential to guarantee equitable access to genetic services. In Latin America, there are significant inequalities related to socioeconomic, geographical, and educational factors (Penchaszadeh, 2001).

In contexts such as Ecuador, these inequities limit access to genetic counseling and affect adolescents' ability to understand and use genetic information in decision-making.

7. Ethical implications in adolescent gynecology

7.1 Reproductive decisions

Genetics in gynecology introduces additional ethical dilemmas related to fertility and reproduction. Adolescents with conditions such as Turner syndrome face complex decisions about their reproductive capacity, which requires an ethical approach that combines clear information, emotional support, and respect for autonomy (McCullough & Chervenak, 2008).

7.2 Prenatal diagnosis

Prenatal diagnosis raises ethical questions related to termination of pregnancy, disability, and quality of life. These decisions are strongly influenced by cultural, social, and legal factors, especially in Latin America (Lyerly et al., 2009).

8. Role of the health professional

The health professional plays a fundamental role as an ethical mediator in genetic communication. Their responsibilities include providing clear information, assessing patient understanding, promoting informed decisions, and respecting cultural and personal values (Resta et al., 2006).

9. Applied ethical framework

An approach based on the classical principles of bioethics is proposed:

- **Autonomy:** promoting the active participation of the adolescent
- **Charity:** Maximizing the Benefits of Genetic Knowledge
- **Nonmaleficence:** minimizing psychological damage
- **Justice:** Ensuring equitable access to services

This framework allows clinical practice to be oriented towards a more comprehensive and patient-centred model.

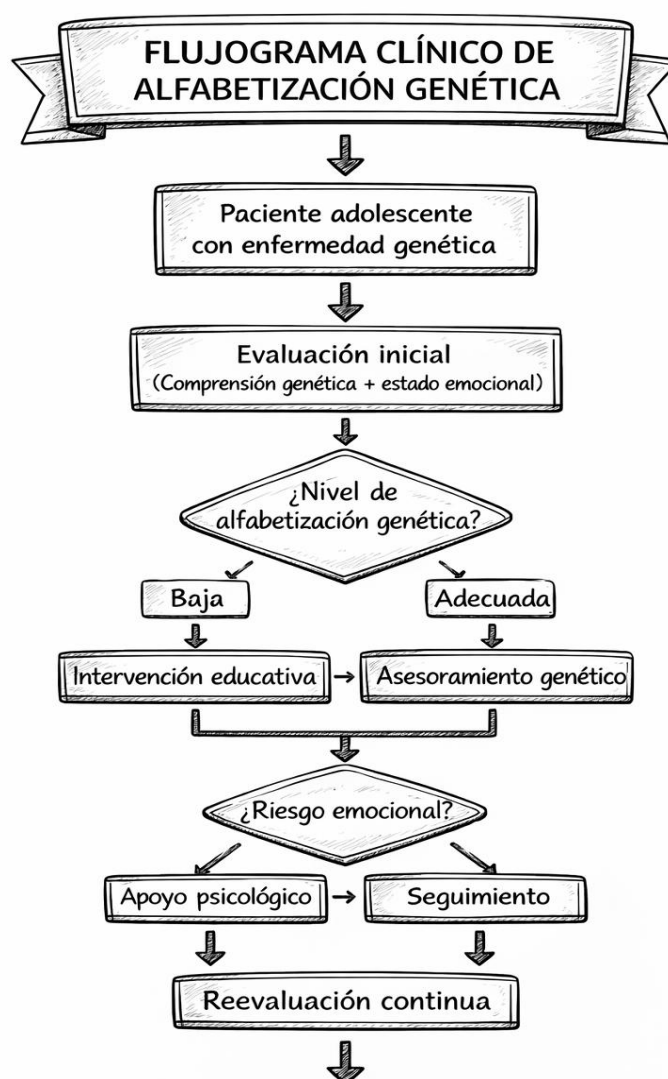
10. Conclusions

Ethical issues in adolescent genetic literacy are critical to appropriate clinical care. The complexity of genetic information, together with the characteristics of adolescent development and Latin American sociocultural particularities, requires a comprehensive ethical approach.

The integration of bioethical principles in clinical practice will improve the quality of care, promote patient autonomy and reduce health inequities. (FIG 4)

Figure 4

The flowchart shows a **structured clinical process** for genetic literacy in adolescents with genetic diseases. It begins with the evaluation of the patient (genetic understanding and emotional state), followed by the classification of the level of literacy, which guides educational or reinforcement interventions. Subsequently, genetic counseling and psychological evaluation are integrated, allowing emotional risk to be identified. According to this, psychological support or follow-up is established, culminating in a **continuous reevaluation** as the axis of comprehensive care



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INTRAPARTUM ASPHYXIA AND NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: PATHOPHYSIOLOGICAL BASES, DIAGNOSIS, AND CLINICAL MANAGEMENT

ASFIXIA INTRAPARTO E ENCEFALOPATIA HIPÓXICO-ISQUÉMICA NEONATAL: BASES FISIOPATOLÓGICAS, DIAGNÓSTICO E MANEJO CLÍNICO

ASFIXIA INTRAPARTO Y ENCEFALOPATÍA HIPÓXICO-ISQUÉMICA NEONATAL: BASES FISIOPATOLÓGICAS, DIAGNÓSTICO Y MANEJO CLÍNICO



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ABSTRACT

Perinatal asphyxia and neonatal hypoxic-ischemic encephalopathy are among the leading causes of neonatal morbidity and mortality and long-term neurological disability worldwide. This condition results from impaired gas exchange leading to hypoxemia, hypercapnia, and metabolic acidosis, triggering a pathophysiological cascade characterized by cellular energy failure, excitotoxicity, oxidative stress, inflammation, and neuronal apoptosis. The incidence is higher in low- and middle-income countries, and its etiology is multifactorial, including intrapartum hypoxic events as well as prenatal and postnatal factors. Clinically, it manifests with altered level of consciousness, hypotonia or hypertonia, neonatal seizures, and multiorgan involvement. The Sarnat classification allows stratification of severity and helps

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guide prognosis. Diagnosis requires a multimodal approach integrating clinical assessment, blood gas analysis, electroencephalographic monitoring, and neuroimaging, with magnetic resonance imaging being the gold standard for detecting early brain injury. Treatment is based on intensive support and neuroprotective strategies, with early-initiated therapeutic hypothermia standing out as an intervention that reduces mortality and neurological sequelae in moderate to severe cases. However, therapeutic limitations persist, and new alternatives such as erythropoietin, melatonin, and cellular therapies are under investigation. Prognosis depends on clinical severity, neuroimaging findings, and electroencephalographic evolution. In conclusion, neonatal hypoxic-ischemic encephalopathy remains a significant clinical challenge, requiring timely prevention and comprehensive multidisciplinary management. Furthermore, long-term follow-up is essential to detect neurodevelopmental impairments and optimize rehabilitation interventions and comprehensive family support, improving functional outcomes in childhood.

Keywords: Perinatal Asphyxia. Hypoxic-Ischemic Encephalopathy. Therapeutic Hypothermia. Neuroprotection. Neonatal Seizures. Biomarkers.

RESUMO

A asfixia perinatal e a encefalopatia hipóxico-isquêmica neonatal constituem uma das principais causas de morbimortalidade neonatal e de incapacidade neurológica a longo prazo em nível mundial. Essa condição resulta de uma alteração das trocas gasosas, levando à hipoxemia, hipercapnia e acidose metabólica, desencadeando uma cascata fisiopatológica caracterizada por falha energética celular, excitotoxicidade, estresse oxidativo, inflamação e apoptose neuronal. A incidência é maior em países de baixa e média renda, e sua etiologia é multifatorial, incluindo eventos hipóxicos intraparto, bem como fatores pré-natais e pós-natais. Clinicamente, manifesta-se por alterações do nível de consciência, hipotonia ou hipertonia, convulsões neonatais e comprometimento multiorgânico. A classificação de Sarnat permite estratificar a gravidade e orientar o prognóstico. O diagnóstico requer uma abordagem multimodal que integra avaliação clínica, gasometria, monitorização eletroencefalográfica e neuroimagem, sendo a ressonância magnética o padrão-ouro para a detecção precoce de lesão cerebral. O tratamento baseia-se em suporte intensivo e estratégias de neuroproteção, destacando-se a hipotermia terapêutica iniciada precocemente como intervenção capaz de reduzir a mortalidade e as sequelas neurológicas em casos moderados e graves. No entanto, persistem limitações terapêuticas, motivo pelo qual novas alternativas, como eritropoetina, melatonina e terapias celulares, estão em investigação. O prognóstico depende da gravidade clínica, dos achados em neuroimagem e da evolução eletroencefalográfica. Em conclusão, a encefalopatia hipóxico-isquêmica neonatal continua sendo um desafio clínico relevante, exigindo prevenção oportuna e manejo multidisciplinar integral. Além disso, o seguimento a longo prazo é fundamental para detectar alterações do neurodesenvolvimento e otimizar intervenções de reabilitação e apoio familiar integral, melhorando os desfechos funcionais na infância.

Palavras-chave: Asfixia Perinatal. Encefalopatia Hipóxico-Isquêmica. Hipotermia Terapêutica. Neuroproteção. Convulsões Neonatais. Biomarcadores.

RESUMEN

La asfixia perinatal y la encefalopatía hipóxico-isquémica neonatal constituyen una de las principales causas de morbimortalidad neonatal y discapacidad neurológica a largo plazo a nivel mundial. Esta entidad resulta de una alteración del intercambio gaseoso que conduce a hipoxemia, hipercapnia y acidosis metabólica, desencadenando una cascada

fisiopatológica caracterizada por falla energética celular, excitotoxicidad, estrés oxidativo, inflamación y apoptosis neuronal. La incidencia es mayor en países de ingresos bajos y medios, y su etiología es multifactorial, incluyendo eventos hipóxicos intraparto y factores prenatales y posnatales. Clínicamente, se manifiesta con alteraciones del estado de conciencia, hipotonía o hipertonia, convulsiones neonatales y compromiso multiorgánico. La clasificación de Sarnat permite estratificar la gravedad y orientar el pronóstico. El diagnóstico requiere un enfoque multimodal que integra evaluación clínica, gasometría, monitoreo electroencefalográfico y neuroimagen, siendo la resonancia magnética el estándar de referencia para detectar lesión cerebral temprana. El tratamiento se basa en soporte intensivo y estrategias de neuroprotección, destacando la hipotermia terapéutica iniciada precozmente como intervención que reduce mortalidad y secuelas neurológicas en casos moderados y graves. No obstante, persisten limitaciones terapéuticas, por lo que se investigan nuevas alternativas como eritropoyetina, melatonina y terapias celulares. El pronóstico depende de la severidad clínica, hallazgos en neuroimagen y evolución electroencefalográfica. En conclusión, la encefalopatía hipóxico-isquémica neonatal continúa siendo un desafío clínico relevante, requiriendo prevención oportuna y manejo multidisciplinario integral. Asimismo, el seguimiento a largo plazo es fundamental para detectar alteraciones del neurodesarrollo y optimizar intervenciones de rehabilitación y apoyo familiar integral y mejorar resultados funcionales en la infancia.

Palabras clave: Asfixia Perinatal. Encefalopatía Hipóxico-Isquémica. Hipotermia Terapéutica. Neuroprotección. Convulsiones Neonatales. Biomarcadores.

1 INTRODUCTION

Perinatal asphyxia continues to be an important cause of neonatal morbidity and mortality and permanent neurological sequelae worldwide. It is estimated that hypoxic-ischemic encephalopathy (HIE) affects approximately 1–3 per 1000 live births in developed countries and a higher proportion in low- and middle-income countries(1,2). HIE represents one of the leading causes of childhood neurological disability, including cerebral palsy, developmental delay, epilepsy, and long-term cognitive disorders(3).

Despite advances in perinatal care, HIE continues to be a relevant public health problem, especially in low- and middle-income countries. Affected newborns present with a wide spectrum of clinical manifestations including altered level of consciousness, neonatal seizures, hypotonia, and autonomic dysfunction.

In recent decades, the understanding of the pathophysiology of hypoxic-ischemic brain injury has evolved considerably. Likewise, advances in neurophysiological monitoring and advanced neuroimaging techniques (4,5). Likewise, the introduction of therapeutic hypothermia has significantly modified the clinical management and prognosis of these patients (6,7).

The development of therapeutic hypothermia has represented the greatest advance in the treatment of this condition in recent decades; however, a considerable percentage of patients continue to have long-term neurological sequelae.

Definition of perinatal asphyxia

Perinatal asphyxia is defined as an alteration in gas exchange that produces hypoxemia, hypercapnia and metabolic acidosis, which can trigger multiple organ dysfunction(8). However, in modern clinical practice, the term neonatal encephalopathy associated with hypoxia-ischemia is preferred, since perinatal asphyxia alone does not necessarily imply brain injury(9).

Currently, the term neonatal encephalopathy associated with a hypoxic-ischemic event is preferred. According to the consensus of the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP), the diagnosis of neonatal encephalopathy related to intrapartum asphyxia requires the presence of several clinical and biochemical criteria, including severe metabolic acidemia, persistent low Apgar score, signs of moderate or severe neonatal encephalopathy, and evidence of multiorgan dysfunction (10).

In addition, the concept of sentinel hypoxic event is recognized, which describes acute obstetric events capable of producing severe fetal hypoxia, such as placental abruption, uterine rupture, umbilical cord prolapse or massive fetal-maternal hemorrhage.

1.1 SUGGESTED DIAGNOSTIC CRITERIA

The main criteria used include:

1. Severe metabolic acidosis in cord blood
2. Apgar score ≤ 5 at 10 minutes
3. Evidence of moderate or severe neonatal encephalopathy
4. Evidence of Multi-Organ Dysfunction

2 EPIDEMIOLOGY

The overall incidence of neonatal hypoxic-ischemic encephalopathy varies significantly according to the level of health development. In developed countries it is estimated at **1–3 per 1000 live births**, while in developing countries it can reach **5–10 per 1000 live births** (11).

Table 1

Region	Estimated incidence
Developed countries	1–3/1000 live births
Developing countries	5–10/1000 live births

Factors influencing the incidence:

- Access to obstetric care
- Intrapartum fetal monitoring
- Availability of neonatal intensive care units (12)

3 ETIOLOGY

Neonatal encephalopathy can be caused by multiple mechanisms.

Acute intrapartum hypoxic events

- Placental abruption
- Uterine rupture
- Umbilical cord prolapse
- Amniotic fluid embolism
- Massive fetal-maternal hemorrhage

Prenatal factors

- Placental insufficiency
- Intrauterine infections
- Fetal growth restriction

Postnatal factors

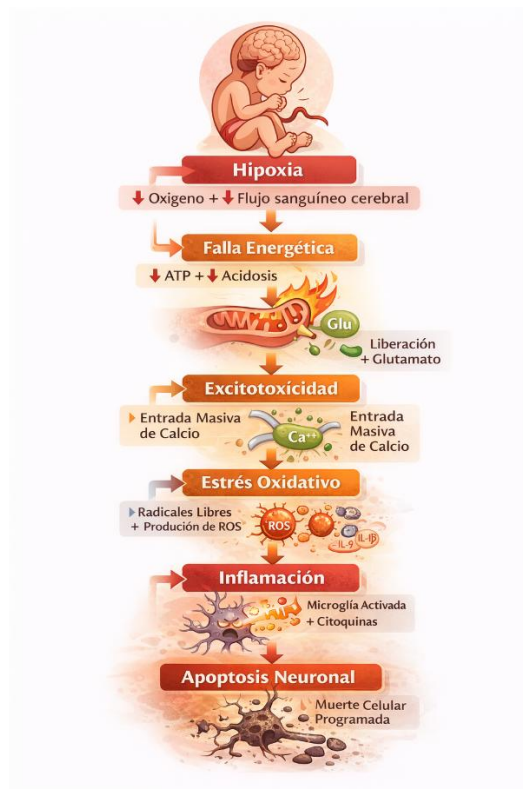
- Respiratory failure
- Neonatal sepsis
- Congenital heart disease

3.1 PATHOPHYSIOLOGY

Hypoxic-ischemic brain injury occurs as a result of reduced oxygen supply and cerebral blood flow. This process triggers a complex cascade of cellular and molecular events including energy depletion, excitotoxicity, free radical accumulation, inflammation, and neuronal apoptosis (13,14). (Fig. 1)

Figure 1

Pathophysiological cascade of hypoxic-ischemic encephalopathy



Source: Authors' elaboration based on Volpe (1), Davidson et al. (13) and Fleiss et al. (30).

The pathophysiology of HIE occurs in three main phases:

1. Primary phase (acute hypoxia)

It is characterized by:

- Decreased cerebral blood flow
- Reduced oxygen supply
- Cellular power failure
- Lactate Accumulation (15)

2. Reperfusion phase

Subsequently, it occurs:

- Glutamate-mediated excitotoxicity
- Massive intracellular calcium input
- Free radical generation

3. Secondary phase

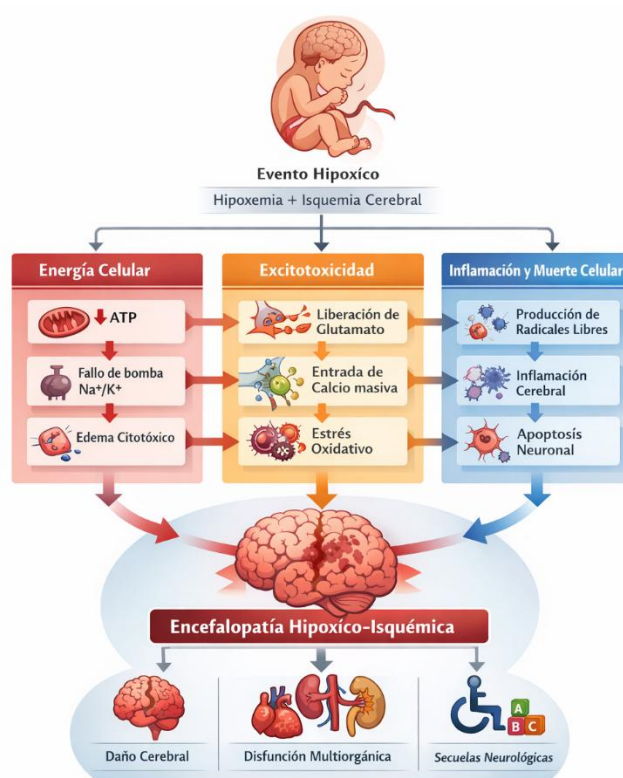
Between **6 and 48 hours later**, a secondary phase of injury occurs characterized by:

- Glutamate-mediated excitotoxicity
- Massive intracellular calcium input
- Free radical production
- Activation of inflammatory cascades and neuronal apoptosis (16,17)

This period constitutes a **critical therapeutic window for neuroprotective interventions**, such as therapeutic hypothermia (6).

These processes can extend brain damage even after perfusion is restored.

Brain damage usually develops in two main phases. The primary phase occurs during the hypoxic-ischemic event and is characterized by cellular energy failure. Subsequently, a secondary phase of injury occurs, between 6 and 48 hours later, associated with oxidative stress, glutamate release and programmed neuronal death. This period represents a critical therapeutic window for neuroprotective interventions such as therapeutic hypothermia. Fig. 2)

Figure 2*Pathophysiology of perinatal asphyxia*

Source: Adapted from Gunn and Bennet (29), Douglas-Escobar and Weiss (3), Davidson et al. (13)

4 CLINICAL MANIFESTATIONS

Neonatal hypoxic-ischemic encephalopathy is characterized by a constellation of neurological signs that appear in the first hours of life. These include altered level of consciousness, hypotonia or hypertonia, decreased primitive reflexes (18), breathing difficulties, and neonatal seizures.

4.1 CLASSIFICATION OF SARNAT

The most widely used clinical classification is the one proposed by **Sarnat and Sarnat**, which divides neonatal encephalopathy into three stages: mild, moderate, and severe (19). This classification is based on state of consciousness, muscle tone, motor activity, reflexes, and the presence of seizures. (Table 2)

Table 2

Clinical classification of neonatal hypoxic-ischemic encephalopathy according to Sarnat

Feature	Stage I (mild)	Stage II (moderate)	Stage III (severe)
Level of consciousness	Irritable	Lethargic	Stupor/coma
Muscle tone	Normal	Hypotonia	Sagging
Moro's Reflex	Over-the-top	Weak	Absent
Suction	Weak	Absent	Absent
Seizures	Rare	Frequently Asked	Variables
Duration	<24 h	2–14 days	Prolonged

Source: Adapted from Sarnat and Sarnat (19).

Clinical manifestations include:

Neurological

- Altered state of consciousness
- Hypotonia
- Neonatal seizures
- Absence of primitive reflexes

Systemic

- Respiratory failure
- Cardiac dysfunction
- Kidney failure
- Intestinal necrosis

Diagnostic evaluation

The diagnostic evaluation of newborns with suspected hypoxic-ischemic encephalopathy requires a multimodal approach that includes clinical evaluation, neurophysiological studies, and neuroimaging (20). (Table 2)

Amplitude integrated electroencephalogram (aEEG) is widely used for continuous monitoring of brain function in neonatal intensive care units. This technique allows detecting subclinical seizures and evaluating early neurological prognosis (21).

Regarding neuroimaging, brain magnetic resonance imaging is the most sensitive diagnostic method for detecting hypoxic-ischemic lesions. Diffusion sequences can identify brain damage in the first 24–48 hours of life (22).

In addition, several serum and cerebrospinal fluid biomarkers have been investigated, such as neuron-specific enolase, S100B protein, GFAP and UCH-L1, which could contribute in the future to the prognostic evaluation of these patients.

Diagnosis is based on a combination of clinical, biochemical, and neurophysiological criteria.

4.2 NEUROPHYSIOLOGICAL STUDIES

Amplitude-integrated electroencephalogram (aEEG) can detect cortical alterations and subclinical seizure activity, and is useful for early prognosis (22).

Neuroimaging

Brain ultrasound

- Useful for evolutionary tracking

MRI

It is the study of choice to evaluate the extent and location of brain damage.

Typical injuries include:

- Basal Nodes
- Thalamus
- White matter
- Cerebral cortex

Complementary exams

Arterial blood gases

- pH <7.0
- Base deficit >12 mmol/L

Electroencephalography (EEG/aEEG)

It allows detecting:

- Subclinical seizures
- Suppression-burst pattern

MRI

Diffusion brain MRI is currently the gold standard for evaluating neonatal brain injury.

Biomarkers

Biomarkers studied include:

- Neuronal Specific Enolase
- Protein S-100
- CK-BB
- Interleukin-6

These reflect neuronal damage and have prognostic value.

Table 3

Diagnostic evaluation in neonatal hypoxic-ischemic encephalopathy.

Study	Clinical utility
Blood gases	Confirmation of metabolic acidosis
EEG / aEEG	Brain Activity Assessment

Brain ultrasound	Initial assessment
MRI	Neurological prognosis

Source: Adapted from Rutherford (10), Lally and Montaldo (31) and Alderliesten (32)

Multi-organ involvement

Perinatal hypoxic-ischemic aggression is not limited to the central nervous system. Various organs may be compromised due to the redistribution of blood flow during the asphyxial episode.

The most common manifestations include acute renal failure, myocardial dysfunction, persistent pulmonary hypertension of the newborn, liver disorders and metabolic disorders. Early identification of these complications is essential to optimize clinical management.

Perinatal asphyxia can cause multi-organ involvement, including:

Nervous System

- Encephalopathy
- Neonatal seizures

Renal system

- Oliguria
- Acute renal failure

Cardiovascular system

- Myocardial ischemia
- Ventricular dysfunction

Respiratory system

- Persistent pulmonary hypertension

Gastrointestinal system

- Ischemic enterocolitis

Hematology System

- Disseminated intravascular coagulation

4.3 TREATMENT

The management of newborns with hypoxic-ischemic encephalopathy is based on intensive support measures and neuroprotection strategies (23)

General measures include maintaining adequate oxygenation and ventilation, correcting metabolic disturbances, controlling blood pressure, and prompt treatment of neonatal seizures.

Therapeutic hypothermia is currently the standard treatment for newborns with moderate or severe HIE. This procedure involves reducing body temperature to

approximately 33–34 °C for 72 hours, starting within the first six hours of life. Various clinical trials have shown that this therapy reduces mortality and improves long-term neurological prognosis (7,25).

New neuroprotective strategies, including erythropoietin, inhaled xenon, melatonin, and cell therapies, are also being investigated, which could complement therapeutic hypothermia in the future.

General measures

- Adequate oxygenation
- Blood pressure control
- Correction of metabolic acidosis
- Blood Glucose Control
- Seizure treatment

Therapeutic hypothermia

Therapeutic hypothermia is the standard treatment for moderate and severe HIE.

Indications

- Gestational age ≥ 36 weeks
- Moderate or severe encephalopathy
- Start within the first 6 hours
- Protocol

Parameter

Value

Temperature

33–34 °C

Duration

72 hours

Reheating

gradual (0.5 °C/h)

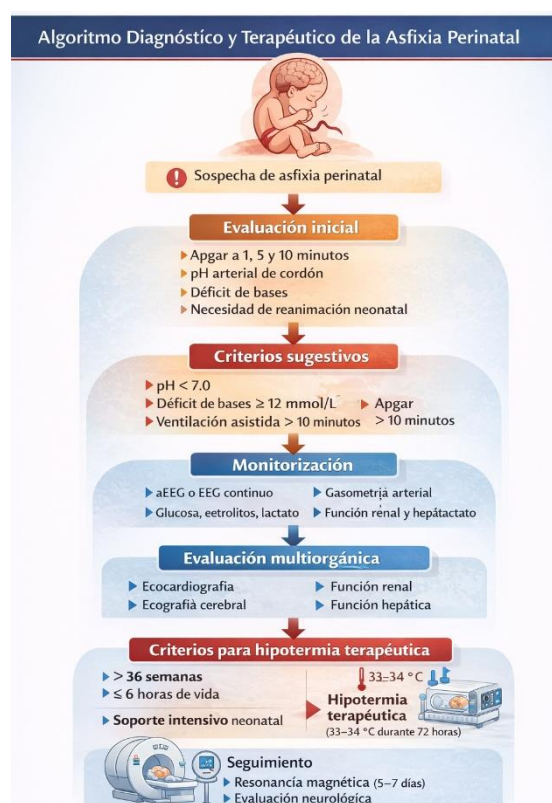
- This treatment has been shown to reduce mortality and improve neurological disability

Emerging therapies

In current research:

- Erythropoietin
- Mesenchymal stem cells
- Inhaled xenon
- Melatonin
- Metabolic therapies

Clinical algorithm for the management of perinatal asphyxia

Figure 3**Diagnostic and therapeutic algorithm for neonatal hypoxic-ischemic encephalopathy**

Source: Adapted from Laptook and Shankaran (7), Jacobs et al. (8), Massaro and Chang (14).

4.4 PROGNOSIS

The prognosis depends mainly on:

- *Degree of encephalopathy*
- *Neuroimaging findings*
- *Electroencephalographic evolution* (26)

The severity of the initial neurological involvement. Newborns with mild HIE usually have a favorable outcome, while those with moderate or severe forms are at increased risk of permanent neurological disability.

Brain MRI and early neurophysiological monitoring are fundamental tools for prognostic evaluation. Long-term follow-up is essential to detect neurological, cognitive, and motor developmental disorders.

Mortality in severe HIE can reach 50–75%, and most survivors have neurological sequelae (27).

Table 4

Grades of toxic ischemic encephalopathy

HIE Grade	Mortality	Neurological sequelae
Mild	<5%	Weird
Moderate	10–20%	Moderate disability
Severe	40–60%	frequent cerebral palsy

Recent studies show that 30–50% of survivors may have long-term cognitive deficits.

Neurological follow-up

Multidisciplinary follow-up is recommended:

- Pediatric Neurology
- Rehabilitation
- Early stimulation
- Neurodevelopmental Assessment (28)

Figure 4

Therapeutic window of hypoxic-ischemic encephalopathy"



Source: Gunn & Bennet, Nature Reviews Neurology.

Table 5

Multi-organ manifestations of perinatal asphyxia.

Organ	Demonstrations
Brain	Encephalopathy, seizures
Kidney	Oliguria, kidney failure
Heart	Myocardial dysfunction, ischemia
Lung	Persistent pulmonary hypertension
Liver	Transaminase elevation
Hematology	Coagulopathy

Source: Adapted from Perlman (33) and Graham et al. (4).

Table 6

Current criteria for neonatal therapeutic hypothermia.

Criteria	Parameter
Gestational age	≥ 36 weeks
Postnatal age	≤ 6 hours
Evidence of choking	$\text{pH} \leq 7.0$ or $\text{BE} \geq 12$
Neurological involvement	Moderate or severe HIE

Source: Adapted from Shankaran et al. (6), Laptook et al. (7) and Jacobs et al. (8).

New emerging biomarkers

You can add a modern section on:

Biomarkers under investigation:

- UCH-L1
- GFAP
- Neuron specific enolase
- S100B

These help to:

- Detect neuronal damage early
- Predict neurological prognosis

5 MEDICO-LEGAL IMPLICATIONS

Lawsuits for alleged obstetric negligence are common after the birth of a newborn with moderate to severe hypoxic-ischemic disease, associated with a risk of adverse outcome. In general terms, the family usually attributes these outcomes to a supposed lack of obstetric care to detect or intervene in a timely manner in the event of possible intrapartum asphyxia.

However, it is essential to consider that, in most cases, the time of onset, duration and susceptibility factors that determine the severity of hypoxic aggression remain unknown. Likewise, the perinatal criteria suggestive of asphyxia do not allow, by themselves, to establish with certainty an intrapartum origin of the brain injury. In fact, a significant proportion of newborns who meet criteria for perinatal asphyxia have a history prior to delivery that may have contributed to the development of hypoxic-ischemic encephalopathy (HIE).

Therefore, given the medico-legal, emotional and social implications associated with perinatal asphyxia, it is essential to carry out an exhaustive and comprehensive analysis of perinatal and postnatal data, including complementary studies, before establishing causal relationships.

Neuropathological studies allow the identification of the characteristic lesions of acute asphyxia in fatal cases, both in terms of their morphology and distribution; however, they may also show ischemic lesions of antenatal origin.

Ultimately, the birth of a child with perinatal asphyxia and an unfavorable outcome creates an emotionally charged situation in which the possibility of litigation for alleged obstetric or neonatal negligence often helps to distance the family from health professionals who could provide support and guidance.

Therefore, it is recommended that each institution establish mechanisms that facilitate parents' access to clear information, emotional support and adequate accompaniment, in order to reduce their feeling of isolation and better cope with the situation, establishing a causal relationship between intrapartum events and neurological damage, which is why it is required:

- Evidence of intrapartum acidosis
- Early neonatal encephalopathy
- Exclusion of other causes

6 CONCLUSIONS

Neonatal hypoxic-ischemic encephalopathy continues to represent a highly relevant clinical challenge in perinatal medicine, due to its important contribution to neonatal mortality and long-term neurological disability, including cerebral palsy, epilepsy, and cognitive disorders (33,36). Despite advances in its pathophysiological understanding, this entity remains complex and multifactorial, which makes it difficult to accurately identify the timing and cause of brain damage (34).

Advances in early diagnosis, particularly through neurophysiological monitoring and neuroimaging techniques, have allowed for better risk stratification and more timely decision-making in affected newborns (34, 38). In this context, therapeutic hypothermia has established itself as the standard of treatment, demonstrating a significant reduction in mortality and neurological disability in moderate to severe cases (34,35). However, its efficacy is not universal, and a considerable number of patients continue to have sequelae, which shows the need for additional therapeutic strategies (35).

In relation to prevention, it is essential to strengthen prenatal and intrapartum surveillance, as well as to optimize perinatal care systems to identify fetuses at risk early and act in a timely manner. Likewise, the standardization of diagnostic criteria and management protocols contributes to improving the quality of care and clinical outcomes (38).

On the other hand, the development of new neuroprotective therapies is a priority in current research. Several studies have explored pharmacological agents, cell therapies, and strategies aimed at modulating inflammation, oxidative stress, and excitotoxicity, with the aim of enhancing the effects of therapeutic hypothermia and improving neurological prognosis (35). However, many of these interventions are still in the experimental phase and require validation in high-quality clinical trials.

Finally, the approach to hypoxic-ischemic encephalopathy must be comprehensive and multidisciplinary, including not only acute management, but also long-term follow-up and neurological rehabilitation. This approach allows optimizing functional outcomes and providing adequate support to families, considering the medical, social, and emotional implications of this condition.

In conclusion, although significant advances have been made in the diagnosis and treatment of neonatal hypoxic-ischemic encephalopathy, important challenges remain in its prevention, management, and prognosis, which underscores the need to continue promoting research and innovation in this field.

Therefore, neonatal hypoxic-ischemic encephalopathy continues to represent a major clinical challenge in perinatal medicine. Advances in early diagnosis, neurophysiological monitoring, and the implementation of therapeutic hypothermia have significantly improved the prognosis of these patients (6,20).

Considering that prevention, timely diagnosis and the development of new neuroprotective strategies continue to be priority areas of research (29).

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HUMAN TERATOGENESIS: GENE-ENVIRONMENT INTERACTION AND FOUNDATIONS FOR PREVENTION

TERATOGÊNESE HUMANA: INTERAÇÃO GENÉTICO-AMBIENTAL E BASES PARA A PREVENÇÃO

TERATOGÉNESIS HUMANA: INTERACCIÓN GENÉTICO-AMBIENTAL Y BASES PARA LA PREVENCIÓN



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ABSTRACT

Human teratogenesis is a complex process resulting from the interaction between environmental factors and maternal-fetal genetic susceptibility, capable of altering embryofetal development and producing structural, functional, and neurodevelopmental anomalies. The vulnerability of the embryo and fetus depends on the timing of exposure, with organogenesis (weeks 3–8) being the period of highest risk for major malformations, whereas in later stages functional and growth alterations predominate. The principles of teratology, described by Wilson, establish that the teratogenic effect is conditioned by dose, duration of exposure, genetic susceptibility, and the pathogenic mechanisms involved, such as oxidative stress, DNA damage, altered cell proliferation, and disruption of angiogenesis. Teratogenic agents are classified as biological, physical, chemical, and maternal factors, all with convergent mechanisms that affect fetal development. Biological teratogens include congenital infections that cause damage through direct invasion and inflammation. Physical agents, such as ionizing radiation and hyperthermia, produce cellular and structural alterations. Chemical agents, including drugs, alcohol, tobacco, and environmental pollutants, interfere with key molecular processes and represent a frequent cause of preventable fetal damage. Maternal factors, such as diabetes, phenylketonuria, and

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nutritional deficiencies, modify the intrauterine environment. Early recognition of risk exposures and the implementation of preventive strategies are essential to reduce the incidence of congenital anomalies and improve perinatal outcomes.

Keywords: Teratogenesis. Embryofetal Development. Environmental Factors. Maternal Factors. Congenital Infections. Teratogenic Drugs.

RESUMO

A teratogênese humana é um processo complexo que resulta da interação entre fatores ambientais e a suscetibilidade genética materno-fetal, capaz de alterar o desenvolvimento embriofetal e produzir anomalias estruturais, funcionais e do neurodesenvolvimento. A vulnerabilidade do embrião e do feto depende do momento da exposição, sendo a organogênese (semanas 3–8) o período de maior risco para malformações maiores, enquanto nas fases posteriores predominam alterações funcionais e do crescimento. Os princípios da teratologia, descritos por Wilson, estabelecem que o efeito teratogênico é condicionado pela dose, duração da exposição, suscetibilidade genética e pelos mecanismos patogênicos envolvidos, como o estresse oxidativo, o dano ao DNA, a alteração da proliferação celular e a disrupção da angiogênese. Os agentes teratogênicos são classificados em biológicos, físicos, químicos e fatores maternos, todos com mecanismos convergentes que afetam o desenvolvimento fetal. Os teratógenos biológicos incluem infecções congênitas que causam dano por invasão direta e inflamação. Os agentes físicos, como a radiação ionizante e a hipertermia, produzem alterações celulares e estruturais. Os agentes químicos, incluindo fármacos, álcool, tabaco e poluentes ambientais, interferem em processos moleculares-chave e representam uma causa frequente de dano fetal prevenível. Os fatores maternos, como diabetes, fenilcetonúria e deficiências nutricionais, modificam o ambiente intrauterino. O reconhecimento precoce de exposições de risco e a implementação de estratégias preventivas são essenciais para reduzir a incidência de anomalias congênitas e melhorar os desfechos perinatais.

Palavras-chave: Teratogênese. Desenvolvimento Embríofetal. Fatores Ambientais. Fatores Maternos. Infecções Congênitas. Fármacos Teratogênicos.

RESUMEN

La teratogénesis humana es un proceso complejo que resulta de la interacción entre factores ambientales y la susceptibilidad genética materno-fetal, capaz de alterar el desarrollo embríofetal y producir anomalías estructurales, funcionales y del neurodesarrollo. La vulnerabilidad del embrión y del feto depende del momento de la exposición, siendo la organogénesis (semanas 3–8) el periodo de mayor riesgo para malformaciones mayores, mientras que en etapas posteriores predominan alteraciones funcionales y del crecimiento. Los principios de la teratología, descritos por Wilson, establecen que el efecto teratogénico está condicionado por la dosis, la duración de la exposición, la susceptibilidad genética y los mecanismos patogénicos implicados, como el estrés oxidativo, el daño al ADN, la alteración de la proliferación celular y la disrupción de la angiogénesis. Los agentes teratogénicos se clasifican en biológicos, físicos, químicos y factores maternos, todos con mecanismos convergentes que afectan el desarrollo fetal. Los teratógenos biológicos incluyen infecciones congénitas que causan daño por invasión directa e inflamación. Los agentes físicos, como la radiación ionizante y la hipertermia, generan alteraciones celulares y estructurales. Los agentes químicos, incluyendo fármacos, alcohol, tabaco y contaminantes ambientales, interfieren con procesos moleculares clave y representan una causa frecuente de daño fetal prevenible. Los factores maternos, como diabetes, fenilcetonuria y deficiencias nutricionales,

modifican el ambiente intrauterino. El reconocimiento temprano de exposiciones de riesgo y la implementación de estrategias preventivas son esenciales para reducir la incidencia de anomalías congénitas y mejorar los resultados perinatales.

Palabras clave: Teratogénesis. Desarrollo Embriofetal. Factores Ambientales. Factores Maternos. Infecciones Congénitas. Fármacos Teratogénicos.

1 OVERVIEW OF TERATOGENESIS

Teratogenesis is a complex biological process by which various environmental factors, in interaction with the genetic susceptibility of the embryo and the mother, alter the normal development of the product of conception, generating structural, functional, metabolic or behavioral abnormalities. This phenomenon does not depend exclusively on the causative agent, but on a dynamic relationship between the time of exposure, the dose, the duration and the biological conditions of the host.

During embryo-fetal development, vulnerability to teratogenic agents is not uniform. In the embryonic period, particularly between the third and eighth week of gestation, organogenesis occurs, a critical stage in which the primordia of the main organs are established. Exposure to harmful agents in this range is more frequently associated with major birth defects. In contrast, during the fetal period, which extends from the ninth week until birth, growth and functional maturation processes predominate, so aggressions usually result in alterations in functional development, especially of the central nervous system.

The central nervous system is a particularly susceptible target, since its development extends from early stages of gestation to the first years of postnatal life. For this reason, many teratogenic exposures do not generate morphological abnormalities evident at birth, but manifest later as neurodevelopmental disorders, cognitive deficits, behavioral alterations or psychiatric diseases.

From a clinical perspective, the identification of teratogenic factors is an essential component of prenatal care. A targeted anamnesis, recognition of risk exposures (pharmacological, infectious, environmental or occupational) and a comprehensive assessment of the maternal context allow effective preventive strategies to be established. In this sense, the classification of teratogens into physical, chemical, biological, environmental and maternal factors facilitates the understanding of fetal risk and guides evidence-based clinical decision-making.

2 FUNDAMENTAL PRINCIPLES OF TERATOLOGY

Teratology is the discipline that studies the causes, mechanisms, and consequences of congenital anomalies induced by environmental or genetic factors, or their interaction. Its conceptual development was consolidated with the principles proposed by James G. Wilson in 1959, which continue to be the fundamental theoretical framework for understanding the action of teratogens.

2.1 CONCEPT OF TERATOGEN

A teratogen is any external agent capable of interfering with normal embryo-fetal development, producing structural, functional, growth or behavioral alterations. These agents include physical, chemical, biological, environmental factors and conditions of the maternal state.

2.2 WILSON'S PRINCIPLES APPLIED TO TERATOGENESIS

1. Dependence on the time of exposure

The susceptibility of the embryo or fetus varies according to the stage of development:

- **Preimplantation period (0–2 weeks):** "all or nothing" phenomenon.
- **Embryonic period (3–8 weeks):** maximum susceptibility to structural malformations.
- **Fetal period (≥ 9 weeks):** functional and growth alterations predominate.

2. Genetic variability of susceptibility

The response to a teratogen depends on the maternal and fetal genotype. Factors such as polymorphisms in metabolizing enzymes, detoxification mechanisms, and DNA repair capacity influence the extent of damage.

3. Dose–response relationship

There is a direct correlation between the intensity/duration of exposure and the likelihood of harm:

- Some teratogens have a **threshold effect**.
- Others can induce harm even with brief but intense exposures.

4. Specific pathogenic mechanisms

Teratogens act through defined biological pathways, including:

- Alteration of cell proliferation, migration and differentiation
- Oxidative stress and DNA damage
- Interference with angiogenesis and uteroplacental flow
- Induction of apoptosis or cell necrosis

5. Spectrum of manifestations

Teratogenic damage can be expressed as:

- Embryonic or fetal death
- Major or minor birth defects
- Intrauterine growth restriction
- Functional or neurodevelopmental alterations

6. Influence of the biological model and the environment

The results observed in animal models cannot always be extrapolated to humans. In addition, environmental, social, and nutritional factors modulate the clinical expression of teratogenic damage.

2.3 CLASSIFICATION OF TERATOGENIC AGENTS

Teratogenic agents are classified as: (Fig. 1)

- **Physical:** ionizing radiation, hyperthermia
- **Chemicals:** drugs (e.g. retinoids, anticonvulsants), alcohol, heavy metals
- **Biologics:** congenital infections (TORCH and others)
- **Environmental and social:** malnutrition, hypoxia, occupational exposure, stress
- **Maternal:** chronic diseases such as diabetes, phenylketonuria, or lupus

Figure 1

The image presents a graphic diagram entitled "Classification of teratogens", the purpose of which is to illustrate the main factors capable of producing congenital malformations or alterations in fetal development during pregnancy. Vargas, 2026



2.4 TERATOGENICITY CRITERIA IN HUMANS

Identifying an agent as a teratogen in humans requires consistent evidence based on:

- Temporal association between exposure and effect
- Presence of a specific pattern of malformations
- Dose–response relationship
- Biological plausibility

- Reproducibility across studies and populations
- Exclusion of alternative causes

The evidence comes mainly from epidemiological studies (cohorts and case-controls), exposure registries and, in a complementary way, experimental models.

2.5 TERATOGENIC RISK ASSESSMENT

Risk assessment involves determining the likelihood of fetal harm by considering:

- Exposure period (critical window)
- Dosage and duration of the agent
- Maternal-fetal genetic susceptibility

Historically, the FDA classification (categories A, B, C, D, and X) was used as clinical guidance; however, this system has been replaced by the **PLLR (Pregnancy and Lactation Labeling Rule)** narrative model, which provides more detailed and contextualized information on fetal risks, clinical considerations, and surveillance data. (Fig. 2)

Figure 2

The image shows a stepwise scheme of the classification of drugs according to their risk during pregnancy, corresponding to the FDA (Food and Drug Administration) classification traditionally used to evaluate the teratogenic potential of drugs. Vargas, 2026



2.6 PREVENTION AND COUNSELLING

The prevention of teratogenesis is based on:

- Preconception planning
- Review of potentially teratogenic drugs
- Folic acid supplementation
- Maternal Disease Management
- Pre-pregnancy vaccination
- Environmental and occupational hazard education

2.7 INTEGRATIVE CONCLUSION

Teratogenesis is the result of a complex interaction between environmental and biological factors that act on a highly vulnerable developing organism. Knowledge of the fundamental principles of teratology makes it possible to understand the variability of teratogenic effects, improve risk assessment and strengthen prevention strategies. In clinical practice, a comprehensive, individualized, evidence-based approach is the most effective tool to reduce the incidence of avoidable birth defects and their long-term consequences.

Biological teratogens

1. Introduction

Biological agents are one of the most relevant causes of teratogenesis, particularly in the context of maternal infections acquired during pregnancy. These include viruses, bacteria and parasites with the ability to cross the placental barrier and infect the embryo or fetus, generating structural, functional and neurodevelopmental alterations.

Fetal susceptibility depends on multiple factors, including gestational age at the time of infection, virulence of the pathogen, infectious burden, and maternal immune response. During the embryonic period (weeks 3–8), exposure is mainly associated with major congenital malformations, while in fetal stages functional alterations, intrauterine growth restriction (IUGR), and long-term neurological sequelae predominate.

From a clinical point of view, congenital infections represent a preventable cause of perinatal morbidity and mortality, which underscores the importance of prenatal screening, vaccination and primary prevention measures.

2. Classification of biological agents

Biological teratogens are classified as:

- Viruses
- Bacteria
- Parasites

Traditionally, these agents are grouped within the **TORCH** complex (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes simplex), to which emerging pathogens such as Zika virus and parvovirus B19 are now added.

3. Pathophysiological mechanisms of infectious teratogenesis

Infectious agents exert their teratogenic effect through multiple mechanisms:

- Direct cytotoxicity and cell lysis
- Interference with cell proliferation, differentiation, and migration
- Disruption of angiogenesis and placental perfusion
- Induction of chronic inflammation (placentitis)
- Activation of apoptosis and DNA damage
- Aberrant fetal immune response

These mechanisms critically affect organogenesis and the development of the central nervous system, explaining the high frequency of neurological alterations in congenital infections.

4. Main teratogenic biological agents

4.1 Viral infections

Viruses are the main biological teratogens due to their high cellular tropism and capacity for intracellular replication.

Rubella virus

Responsible for congenital rubella syndrome, characterized by the classic triad:

- Congenital heart disease
- Cataracts
- Sensorineural hearing loss

The risk of fetal harm is highest during the first trimester, reaching up to 90% in early infections.

Cytomegalovirus (CMV)

It is the most common cause of congenital infection worldwide.

Demonstrations:

- Microcephaly
- Periventricular calcifications
- Chorioretinitis
- Hearing and cognitive deficit

CMV presents marked neurotropism and can produce sequelae even in asymptomatic newborns.

Herpes simplex virus (HSV)

It is mainly transmitted during childbirth.

Demonstrations:

- Neonatal encephalitis
- Cutaneous-mucosal lesions
- Disseminated disease

Intrauterine infection is rare but serious.

Varicella-zoster virus

Associated with congenital chickenpox syndrome:

- Hypoplasia of the extremities
- Skin scars
- Neurological and ocular alterations

Increased risk between 8–20 weeks of gestation.

Virus del Zika

Emerging agent with high neurotropism.

Manifestations of congenital Zika syndrome:

- Severe microcephaly
- Cortical alterations
- Intracranial calcifications
- Arthrogryposis

It represents a paradigm of modern viral teratogenesis.

Parvovirus B19

It produces severe fetal anemia due to destruction of erythroblasts.

Complications:

- Non-immunological hydrops fetalis
- Fetal heart failure
- Intrauterine death

HIV and hepatitis B/C

They are not direct teratogens, but they can alter the fetal environment and be associated with vertical transmission with systemic consequences.

4.2 Bacterial infections

Treponema pallidum (syphilis)

It causes congenital syphilis, with manifestations such as:

- Hydrops fetalis
- Anemia
- Hepatosplenomegaly

- Bone and neurological alterations

In late stages:

- Hutchinson's Triad (teeth, deafness, keratitis)

Listeria monocytogenes

Associated with:

- Miscarriage
- Preterm delivery
- Neonatal sepsis

The damage is related to placental invasion and inflammatory response.

4.3 Parasitic infections

Toxoplasma gondii

Intracellular protozoan with high clinical relevance.

Classical triad:

- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications

Transmission increases with gestational age, but severity is greater in early infections.

Trypanosoma cruzi (Chagas disease)

It causes congenital infection with:

- Heart disease
- Hepatosplenomegaly
- Neurological involvement

Important in endemic regions of Latin America.

5. Clinical manifestations

Congenital infections have a broad spectrum:

- Structural malformations
- Microcephaly
- Intrauterine growth restriction
- Hepatosplenomegaly
- Hematological alterations
- Neurological and cognitive deficit
 - Long-term sequelae

Many infections can be subclinical at birth and manifest later.

6. Prenatal diagnosis

Diagnosis is based on a combination of tools:

- **Maternal Serology:** IgM, IgG, Avidity Tests
- **Molecular biology:** PCR in blood or amniotic fluid
- **Fetal ultrasound:** ventriculomegaly, calcifications, hydrops
- **Fetal MRI:** Advanced Neurological Evaluation
- **Amniocentesis:** etiological confirmation

Early diagnosis allows for timely intervention and better prognosis.

7. Prevention

Preventive strategies include:

- Routine prenatal screening
- Preconception vaccination (rubella, chickenpox, hepatitis B)
- Hygienic-dietary measures (toxoplasmosis, CMV)
- Sexual and reproductive health education
- Maternal Disease Management
- Surveillance in high-risk pregnancies

8. Fetal and neonatal follow-up

- Serial ultrasound and fetal Doppler
- Assessment of fetal growth and well-being
- Intrauterine molecular diagnosis
- Comprehensive postnatal evaluation
- Neurological, auditory and visual monitoring

9. Conclusion

Biological agents represent a significant and largely preventable cause of teratogenesis. Its impact on embryo-fetal development depends on the interaction between the pathogen, the timing of infection, and the host's response. Early recognition, systematic screening and prevention strategies are fundamental pillars to reduce perinatal morbidity and mortality and long-term sequelae.

Table 1

Main teratogenic biological agents

Agent	Type	Demonstrations	Mechanism
Rubella	Viruses	Heart disease, cataracts	Mitotic inhibition
CMV	Viruses	Microcephaly, calcifications	Neurotropism
HSV	Viruses	Encephalitis	Cytotoxicity
Zika	Viruses	Severe microcephaly	Neuronal alteration
T. pallidum	Bacteria	Hydrops, anemia	Inflammation
Listeria	Bacteria	Neonatal sepsis	Placental invasion
Toxoplasma	Parasite	Chorioretinitis	Tissue necrosis

T. cruzi	Parasite	Heart disease	Chronic inflammation
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Figure 3

Pathogenesis schematic (to be designed)

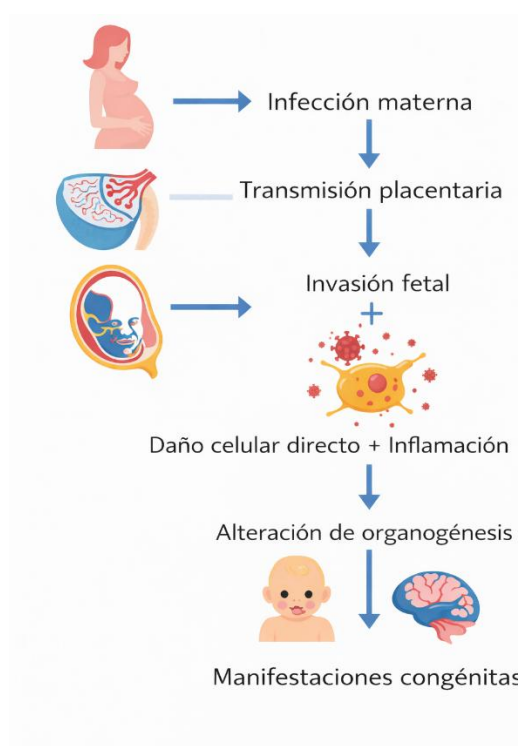


Fig. 3. Maternal infection → Placental transmission → Fetal invasion → Direct cell damage + Inflammation → Alteration of organogenesis → Congenital manifestations.

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Physical teratogens

3.1 Introduction

Physical agents constitute a relevant group of teratogens that exert their effect through direct cell damage, DNA alterations, interference in cell proliferation and modifications of the intrauterine environment. Unlike biological and chemical agents, their impact depends fundamentally on quantifiable variables such as the intensity, duration and time of exposure during pregnancy.

The susceptibility of the embryo and fetus varies according to the stage of development. During organogenesis (weeks 3–8), physical agents can induce major structural malformations. In later stages, the effects are mainly related to growth disturbances, functional maturation and neurological damage.

3.2 Ionizing radiation

Ionizing radiation is the best characterized teratogenic physical agent. Its biological effect derives from the transfer of energy at the molecular level, producing direct and indirect damage to DNA.

Mechanisms of action

- DNA strand breaks and mutations
- Generation of free radicals (oxidative stress)
- Induction of cell apoptosis

- Alterations in tissue differentiation
- Vascular and placental damage

The **Bergonié-Tribondeau** principle states that immature cells with a high proliferative rate (such as embryonic cells) are more sensitive to radiation.

Critical period and effects

- Preimplantation (0–2 weeks): all-or-nothing effect
- Organogenesis (3–8 weeks): structural malformations
- Fetal period (8–25 weeks): neurological and cognitive damage

Demonstrations:

- Microcephaly
- Intrauterine growth restriction (IUGR)
- Intellectual disability
- Neurobehavioral alterations
- Increased risk of childhood cancer

Dosage and risk

- **<50 mGy**: no significant increase in malformations
- **100–150 mGy**: increased teratogenic risk
- **>300 mGy**: High risk of severe neurological damage

Routine diagnostic exposures (plain X-rays, CT scans with standard protocols) are generally below the risk threshold.

Sources of exposure

- X-rays: <1 mGy
- CT scan: 10–50 mGy
- Radiation therapy or nuclear accidents: >100 mGy

Prevention

- Rational use of radiological studies
- Abdominal shield protection
- Preference for non-radiation methods (ultrasound, MRI)

3.3 Non-ionizing radiation

Ultraviolet (UV) radiation

UV radiation is not considered a potent direct teratogen, but it can induce indirect effects:

- Decrease in maternal folic acid
- Oxidative stress
- Metabolic alterations

This can increase the risk of neural tube defects with prolonged exposures.

Diagnostic Ultrasound

Ultrasound uses high-frequency mechanical waves (2–10 MHz) and not ionizing radiation, so it is considered safe in clinical practice.

Theoretical mechanisms

- Thermal effect (minimal temperature rise)
- Cavitation (not demonstrated in humans)

Safety principle

- **ALARA (As Low As Reasonably Achievable)**

There is no conclusive evidence of teratogenicity when used medically.

Electromagnetic Fields (EMFs)

They include:

- Mobile phones
- Wi-Fi
- Power lines
- MRI

The current evidence is **inconclusive**, with no clear demonstration of teratogenicity in humans at normal environmental levels. MRI is considered safe, especially from the second trimester onwards.

3.4 Maternal hyperthermia

Hyperthermia (maternal temperature ≥ 39 °C) is a relevant physical teratogen, especially in the first trimester.

Mechanisms

- Protein denaturation
- Alteration of DNA replication
- Interference in cell migration
- Induction of apoptosis

Associated malformations

- Neural tube defects
- Cleft lip and palate
- Congenital heart disease
- Microphthalmia
- Neurodevelopmental alterations

The risk is greatest during neural tube closure (weeks 3–6).

Sources

- Prolonged maternal fever
- Infections
- Saunas, jacuzzis
- Extreme Environmental Exposure

Prevention

- Early fever control
- Avoid exposure to extreme heat
- Adequate hydration

3.5 Mechanical factors

Mechanical factors affect fetal development through physical restraint or intrauterine compression.

Main causes

- Oligohydramnios
- Uterine malformations
- Multiple pregnancy
- Amniotic bands

Demonstrations

- Positional deformities (clubfoot, plagiocephaly)
- Congenital hip dislocation
- Pulmonary hypoplasia
- Fetal amputations (amniotic bands)

These effects are more related to morphomechanical alterations than to direct cellular damage.

3.6 Noise, vibration and mechanical trauma

Loud noise (>85 dB)

- Risk of fetal hearing loss
- Low birth weight
- Preterm birth
- Maternal stress (cortisol axis)

Vibration

- Decreased uteroplacental flow
- IUGR
- Miscarriage

Abdominal trauma

- Placental abruption

- Fetal hypoxia
- Stillbirth
- Direct fetal injury

3.7 General pathophysiological mechanisms

Physical agents induce teratogenesis by:

- Direct DNA damage
- Oxidative stress
- Alteration of cell proliferation
- Apoptosis
- Interference in organogenesis
- Fetal mechanical compression

3.8 Clinical manifestations

- Congenital malformations
- Microcephaly
- Intrauterine growth restriction
- Neurocognitive deficit
- Musculoskeletal deformities

3.9 Prevention and management

- Rational use of medical radiation
- Radiation protection
- Maternal fever control
- Avoid extreme physical exposures
- Prenatal surveillance with ultrasound
- Early identification of mechanical factors

Table 2

Teratogenic physical agents

Agent	Mechanism	Critical period	Demonstrations	Agent
Ionizing radiation	DNA damage	3–15 weeks	Microcephaly, IUGR	Ionizing radiation
Hyperthermia	Protein alteration	3–6 weeks	NTDs, heart disease	Hyperthermia
Oligohydramnios	Fetal compression	2nd–3rd trimester	Pulmonary hypoplasia	Oligohydramnios
Amniotic bands	Mechanical restraint	Variable	Amputations	Amniotic bands
Vibration	Hypoperfusion	Variable	IUGR, Prematurity	Vibration
Loud noise	Neuroendocrine stress	Variable	Hearing loss	Loud noise

Figure 4*Teratogenesis by physical agents*

Fig. 4. Teratogenesis by physical agents → Cell damage / mechanical compression → Alteration of proliferation and differentiation → Failure in organogenesis → **Congenital manifestations.**

3.10 Conclusion

Physical agents represent a heterogeneous group of teratogens whose impact depends on the nature of exposure and gestational timing. Ionizing radiation is the best-established risk, while other factors such as hyperthermia and mechanical mechanisms can also cause significant damage. Most of these effects are preventable through appropriate protection, education, and prenatal care strategies, highlighting the importance of a preventive approach in clinical practice.

4. Chemical factors

4.1 Introduction

Chemical agents constitute one of the broadest, most complex and clinically relevant groups of teratogens, due to their high prevalence of exposure and the diversity of mechanisms by which they can interfere with embryo-fetal development. They include drugs, consumer substances, heavy metals, environmental pollutants, and industrial compounds, many of which cross the placenta by passive diffusion or by specific transporters, reaching fetal concentrations comparable to or higher than maternal concentrations [1,2].

The teratogenic potential depends on multiple factors, including:

- Dose and duration of exposure
- Liposolubility and molecular weight of the compound
- Plasma protein binding
- Maternal-fetal biotransformation capacity
- Time of exposure during pregnancy

The period of greatest susceptibility corresponds to organogenesis (weeks 3–8), during which major structural malformations may occur. In later stages, functional, growth, and neurodevelopmental alterations predominate [1,3].

4.2 Drugs

Drugs represent the most studied cause of chemical teratogenesis. Its effect is related to interference in fundamental processes such as DNA synthesis, cell proliferation, angiogenesis, and molecular signaling [4].

Main teratogenic drugs

- **Thalidomide** A potent antiangiogenic agent associated with phocomelia, microtia and visceral malformations. It constitutes the historical paradigm of pharmacological teratogenicity.
- **Isotretinoin (retinoids)**

It causes fetal retinoid syndrome: craniofacial, cardiac, CNS, and thymus abnormalities. There is no safe dose.

- **Valproic acid**

High risk of neural tube defects, facial dysmorphisms, and neurocognitive impairments. Risk of major malformations ~10%.

- **Warfarin** Characteristic embryopathy: nasal hypoplasia, punctate epiphyses, and neurological abnormalities (6–12 weeks).
- **Methotrexate and chemotherapy**

They inhibit cell proliferation → abortions, multiple malformations and growth restriction.

- **ACE and ARA II**

Especially in 2nd–3rd trimester: oligohydramnios, renal dysplasia, pulmonary hypoplasia.

- **Misoprostol** Associated with fetal vascular disruption → **Möbius syndrome, arthrogryposis and limb defects.**
- **Lithium** Increased risk of congenital heart disease (especially **Ebstein's anomaly**).

Risk Classification

The classic FDA classification (**A, B, C, D, X**) has been replaced by the **PLLR (Pregnancy and Lactation Labeling Rule)** system, which emphasizes individualized risk-benefit assessment based on clinical evidence [5].

Drugs with a proven teratogenic effect (Table 3)

Table 3

Main drugs with high teratogenic risk in humans

Pharmacological group	Drug(s)	Critical exposure period	Main teratogenic effects	Level of evidence
Systemic retinoids	Isotretinoin, Acitretin, Etretinate	3rd–8th week	Craniofacial, cardiac, CNS malformations, thymic aplasia, microtia	High
Antiepileptics	Valproic Acid, Carbamazepine, Phenytoin, Topiramate	4th–10th week	Neural tube defects, heart disease, cleft lip/palate, cognitive delay	High
Oral anticoagulants	Warfarin	6th–12th week	Nasal hypoplasia, punctate epiphyses, growth retardation, fetal hemorrhage	High
Antimetabolites	Methotrexate	6th–8th week	Miscarriages, neural tube defects, craniosynostosis, limb abnormalities	High
Alkylating agents	Cyclophosphamide, Busulfan, Chlorambucil	First trimester	Multiple malformations, growth restriction, stillbirth	High
Hormone modulators	Diethylstilbestrol (DES), Danazol	First trimester	Genital tract abnormalities, vaginal adenocarcinoma (DES), virilization	High
5- α -reductase inhibitors	Finasteride, Dutasteride	8th–12th week	Genital ambiguity, hypospadias	Moderate
Antihypertensives	ACE, ARA II	2nd–3rd trimester	Oligohydramnios, renal dysplasia, pulmonary	High

			hypoplasia, neonatal death	
Anti-infectives	Thalidomide, Misoprostol, Ribavirin, Tetracyclines	Variable (mainly 1 st quarter)	Phocomelia, cranial defects, multiple embryopathy, dental disorders	High
Psychotropic	Lithium, Paroxetine	2nd–8th week	Ebstein's anomaly, congenital heart disease	Moderate–High

The level of evidence is based on observational studies, pregnancy registries, and meta-analyses. Thus, some drugs (retinoids, valproate, thalidomide) do not have a known safe dose. Preconceptional exposure is particularly relevant in acitretin and etretinate.

4.3 Substances of consumption and drugs of abuse

Alcohol

Alcohol is the most common teratogen and the leading preventable cause of fetal nerve damage.

Mechanisms:

- Oxidative stress
- Alteration of neuronal migration
- Disruption of synaptogenesis

Main consequence:

- Fetal alcohol spectrum disorders (FASDs), including fetal alcohol syndrome (FAS)

Demonstrations:

- Cognitive deficit
- Characteristic facial features
- Failure to thrive
- Behavioral alterations

There is no safe level of consumption during pregnancy [6,7].

Tobacco

Tobacco exerts its effect mainly by nicotine and carbon monoxide.

Mechanisms:

- Uteroplacental vasoconstriction
- Chronic fetal hypoxia
- Oxidative stress

Consequences:

- Low birth weight
- Prematurity
- Intrauterine growth restriction
- Sudden infant death [8,9]

Cocaine

It produces intense vasoconstriction → fetal hypoxia.

Effects:

- Placental abruption
- Fetal infarctions
- Vascular malformations
- IUGR

Cannabis and methamphetamines

The evidence is variable, but they have been associated with:

- Neurodevelopmental alterations
- Cognitive and behavioral deficits
- Low birth weight

4.4 Heavy metals

Heavy metals are potent neuroteratogens that accumulate in fetal tissues.

- **Lead**
 - Decreased IQ
 - Behavioral disorders
 - ADHD
- **Mercury (methylmercury)**
 - Microcephaly
 - Cerebral palsy
 - Sensory and motor deficits

Mechanism:

- Alteration of synaptogenesis
- Interference with myelination
- Direct neurotoxicity [10,11]

4.5 Environmental pollutants and endocrine disruptors

Environmental pollutants represent an emerging public health problem.

Main agents

- Bisphenol A (BPA)
- Phthalates
- Dioxins
- PCBs

Mechanisms

- Endocrine disruption

- Impaired hormone signaling
- Abnormal metabolic programming

Effects

- Reproductive alterations
- Metabolic disorders
- Neurodevelopmental disorders [12]

4.6 Occupational and Industrial Exposure

Includes:

- Pesticides (organophosphates, carbamates)
- Organic solvents
- Hydrocarbons

Effects:

- Miscarriages
- CNS malformations
- Heart defects
- IUGR

4.7 Pathophysiological mechanisms

Chemical agents induce teratogenesis in multiple ways:

- Alteration of DNA synthesis and repair
- Oxidative stress
- Interference in cell signaling
- Endocrine disruption
- Inhibition of angiogenesis
- Direct toxicity to fetal tissues [1,4]

4.8 Clinical manifestations

The manifestations depend on the agent and the time of exposure:

- Structural congenital malformations
- Neurocognitive deficits
- Intrauterine growth restriction
- Behavioral disorders
- Endocrine and metabolic disruptions [6,10]

4.9 Prevention and management

Preventive strategies include:

- Rigorous evaluation of drug use during pregnancy
- Preconception counseling

- Suspension of known teratogenic substances
- Avoid alcohol, tobacco, and drug use
- Reduction of environmental and occupational exposure
- Use of teratological databases (TERIS, LactMed)
- Strict prenatal care [3,5]

Table 4

Main teratogenic chemical agents

Agent	Type	Mechanism	Demonstrations	Agent
Thalidomide	Drug	Antiangiogenesis	Focomelia	Thalidomide
Isotretinoin	Drug	Gene alteration	Craniofacial defects	Isotretinoin
Valproate	Drug	Folate Alteration	DTN	Valproate
Alcohol	Substance	Neurotoxicity	SAF	Alcohol
Tobacco	Substance	Hypoxia	Low weight	Tobacco
Lead	Metal	Neurotoxicity	Cognitive deficit	Lead
Mercury	Metal	Neuronal damage	Motor alterations	Mercury
BPA	Environmental	Endocrine disruption	Hormonal alterations	BPA

Figure 5

Schematic of teratogenesis by chemical agents

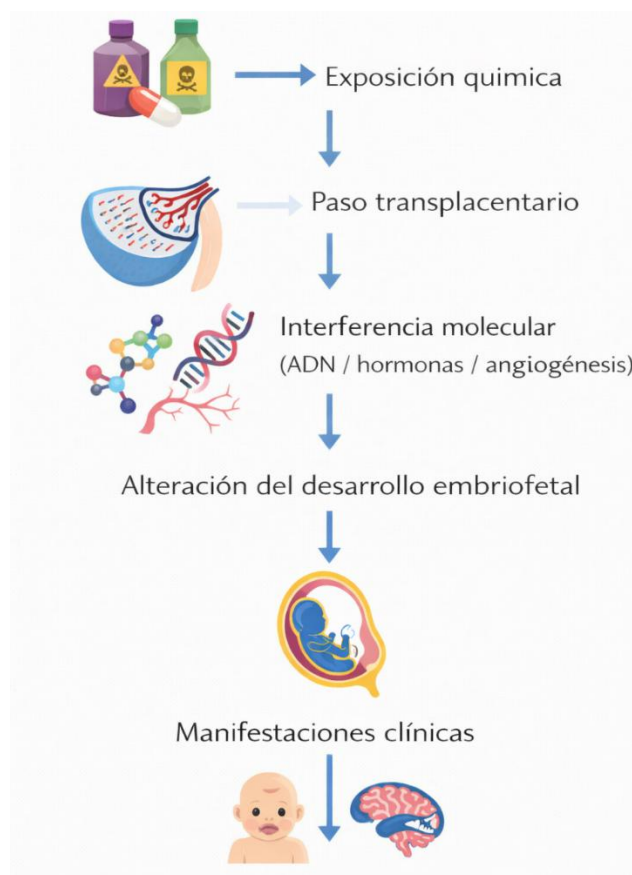


Fig. 5 Chemical exposure → Transplacental passage →Molecular interference (DNA/hormones/angiogenesis) →Impaired embryofetal development → Clinical manifestations

5. Maternal factors as endogenous teratogens

5.1 Introduction

Maternal factors constitute a group of endogenous teratogens in which fetal damage results from alterations in the intrauterine environment secondary to the mother's own conditions. These conditions modify the supply of oxygen, nutrients, hormones, and metabolic signals essential for embryo-fetal development [1,2]. (Table 5)

Unlike exogenous agents, maternal factors exert a continuous effect during pregnancy. Its impact depends on the degree of clinical control of the disease, the time of exposure, and the interaction with other environmental or genetic factors [3].

5.2 Pregestational diabetes mellitus

Pregestational diabetes mellitus is one of the best-established models of maternal teratogenesis. Exposure of the embryo to hyperglycemia during the period of organogenesis (weeks 3–8) significantly increases the risk of congenital malformations [4].

Main manifestations

- Congenital heart disease (VSD, TGA, tetralogy of Fallot)
- Neural tube defects
- Caudal regression syndrome (specific marker)
- Renal and gastrointestinal abnormalities

Pathophysiological mechanisms

- Hyperglycemia-induced oxidative stress
- Alteration of embryonic energy metabolism
- Disruption of gene expression and cell signaling
- Fetal hyperinsulinism (anabolic and dysmorphogenic effect)

Key clinical aspect

There is a direct relationship between elevated HbA1c levels in the periconceptional period and the risk of malformations. Adequate glycemic control prior to pregnancy significantly reduces this risk.

Clinical differentiation

- **Pregestational diabetes** → structural malformations
- **Gestational diabetes** → macrosomia and neonatal metabolic disorders

5.3 Maternal Phenylketonuria (PKU)

Uncontrolled maternal phenylketonuria is a classic example of metabolic teratogenesis. The accumulation of phenylalanine in maternal blood crosses the placenta and exerts a direct neurotoxic effect on the fetus [6].

Demonstrations

- Microcephaly
- Intellectual disability
- Congenital heart disease
- Intrauterine growth restriction

Key features

- Damage occurs regardless of fetal genotype
- There is a dose-dependent relationship with phenylalanine levels
- It is a highly preventable condition

Prevention

Strict diet low in phenylalanine started before conception and maintained throughout gestation.

5.4 Nutritional deficiencies

Maternal nutritional deficiencies affect critical processes such as DNA synthesis, cell proliferation, and tissue differentiation.

Main deficiencies

- **Folic acid** → neural tube defects (anencephaly, spina bifida)
- **Iodine** → congenital hypothyroidism and neurodevelopmental disorders

These findings support universal folic acid supplementation and adequate micronutrient intake during pregnancy [7,8].

5.5 Maternal hypoxia

Conditions that generate maternal hypoxia (severe anemia, respiratory or heart disease) decrease the oxygen supply to the fetus, affecting growth and development [3].

Consequences

- Intrauterine growth restriction (IUGR)
- Low birth weight
- Perinatal complications

Mechanism

Alteration of placental angiogenesis and fetal metabolism, with redistribution of blood flow (Fig. 6).

5.6 Maternal thyroid disorders

Maternal thyroid hormones are essential for fetal neurodevelopment, especially in the first trimester.

Untreated hypothyroidism

- Cognitive deficit
- Psychomotor delay
- Increased risk of neurodevelopmental disorders

Clinical significance

It is not a classic structural teratogen, but it is a powerful **disruptor of neurodevelopment**.

5.7 Autoimmune Diseases: Systemic Lupus Erythematosus

Maternal systemic lupus erythematosus (SLE) can affect the fetus through the transplacental passage of autoantibodies.

Main effects

- Congenital heart block
- Neonatal lupus
- Intrauterine growth restriction
- Preterm birth

Important Consideration

Teratogenic risk is often associated with the **drugs used** (e.g., immunosuppressants), rather than with the disease itself.

5.8 Maternal obesity

Maternal obesity is associated with a pro-inflammatory state and metabolic alterations that increase the risk of:

- Neural tube defects
- Heart malformations
- Fetal macrosomia
- Obstetric complications

5.9 Maternal psychological stress

Severe maternal stress acts as a functional teratogen by activating the hypothalamic–pituitary–adrenal axis.

Mechanisms

- Elevated fetal cortisol
- Oxidative stress
- Uteroplacental vasoconstriction

Consequences

- Prematurity
- Low birth weight
- Neurodevelopmental alterations

5.10 Global pathophysiological mechanisms

Maternal factors induce teratogenesis through convergent mechanisms:

- Metabolic alterations
- Oxidative stress
- Fetal hypoxia
- Endocrine disruption
- Nutritional deficiencies
- Alteration of the intrauterine environment

5.11 Clinical manifestations

Clinical consequences are variable and include:

- Structural congenital malformations
- Microcephaly
- Intrauterine growth restriction
- Neurocognitive deficits
- Neonatal metabolic disorders

5.12 Prevention and management

Key strategies include:

- Preconception control of maternal diseases
- Metabolic optimization (especially in diabetes)
- Folic acid and iodine supplementation
- Strict prenatal follow-up
- Maternal education and multidisciplinary counseling

Table 5

Main examples of maternal teratogens

Maternal condition	Mechanism	Effects on the fetus
Poorly controlled diabetes mellitus	Oxidative stress	Heart malformations, neural tube defects, fetal macrosomia, stillbirth
Phenylketonuria (PKU) without diet	Neurotoxicity	Microcephaly, mental retardation, heart defects, IUGR
Untreated hypothyroidism	Thyroid disruption	Mental retardation, low weight, alterations in brain development
Systemic lupus erythematosus (SLE)	Endothelial and placental alteration	Congenital heart block, preterm birth, fetal growth restriction
Chronic kidney disease		IUGR, preterm birth, oligohydramnios
Severe obesity	Inflammation	Risk of neural tube defects, macrosomia, preeclampsia, stillbirth

Maternal Infections (TORCH)	Inflammation	Deafness, microcephaly, hydrocephalus, chorioretinitis, brain calcifications
Severe maternal malnutrition	DNA alteration	IUGR, neurological abnormalities, low birth weight
Chronic hypoxia (severe asthma, COPD)	↓ Fetal O ₂	IUGR, chronic fetal distress, preterm birth
Severe psychological stress or trauma	Hormonal and placental alterations	Hormonal alterations that affect fetal growth and neurodevelopment
Thyroid disorders (hyperthyroidism)	Thyroid disruption	Malformations, fetal loss, preterm birth

Figure 6

Maternal teratogenesis scheme



Fig. 6. Maternal condition → Alteration of the intrauterine environment → Deficit of oxygen/nutrients/signals → Alteration of embryo-fetal development → Clinical manifestations

5.13 Conclusion

Maternal factors represent a fundamental and potentially preventable cause of teratogenesis. Its impact depends to a large extent on clinical control and preconceptional

management. Early identification and timely intervention can significantly reduce fetal morbidity, highlighting the importance of a comprehensive approach to prenatal care.

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ANNEX 1

GLOBAL FIGURE. Comparative classification of teratogens and mechanisms of embryo-fetal damage

INTEGRATED SCHEME

TERATOGENIC EXPOSURE

— 1. BIOLOGICAL TERATOGENS

(Viruses, bacteria, parasites) | — Examples: TORCH, Zika, syphilis | — Mechanism: |
 • Direct fetal infection | • Intrauterine inflammation | • Tissue necrosis | —
 Manifestations: • Microcephaly • Brain calcifications • Deafness, chorioretinitis

— 2. PHYSICAL TERATOGENS

(Radiation, hyperthermia, trauma) | — Examples: ionizing radiation, maternal fever | —
 Mechanism: | • Direct DNA damage | • Cellular apoptosis | • Alteration of cell proliferation
 | — Manifestations: • Structural malformations • Growth restriction • Neurological
 alterations

— 3. CHEMICAL TERATOGENS

(Drugs, toxicants, pollutants) | — Examples: | • Drugs: thalidomide, valproate | •
 Substances: alcohol, tobacco | • Metals: lead, mercury | • Endocrine disruptors: BPA | —
 Mechanism: | • Oxidative stress | • DNA alteration | • Endocrine disruption | •
 Antiangiogenesis |
 — Manifestations: • Congenital malformations • Neurocognitive deficit • IUGR

— 4. MATERNAL FACTORS

(Maternal Internal Conditions) | — Examples: | • Diabetes | • PKU | •
 Hypothyroidism | • Obesity | • Hypoxia | — Mechanism: | • Metabolic Disorders | •
 Fetal Hypoxia | • Nutritional Deficiencies | • Hormonal Disruption | — Manifestations: •
 Congenital Heart Disease • Neural Tube Defects • Microcephaly • IUGR

COMMON PATHOPHYSIOLOGICAL AXIS

Teratogenic agent ↓ Transplacental passage / Maternal alteration ↓ Molecular interference (DNA, cell signaling, hormones, angiogenesis) ↓ Alteration of embryo-fetal development ↓ Clinical manifestations (malformations, IUGR, neurodevelopment)

Table 6

Global comparison table

Type of teratogen	Source	Main mechanism	Critical moment	Key example	Typical manifestation	Type of teratogen
Biological	Exogenous	Direct infection	1st trimester	TORCH	Microcephaly	Biological
Physical	Exogenous	DNA damage	Organogenesis	Radiation	Malformations	Physical
Chemical	Exogenous	Oxidative stress/disruption	Variable	Valproate	DTN	Chemical
Maternal	Endogenous	Metabolic Alteration	Continuous	Diabetes	Heart Disease	Maternal

KEYS FOR DISCUSSION

This outline allows you to highlight strengths in your chapter:

1. Pathophysiological convergence

Although the agents are different, they all converge in:

Molecular damage

Alteration of cell development

Disruption of the fetal microenvironment

2. Importance of exposure time

Preimplantation → embryonic death

Organogenesis (3–8 weeks) → structural malformations

Fetal period → functional alterations

3. Multifactorial interaction

Fetal genetics

Maternal status

Combined environmental exposure

ANTICANCER ACTIVITY OF AMINOCHALCONES. SCIENTIFIC And TECHNOLOGICAL PROSPECTING

ATIVIDADE ANTICANCER DE AMINOCHALCONAS. PROSPECÇÃO CIENTÍFICA E TECNOLÓGICA

ACTIVIDAD ANTICANCERÍGENA DE AMINOCHALCONAS. PROSPECTIVA CIENTÍFICA Y TECNOLÓGICA



<https://doi.org/10.56238/sevened2026.020-021>

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ABSTRACT

Chalcones are a group of polyphenolic compounds derived from plants that exhibit a wide variety of biological activities, notably their cytotoxic capacity. The aim of the present study is to describe available articles regarding the cytotoxic characteristics of aminochalcones, and analyzed patent deposits this theme. The research was conducted by searching for the terms "Aminochalcones" AND/OR "cancer" "Biological action" AND/OR "Technological prospecting" in the Medical Subject Headings (MeSH) database as equated terms referring to the toxicological properties of aminochalcones. Patentaries bases using INPI, EPO, USPTO e WIPO was used to research innovation and Technology. Out of the 2,179 articles, only 10 were selected, with 2015 being the year of highest scientific productivity. Regarding patents, China ranks first, so out of the 112 patents observed, only 7 stand out due to their methodological relevance and innovations. The majority of researchers do not request patent deposits for the toxicological activity containing the study's technology. Patents, in summary, create favorable environments for the scientific and technological development of a country. Based on the data obtained, it is inferred that the quantity of publications regarding the anticancer properties of chalcones has increased over time; however, such compounds still have limited investigations, despite holding potential anticancer properties.

Keywords: Chalcones. Cytotoxicity. *In vitro*. Anticancer.

RESUMO

As chalconas são um grupo de compostos polifenólicos derivados de plantas que possuem uma ampla variedade de atividades biológicas, destacando-se sua capacidade citotóxica. O

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objetivo do presente estudo é descrever sobre artigos disponíveis a respeito das características citotóxicas de aminochalconas e análise dos depósitos de patente nesta temática. A pesquisa foi realizada por meio da busca dos termos: “Aminochalcones” AND/OR “cancer” “Biological action” AND/OR “Technological prospecting” usando o Medical Subject Headings (MeSH) como termos equacionados referentes às propriedades toxicológicas das aminochalconas. As bases patentárias INPI, EPO, USPTO e WIPO foram usadas para pesquisa de tecnologia e inovação. Dos 2.179 artigos, apenas 10 foram selecionados, sendo 2015 o ano de maior produtividade científica. Quanto às patentes, a China ficou em primeiro lugar como depositária, de forma que das 112 patentes avaliadas, apenas 7 se destacaram pela relevância metodológica e inovações. Com base nos dados obtidos, infere-se que a quantidade de publicações acerca das propriedades anticâncer das chalconas aumentou ao longo do tempo, todavia, tais compostos ainda apresentam investigações limitadas, mesmo detendo potencial propriedade anticancerígena.

Palavras-chave: Chalconas. Citotoxicidade. *In vitro*. Anticâncer.

RESUMEN

Las chalconas son un grupo de compuestos polifenólicos derivados de plantas que presentan una amplia variedad de actividades biológicas, destacándose su capacidad citotóxica. El objetivo del presente estudio es describir los artículos disponibles acerca de las características citotóxicas de las aminochalconas y analizar los depósitos de patentes en esta temática. La investigación se realizó mediante la búsqueda de los términos: “Aminochalcones” AND/OR “cancer” “Biological action” AND/OR “Technological prospecting”, utilizando los Medical Subject Headings (MeSH) como términos estandarizados relacionados con las propiedades toxicológicas de las aminochalconas. Las bases de datos de patentes INPI, EPO, USPTO y WIPO fueron utilizadas para la prospección tecnológica y de innovación. De los 2.179 artículos identificados, solo 10 fueron seleccionados, siendo 2015 el año de mayor productividad científica. En cuanto a las patentes, China ocupó el primer lugar como principal solicitante, de modo que, de las 112 patentes evaluadas, solo 7 se destacaron por su relevancia metodológica e innovaciones. Con base en los datos obtenidos, se infiere que la cantidad de publicaciones sobre las propiedades anticancerígenas de las chalconas ha aumentado con el tiempo; sin embargo, estos compuestos aún presentan investigaciones limitadas, a pesar de su potencial propiedad anticancerígena.

Palabras clave: Chalconas. Citotoxicidad. *In vitro*. Anticancerígeno.

1 INTRODUCTION

The World Health Organization (WHO) reported that 65-80% of the population in developing countries depended on medicinal plants as the only form of access to basic health care (OKPUZOR et al., 2021). Nature is characterized as the best source of medicines, where most modern pharmaceuticals are derived or inspired by medicinal plants (FANG et al., 2021)

Plants containing chalcones have long been used in clinical practice and continue to expand rapidly around the world. The first chalconic structures were isolated from plant species in 1910, being present in the families Asteraceae, Moraceae, Fabaceae and Aristolochiaceae (IWASHINA T, 2000).

Chalcones are a group of polyphenolic compounds that have a wide variety of biological activities, and were discovered by Alexander Borodin in 1869, who isolated it from the Chinese licorice, *Glycyrrhiza inflata*. Subsequently, chalcones were recognized by numerous researchers for their clinical applications that led to other synthetic and natural chalcones such as Butein, Boesenbergine A, and Lophirone B (RANI et al., 2019; DAN; DAI, 2020; JASIM, 2021). The literature describes aminochalcones as promising agents with antitumor (KALMOUCH et al., 2020), antimicrobial (EL-MESSERY et al., 2018), antioxidant (MPHAHLELE; AGBO; CHOONG, 2021), antiproliferative (LU et al., 2020), cytotoxic (DIMMOCK et al., 2003) and antiparasitic (DE BRITO et al., 2022).

The cytotoxic activity of aminochalcones, a group of mattresses, has been an area of interest due to the possibility of an increased electrophilic attack on cellular proteins through covalent bonds. Covalent inhibitors are an emerging area of drug discovery, and aminochalcones have the potential to serve as clues for the development of inhibitors that target specific cellular proteins (MPHAHLELE; AGBO; CHOONG, 2021; ZHOU; PARADIES, 2021).

The most studied aminochalcone contains an NH₂-substitution at position 4 on ring A. The amino group on ring A increases the magnitude of the positive charge on the olefin carbon atom adjacent to ring B (PARK D Y et al., 2018; LEE S Y, CHEON C H, 2018). This has been proposed to increase the electrophilic attack of these compounds on cancer cells (CHELGHOUM M et al., 2012).

In this sense, the present study aimed to describe the available articles regarding the cytotoxic characteristics of aminochalcones.

2 METHODOLOGY

This is a scientific and technological prospecting study, where the following terms were chosen from the Medical SubjectHeadings (MeSH) database: "Aminochalcones" AND/OR "cancer" "Biologicalaction" AND/OR "Technological prospecting" as terms equated referring to the toxicological properties of aminochalcones.

Non-original studies, duplicates, reviews, articles not available in full, as well as research whose theme did not address the toxicological and anticancer properties of aminochalcones were excluded.

To carry out the scientific study and technological prospection, a search was made in the PubMed, Science Direct and Web of Science databases. For the search for technologies and innovations, a search was made in the INPI, EPO, USPTO and WIPO databases.

3 RESULTS

The scan of the databases revealed a total of 2,179 articles, however, the articles presented information only about chalcones in isolation. Thus, only 10 articles were selected (Table 1)

Table 1

Main information found in the scientific articles

Author/Year	Type of study	Objective	Considerations and results
Xia et al (2000)	In Vitro (Cell Culture)	Identify the design, synthesis and biological evaluation of 2'-amino chalcone	Discovery of a new class of 2'-amino chalcones as potential antitumor agents in cell lines of: Human squamous cell carcinoma of the nasopharynx (KB); human squamous cell carcinoma of the nasopharynx expressing PGP (KB-VIN); osteosarcoma (Hos); human melanoma (SKMEL-2); human ileocecal carcinoma (HCT-8); human breast cancer (MCF-7), human lung adenocarcinoma (A-549) and human ovarian cancer (1A9).
Dimmock et al (2003)	In Vitro (Cell Culture)	To evaluate the cytotoxic activity of 4'-aminochalcones	The cell lines were: human Molt 4/C8 T lymphocytes and EMFs, as well as P388 and L1210 murine leukemia cells. It was observed that aminochalcone presented a selective toxicity to tumor strains.
Abuo-rahma et al (2012)	In Vivo (Rats)	To evaluate the anti-inflammatory effects of chalcone-releasing hybrids of the amino group in the presence of ulcers.	Significant anti-inflammatory activity using carrageenan-induced adult male albino rat paw edema method compared to indomethacin.
Prasad; Rani; Rao (2013)	In vitro	To evaluate the antioxidant activity of a series of 4'-aminochalcones replaced.	Antioxidant activity of chalcones 9 and 10 composed of 3,4,5-trimethoxyphenyl and 4-dimethylaminophenyl as B-ring moieties of chalcones, respectively, exhibited maximum activity in various antioxidant assays, which may be due to free radical scavenging activity.

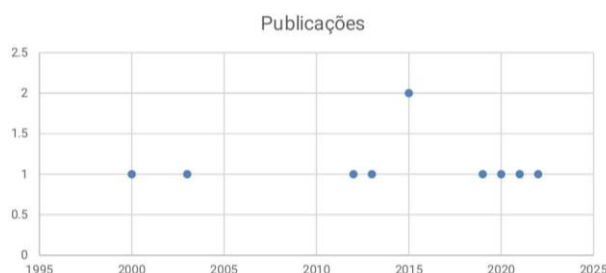
Ruanwas; Chantrapromma; Fun (2015)	In Vitro	To evaluate the synthesis, characterization, antioxidant and antibacterial activities of 2-Aminochalcones	Compound 1 ((2E)-1-(2-aminophenyl)-3-phenyl-2-propen-1-one), which does not have a substituent group in the B ring, showed the highest antioxidant activity with 18.71% inhibition of free radical production.
Radhakrishnan et al (2015)	<i>In Vitro</i> (Cell Culture)	To evaluate the synthesis and biological evaluation of hydroxy-substituted aminochalcone for antityrosinase activity in B16 cells	Compounds inhibited melanin production and tyrosinase activity in B16 cells.
Novilla et al (2019)	In Vitro (Cell Culture)	To evaluate the anticancer activity and selectivity of seven chalcone derivatives against the K562 and HL-60 leukemia cell lines.	The study revealed that the number and position of methoxy groups in chalcone derivatives influenced selectivity for leukemia cells.
Lu et al (2020)	In Vitro (Cell Culture)	To investigate fourteen effective chalcone derivatives with anticancer activity.	Some of the compounds showed moderate to good activity against three human tumor cells (human gastric carcinoma cells - MGC-803, human cervical cancer - HCT-116 and human breast cancer - MCF-7) and compound 13e ((E)-4-chloro-N-(4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl) phenyl) butanamide) exhibited the best antiproliferative activity against such cells.
Oyeneyin et al (2021)	In Vitro (Cell Culture) and in Silico (MCF-7 Breast Cancer)	To investigate Aminochalcone derivatives as antiproliferative agents against MCF-7 Breast Cancer Cell Lines	All molecules were free of cytotoxicity, as well as the standard drug, 5-Fu (fluorouracil).
De Brito et al., (2022)	In Vitro (Cell Culture) and in Silico	Perform a structural and spectroscopic analysis and antiproliferative activity of chalcone derivative (E)-1-(4-aminophenyl)-3-(benzo[b]thiophen-2-yl)prop-2-en-1-one	Regarding activity against <i>T. cruzi</i> , the compound exhibited more activity in the trypomastigote forms than in the epimastigote forms, with lower toxicity in the LLC-MK2 host cells. In addition, it had a more potent inhibitory effect than benznidazole.

Source: The authors.

When observing the number of articles per year, it was shown that in 2015 there was a higher productivity (Figure 1).

Figure 1

Distribution of the quantity of articles



Source: The authors.

Table 2

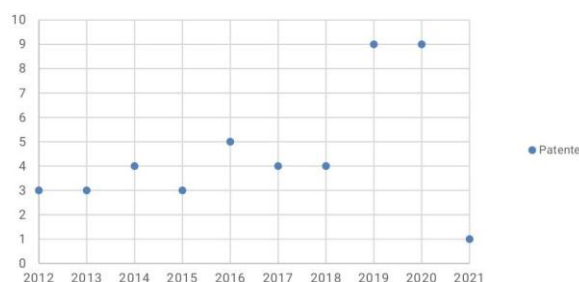
Patents of the research technology in the abstract field, in the INPI, EPO, USPTO and WIPO databases

Keyword	INPI	EPO	USPTO	WIPO
<i>Amino chalcone</i>	0	5	16	122
<i>Amino chalcone/aminochalcone</i>	0	0	0	0

Source: The authors.

Figure 2

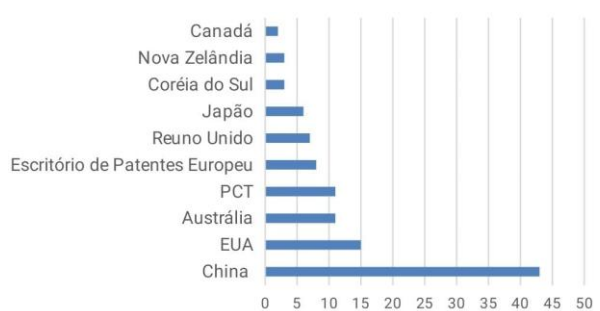
Distribution of the number of patents per year



Source: The authors.

Figure 3

Distribution of patents by countries and patent production institutions



Source: The authors.

Table 3

Main innovations proposed by the patents filed

Patent Number/ Owner	Title	Innovation
201811030086/ Awasthi Satish Kumar	Novel hybrid 1,2,4,5-tetraoxane and analogs as antimalarial drugs	Incorporation of aminochalcones into tetraoxanes for the production of hybrid drugs, in order to increase their solubility in protic solvents. Sodium triacetoxyborohydride efficiently used as a reducing agent in the synthesis of novel tetraoxane-chalcone hybrid analogues.
201811030086/ Awasthi Satish Kumar	Novel hybrid 1,2,4,5-tetraoxane and analogs as antimalarial drugs	It refers to the novel hybrid antimalarial analogues 1,2,4,5 - tetraoxane - aminochalcones and the method of preparation. Hybrid analogues were synthesized by an economic synthesis method
0328669/ Hayashi Akio	Chalcone derivative compounds	Chalcone-derived compounds represented by the general formula (I) or (II), where R1 and R2 each represent a halogen atom, a hydroxy group, an amino group, a dimethylamine group, a nitro group, a cyan group, a phenyl group, an acetyl group, an alkyl group containing 1 to 18 carbon atoms, or an alkoxy group containing 1 to 22 carbon atoms, N1 and N2 each represent an integer from 0 to 21, and m1 and m2 each represent an integer from 0 to 5.
1020200142470 Lee EungSeok	Novel 1-tetralone chalcone-based compound, and composition for preventing or treating inflammatory diseases and containing same as active ingredient	The present invention refers to a new compound based on 1-tetralone chalcone and a composition for the prevention or treatment of inflammatory diseases and containing it as an active ingredient. A compound derived from 6-amino-1-tetralone chalcone according to the present invention is represented by the chemical formula 1. In chemical formula 1, R is selected from halogen, trifluoroalkyl C1-C4 and trifluoroalkoxy C1-C4. According to the present invention, a composition can be provided to prevent, relieve or treat inflammatory diseases.
108863930/ Gao Wenchao	Synthetic method of 3-sulfo-2,3-dihydroquinoline-4(1H)-ketone compounds	It describes a synthetic method of 3-sulfo-2,3-dihydroquinoline-4(1H)-ketone compounds and pertains to organic synthesis. Taking aminochalcone as raw material and having diethyl boron ether trifluoride as catalyst, an electrophilic sulfur reagent is used to induce aminochalcone to perform the intramolecular reaction of electrophilic cyclization.
1506157/ Nielsen Simon Feldbaek	Amino-chalcones functional	The invention provides novel derivatives of functional aminochalcones and their analogues. The use of compounds, or compositions that comprise them as pharmaceutically active agents, in particular against bacterial and parasitic infections, is also disclosed. The invention also refers to a method for detecting

inhibitory effects against, for example, bacteria, parasites, fungi, and helminths.

109232621/ Shaojinjun	Preparationmethod substituted fluoroboratefluorescentnearinfrareddye	for amino aza-	The invention corresponds to an organic photoelectric functional material and specifically describes a method of preparation of a BODIPY aza based near-infrared fluorescent dye and application of the near-infrared fluorescent dye for Hg ²⁺ detection, cell imaging and biomarker. The material is a near-infrared micromolecular dye based on BODIPY aza, and the wavelength of near-infrared absorption and emission is adjusted by the change of the Ar group. The material can be used as fluorescent material in the near infrared and has good application prospects in ion detection, cell imaging, and biomarker.
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Source: The authors.

4 DISCUSSION

In vivo tests, aminochalcones showed activity for the treatment of gastric and duodenal ulcers, bronchial asthma, poisoning by food and medications, and skin diseases such as eczema and urticaria, as well as relief of rheumatic pain and other types of pain and healing effect on ulcers, as well as anti-inflammatory activity. (ABUO-RAHMA et al., 2012).

In vitro studies have demonstrated improved antiproliferative activity of chalcones with amino substituted groups (XIA Yi et al., 2000) corroborating with the studies of Radhakrishnan et al. (2015) who demonstrated that methoxylated chalcones with a 3'-amino group had submicromolar mean inhibitory concentration values against murine melanoma B16 cells and Novilla et al. (2019) in evaluating the anticancer selectivity of chalcone derivatives in K562 and HL-60 leukemia cell lines.

Research proposes that the presence of the amino function increases the reactivity of chalcones as Michael acceptors. The electron-removing effect of the protonated ammonium function would increase the electrophilicity of the β carbon at the ninth bond, thus increasing its reactivity as a Michael acceptor, when evaluated the cytotoxic activity of 4'-aminochalcones (DIMMOCK J. R. et al., 2003)

Studies conducted in vitro and in silico, Oyeneyin et al. (2021) showed that some aminochalcone derivatives were obtained through the functional density theory; some of the optimized molecules were also anchored to the active site of a human serine/threonine-protein kinase receptor, 3FC2, to obtain their binding affinities.

De Brito et al. (2022) in *In vitro* and *In Silico* research evidenced antiproliferative activity in LLC-MK2 host cells. Aminochalcone showed cytotoxicity at the concentrations tested, and was described by the authors as a potent candidate for the development of a new option for the treatment of Chagas disease.

According to studies conducted by Ruanwas et al. (2015), in a DPPH assay on aminochalcones, proved their ability to scavenge free radicals. The mentioned activity was satisfactory and comparable to that of ascorbic acid, a reference compound known for its high antioxidant properties when evaluated in 4'aminochalcones substituted in studies carried out by Prasad et al, 2013.

To carry out an analysis on the most appropriate prospection, a good number of patents must be observed, the fact that aminochalcones have a relatively low value of patents may be related to their relatively recent innovation and discovery as an anticancer agent¹¹ (LU, C. F. et al, 2020)

When comparing the number of articles published with the data in Table 1, in relation to the number of patent documents published, it can be observed that most of the research related to aminochalcones is published in the form of articles and researchers do not request patent applications. Table 2 presents all the keywords searched in their respective patent search databases.

Initially, the results observed in the global database (WIPO) were analyzed, in which the largest number of patents was obtained, a number of 112 patents, through the platform it was only possible to observe the patents distributed in the 2012-2021 time interval by eight countries, a cooperative (PCT-Treaty of Patent Cooperatives) and a European patent office.

The distribution among the countries showed a concentration of patents located in China, with a total of 43 patents, followed by the USA with 15 of the productions and in third is Australia and the Patent Cooperation Treaty (PCT) with 11 publications of each.

The present research showed that it is necessary to reflect on the role of patents in technological development, both in increasing the market potential and in research in general.

The largest producers of the most relevant patents, observed by the WIPO database, stand out, with a total of five major producers, highlighting Emmerling Michael e Spangenberg German who have filed a total of 10 patents each.

Patents, in short, create favorable environments for the scientific and technological development of a country, hence the importance of prospecting studies.

5 CONCLUSION

Based on the data obtained, it is inferred that the number of publications on the anticancer properties of aminochalcones has increased over time, however, these compounds still have limited investigations and the number of in vitro studies exceeds the in vivo results. The position of the substitutions in the amino group in chalcones influences the selectivity in cancer cell lines. China and the US are the champions in patent filings when it comes to production efficiency. The use of aminochalcones as an antitumor potential depends on designs that seek to unravel their properties, minimize unwanted interactions, and carry out further experiments to prove their pharmacological effects and possible future use in clinical studies.

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PRESENCE OF LACTOSE IN MEDICATIONS FOR THE TREATMENT OF HYPERTENSION

PRESENÇA DE LACTOSE EM MEDICAMENTOS PARA O TRATAMENTO DA HIPERTENSÃO

PRESENCIA DE LACTOSA EN MEDICAMENTOS PARA EL TRATAMIENTO DE LA HYPERTENSION



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ABSTRACT

Introduction: Medications used to treat hypertension in the Brazilian population, containing lactose as an excipient in solid pharmaceutical form, cause undesirable effects in patients with lactose intolerance.

Objective: To ascertain the presence of lactose as an excipient in medications in solid pharmaceutical form available on the market that are used to treat hypertensive patients.

Methodology: To evaluate the medications present in the National List of Essential Medicines (Rename), indicated for the treatment of hypertension or comorbidities that may occur alongside hypertension. Generic, similar, and reference medications were selected from the market to evaluate the drug information and determine the presence or absence of lactose.

Results: Of the 151 medications analyzed and grouped according to pharmaceutical forms, therapeutic classes, brands, and categories, data regarding the presence of lactose were collected from the electronic drug information database of the National Health Surveillance Agency (ANVISA) and from pharmaceutical industry websites. It was detected that lactose is

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present in 60.93% of the selected medications, being more frequent in tablets (60.87%) and coated tablets (39.13%), and no lactose was found in dragees, respectively. It was predominantly found in reference medications (47.83%), followed by generics (31.52%), and similar medications presented a proportion of 20.65%.

Conclusion: Lactose is one of the most used excipients in solid medications, as it provides greater resistance to the form. 60.93% of the analyzed medications contain lactose in their formulation; therefore, it is essential to include a warning phrase on medication boxes due to the risk posed to people with lactose intolerance.

Keywords: Hypertension. Intolerance. Lactose. RENAME.

RESUMO

Introdução: Medicamentos utilizados no tratamento de hipertensos na população brasileira, tendo a lactose como excipiente em forma farmacêutica sólida, ocasionando efeitos indesejáveis nos pacientes com intolerância à lactose.

Objetivo: Constatar a presença de lactose como excipiente em medicamentos na forma farmacêuticas sólidas disponíveis no mercado que são utilizados no tratamento de pacientes hipertensos.

Metodologia: Avaliar os medicamentos presentes na RENAME, indicados para o tratamento de hipertensão ou comorbidade que possam vir junto a hipertensão. Foram selecionados medicamentos genéricos, similares e referências no mercado para avaliar o bulário e constatar ou não a presença da lactose.

Resultados: Dos 151 medicamentos analisados e agrupados de acordo com as formas farmacêuticas, classes terapêuticas, marcas e categorias, dados quanto a presença de lactose no bulário eletrônico da Agência Nacional de Vigilância Sanitária (ANVISA) e nos sites da indústria farmacêutica. Detectou-se que a lactose está presente em 60,93% dos medicamentos selecionados, sendo mais frequentes nos comprimidos (60,87%) e comprimidos revestidos (39,13%) e nas drágeas não foi encontrado a presença de lactose, respectivamente. Ela foi constatada, predominante, em medicamentos referência (47,83%), seguida de genéricos (31,52%) e os medicamentos similares apresentaram a proporção de 20,65%.

Conclusão: A lactose é um dos excipientes mais utilizados nos medicamentos sólidos, por proporcionar uma maior resistência a forma. 60,93% dos medicamentos analisados a lactose está presente em sua formulação, portanto, é fundamental frase de alerta nas caixas dos medicamentos, devido ao risco causado a pessoas com intolerância.

Palavras-chave: Hipertensão. Intolerância. Lactose. RENAME.

RESUMEN

Introducción: Los medicamentos utilizados en el tratamiento de pacientes hipertensos en la población brasileña contienen con frecuencia lactosa como excipiente en formas farmacéuticas sólidas, ocasionando efectos indeseables en pacientes con intolerancia a la lactosa.

Objetivo: Verificar la presencia de lactosa como excipiente en medicamentos en formas farmacéuticas sólidas disponibles en el mercado que se utilizan en el tratamiento de pacientes con Hipertensión.

Metodología: Evaluar los medicamentos incluidos en la RENAME, indicados para el tratamiento de la hipertensión o comorbilidades asociadas; se seleccionaron medicamentos genéricos, similares y de referencia disponibles en el mercado para analizar los prospectos y constatar la presencia o ausencia de lactosa.

Resultados: De los 151 medicamentos analizados y agrupados según formas farmacéuticas, clases terapéuticas, marcas y categorías, los datos sobre la presencia de lactosa se obtuvieron de los prospectos electrónicos de la Agência Nacional de Vigilância Sanitária (ANVISA) y de los sitios web de la industria farmacéutica; se detectó que la lactosa está presente en el 60,93% de los medicamentos seleccionados, siendo más frecuente en comprimidos (60,87%) y comprimidos recubiertos (39,13%), mientras que no se encontró en grageas; se constató predominantemente en medicamentos de referencia (47,83%), seguido de genéricos (31,52%) y los similares representaron el 20,65%.

Conclusión: La lactosa es uno de los excipientes más utilizados en medicamentos sólidos por proporcionar mayor resistencia estructural; el 60,93% de los medicamentos analizados contienen lactosa en su formulación, por lo tanto, es fundamental incluir advertencias en los envases debido al riesgo para personas con intolerancia.

Palabras clave: Hipertensión. Intolerancia. Lactosa. RENAME.

1 INTRODUCTION

Dosage forms is the final state that the active ingredients present after being submitted to pharmaceutical operations, in order to facilitate administration and obtain the greatest desired therapeutic effect, with precise dosage and excellent stability. They are presented in a more practical way to be administered, as agglomerated solids, including tablets, tablets, capsules, tablets, pills and granules, with tablets being the most considerable form in the pharmaceutical industry. (BARRIENTOS, et al. 2018).

Aiming at maximum excellence in drug production, known inactive ingredients of excipients are combined and added to give adequate stability to their dosage form. Lactose is a type of sugar most used in manufacturing since the 60s as a solid excipient, as it has excellent physicochemical stability, mild flavor, availability, high crushing resistance, low cost and benefits, the disadvantages of using lactose as an excipient and that a percentage of the population is intolerant to it (BARRIENTOS, et al. 2018).

Hypolactasia, also known as lactose intolerance, is a syndrome of varying gastrointestinal symptoms following consumption of lactose-containing foods, resulting in a minimal ability to digest lactose and glucose at the brush border of the mucosa of the small intestine. When lactose is not digested, it is fermented by the intestinal microbiota, causing symptoms of lactose intolerance such as: flatulence, pain, bloating, diarrhea, borborygmus, even vomiting (COSTANZO, et al 2019).

The Brazilian legislation, RDC 47 of September 8, 2009, points to the qualitative description of the excipients in the package insert of medicines and the attachment of expressions aiming to take all the necessary measures for the use of medicines. The alert guidelines regarding active ingredients and excipients in package inserts and drug labeling are regulated by RDC 60, of December 17, 2010, but the presence of excipients in package inserts and labeling do not have a detailed legislation on which excipients were used in the preparation, aiming only at the rational use of drugs. Lactose has been one of the most used excipients, as it favors the absorption of calcium in the body, in addition to its multifunctionality. However, it is not discriminated in the boxes, making it implicit to the consumer, and may lead to reactions according to the degree of sensitivity of the individual who has lactose intolerance (NOVAES, 2020).

Lactose can be found as an adjuvant in several medications, such as drugs that are used in the treatment and control of Systemic Arterial Hypertension (SAH), also known as high blood pressure, remains one of the main determinants of morbidity and mortality in the country and in the world. The predominance of hypertension in the Brazilian population is around 38 million people, according to the national health survey, becoming increasingly

precocious, representing a serious Public Health problem in Brazil and in the world (MELO, et al. 2020).

Although there is an increase in global SAH rates, this increase does not occur in a similar way between economies. Middle- and low-income countries have shown more significant growth (31.5%) than high-income countries (28.5%). The increase in the number of people with SAH reflects different aspects of the population's living condition (MELO, et al. 2020).

Population aging, added to unhealthy lifestyles, with the preference for processed, fatty, saltier foods, alcohol consumption, smoking, people with diabetes, dyslipidemia and lack of physical activity, have contributed to this increase. Other aspects such as the knowledge, control and treatment of SAH are also highly sensitive to individual and socioeconomic attributes (MELO, et al. 2020). Aiming at the treatment of chronic diseases such as hypertension and the reduction of morbidity and mortality, non-drug measures or those associated with antihypertensive drugs are used, including coptopril, simvastatin and enalapril maleate, drugs that have lactose as an excipient in their formulation (MOURA, et al. 2015)

The reason for the present study was to verify the presence of lactose as an excipient in drugs in the solid pharmaceutical form available on the market that are used in the treatment of hypertensive patients.

2 METHODOLOGY

This is a descriptive study, with a quantitative approach, carried out in April and June 2022. The therapeutic class used in the study followed the guidance of the National List of Medicines (RENAME) by anatomical chemical therapeutic classification (ATC) for drugs of the cardiovascular system (BRASIL, 2022). From the therapeutic classes described for the cardiovascular system, drugs definitively for hypertension were selected, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and drugs associated with the care of patients with hypertension as lipid-modifying agents.

A total of 151 drugs from 32 brands were selected, grouped according to pharmaceutical forms, therapeutic classes and categories. The pharmaceutical forms analyzed were: tablets, coated tablets and tablets.

The excipients indicated in the professional brochures available in the electronic leaflet of the National Health Surveillance Agency (ANVISA) and on the websites of the pharmaceutical industry were carefully analyzed.

3 RESULTS

Of the 151 drugs selected for the study, 92 (60.93%) contained lactose in the excipients. Table 1 shows the distribution of the drugs, according to the pharmaceutical form. Among all the drugs that contained lactose, the tablets were the most frequent (60.87%), followed by the coated tablets (39.13%) and the presence of lactose was not found in the pills.

Table 1

Presence of lactose according to the pharmaceutical form of the drugs used in the treatment of hypertension. Brazil, June 2022

Pharmaceutical form	n	Presence of lactose n (%)	Proportion* (%)
Tablet	81	56 (69,14)	60,87
Coated tablet	68	36 (52,94)	39,13
Dragea	2	0 (0,00)	0,00
TOTAL	151	92 (60,93)	100,00

* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).

Source: The authors.

In the therapeutic classes according to ATC analyzed (Table 2), it was found that almost all drugs in these classes contained lactose in their excipients. Lipid-modifying agents (38.04%) and agents acting on the renin-angiotensin system (23.91%) had the highest proportion of lactose in their excipients. Beta-blockers and diuretics contributed with a frequency of more than 10% and hypertensive and calcium-blockers contributed with a frequency of less than 10%.

Considering the categories of drugs analyzed, the highest occurrence of lactose was found in reference drugs (47.83%), followed by generics (31.52%) and similar drugs presented a proportion of 20.65%.

Table 2

Presence of lactose according to the therapeutic class according to PCI of the drugs used in the treatment of hypertension. Brazil, June 2022

Therapeutic class	n	Presence of lactose n (%)	Proportion* (%)
Lipid-modifying agents	41	35 (85,37)	38,04
Agents acting on the Renin-Angiotensin System	25	22 (88,00)	23,91
Antihypertensive	20	7 (35,00)	7,61
Beta-blockers	37	15 (40,54)	16,30
Calcium channel blockers	11	2 (18,18)	2,17
Diuretics	17	11 (64,71)	11,96

TOTAL	151	92 (60,93)	100,00
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* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).

Source: The authors.

The classes of drugs used in the treatment of hypertension were related to the categories of reference, generic and similar drugs. The presence and absence of lactose are presented in Table 3. In this relationship, considering the total number of drugs evaluated, lactose was found more frequently in the reference lipid-modifying agents and the agents that act on the reference renin-angiotensin system.

Table 3

Presence of lactose according to the category of drugs used in the treatment of hypertension. Brazil, June 2022

Classification of medicinal products	n	Presence of lactose n(%)	Proportion * (%)
References	67	44 (65,67)	47,83
Generic	49	29 (59,18)	31,52
Similar	35	19 (54,29)	20,65
TOTAL	151	92 (60,93)	100,00

* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).

Source: The authors.

Table 4

Distribution of the drug classes used in the treatment of hypertension, according to the presence or absence of lactose. Brazil, June 2022

Class/Category	References		Generic		Similar	
	Yes	No	Yes	No	Yes	No
Lipid-modifying agents	19	2	12	3	4	1
Agents acting on the Renin-Angiotensin System	9	3	8	0	5	0
Antihypertensive	4	6	1	4	2	3
Beta-blockers	6	7	5	8	4	7
Calcium channel blockers	0	5	0	2	2	2
Diuretics	6	0	3	3	2	3

Source: The authors.

The classes of drugs used in the treatment of hypertension were related to the categories of reference, generic and similar drugs. The frequencies of presence and absence of lactose are presented in Table 4. In this relationship, considering the total number of drugs used in the treatment of hypertension evaluated, lactose was found in higher frequency in reference (12.58%) and generic (7.94%) lipid-modifying agents, followed by drugs that act

on the reference Renin-Angiotensin System (5.96%) and generics (5.29%). Antihypertensive drugs, beta-blockers, and calcium channel blockers had a higher frequency of lactose-free drugs when compared to the same class with lactose. In the class of diuretic drugs in the reference drug category, 100% of this category had lactose in the formulation.

4 DISCUSSION

The present study showed that more than half of the evaluated drugs used in the treatment of hypertension contain lactose in their formulation. This substance is present, in greater proportion, in the form of tablets and coated tablets, respectively. Because of the characteristics, the main studies related to the functionality of lactose in solids have been reported in studies in the development of tablet formulations (GOHEL; JOGANI, 2005). The present study reported that the presence of lactose among the tablets and coated tablets was 60.93% in the medications evaluated for hypertension. Lactose is widely used in the development of the tablet and coated tablet dosage forms because they provide the formulations with appropriate conditions to prevent possible alterations such as adhesion to punctures and lack of uniformity of the tablet's appearance (STEFANI et al, 2009).

Lactose can be found in medications administered orally and could bother patients with lactose intolerance. However, it is likely that the amount of this sugar is too small to cause symptoms related to intolerance (PHILPOTT et al, 2014). Commercially, lactose is produced from cow milk whey and is widely used for the purpose of diluting and filling in capsules and tablets (LUYT et al., 2014). Symptoms of lactose intolerance arise from malabsorption resulting from little or no lactase enzyme activity. There is considerable variation considering the characteristics of each person in the severity of gastrointestinal symptoms according to the amount of lactose ingested and also the digestion capacity of each individual (DI RIENZO et al., 2013).

The dose of lactose in most pharmaceutical products usually does not exceed 2 g/day. Therefore, it is unlikely that more severe symptoms can be attributed to lactose in a solid drug administered orally, especially in adults who have not been previously diagnosed with severe lactose intolerance (LUYT et al., 2014).

Studies carried out by Montalto et al. (2008) evaluated the influence of lactose in patients with lactose intolerance. In this study, we evaluated the excretion of H₂ in the exhaling air and symptoms of lactose intolerance in patients with lactose intolerance after ingestion of a capsule containing 400 mg of lactose or placebo through the randomized, crossover, double-blind, controlled study. 77 patients with lactose intolerance were evaluated in the H₂ breath tests with 400 mg lactose and 400 mg placebo. Gastrointestinal symptoms

occurring within 8 hours of ingestion of the different substrates were assessed by a visual-analogue scale. With this study, it was possible to verify that the ingestion of 400 mg of lactose did not cause a significant difference in the results.

In the study conducted by Areias, Sousa and Paulino (2014), the presence of lactose and parabens in oral drug formulations used by elderly patients with vestibular diseases was evaluated. In this study, it was found that of the medications used by this group, 80% of the elderly in the study used medications containing lactose and 61% of them were exposed to lactose concomitantly using 2 or more medications containing this excipient, which could be considered a greater risk for the elderly who were more sensitive or intolerant to lactose. The most cited antihypertensive drugs in this study were captopril and enalapril and the diuretic hydrochlorothiazide. It is important to emphasize that all these drugs are commonly used in the treatment of the elderly, especially those affected by vestibular diseases and their comorbidities.

However, a case study evaluated a 72-year-old male patient with a history of lactose intolerance, who was supported by acute myocardial infarction. The patient was discharged with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel), rosuvastatin, perindopril and carvedilol. However, he was re-admitted in the following days due to abdominal pain, flatulence, diarrhea and nausea, despite not ingesting lactose-containing food products. To solve the problem, a new prescription was made with lactose-free formulations of fluvastatin, metoprolol, lisinopril and isosorbide mononitrate. He was also advised to use clopidogrel in conjunction with probiotics and lactase supplementation, since he is allergic to aspirin and all clopidogrel and triflusal m formulations contain lactose. Shortly thereafter, the patient was completely asymptomatic in both gastrointestinal and cardiovascular terms (BARRA, MARQUES, 2012).

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WORLD EPIDEMIOLOGY OF LEISHMANIASIS: A NARRATIVE REVIEW

EPIDEMIOLOGIA MUNDIAL DA LEISHMANIOSE: UMA REVISÃO NARRATIVA

EPIDEMIOLOGÍA MUNDIAL DE LA LEISHMANIASIS: UNA REVISIÓN NARRATIVA



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ABSTRACT

Leishmaniasis is a neglected tropical disease caused by protozoa of the genus *Leishmania*, transmitted by the bite of infected female sandflies. Endemic in 99 countries, the disease affects more than 12 million people and represents a major global public health challenge, with World Health Organization (WHO) estimates of 30,000 new cases of visceral leishmaniasis (VL) and more than 1 million cases of cutaneous leishmaniasis (CL) annually. This study is a narrative review aimed at synthesizing the global epidemiology of leishmaniasis, with emphasis on patterns of incidence, prevalence, mortality, geographic distribution, and socioeconomic and environmental determinants of transmission. The databases consulted were PubMed, MedLine, LILACS, CAPES, PLOS and SciELO, in addition to official data from WHO and PAHO. In 2024, 85% of global VL cases were concentrated in seven countries: Brazil, Ethiopia, India, Kenya, Somalia, Sudan and South Sudan. For CL, Afghanistan, Algeria, Brazil, Colombia, Iran, Peru and Syria accounted for 83% of global incidence. The geospatial distribution of the disease is determined by ecological, sociodemographic and geopolitical factors, with systematic underreporting compromising the true magnitude of the problem. Elimination initiatives have achieved notable progress, such as Bangladesh's validation as the first country to eliminate VL as a public health problem in 2023.

Keywords: Leishmaniasis. Epidemiology. Incidence. Neglected Tropical Diseases. Sandflies.

RESUMO

A leishmaniose é uma doença tropical negligenciada causada por protozoários do gênero *Leishmania*, transmitida pela picada de flebotomíneos fêmeas infectados. Endêmica em 99 países, a doença acomete mais de 12 milhões de pessoas e representa um dos principais desafios de saúde pública global, com estimativas da Organização Mundial da Saúde (OMS) de 30.000 novos casos de leishmaniose visceral (LV) e mais de 1 milhão de casos de leishmaniose cutânea (LC) anualmente. Este estudo trata-se de uma revisão narrativa que

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objetivou sintetizar a epidemiologia mundial da leishmaniose, com enfoque nos padrões de incidência, prevalência, mortalidade, distribuição geográfica e determinantes socioeconômicos e ambientais da transmissão. As bases de dados consultadas foram PubMed, MedLine, LILACS, CAPES, PLOS e SciELO, além de dados oficiais da OMS e da Organização Pan-Americana da Saúde (OPAS). Em 2024, 85% dos casos globais de LV concentraram-se em sete países: Brasil, Etiópia, Índia, Quênia, Somália, Sudão e Sudão do Sul. Para a LC, Afeganistão, Argélia, Brasil, Colômbia, Irã, Peru e Síria responderam por 83% da incidência global. A distribuição geoespacial da doença é determinada por fatores ecológicos, sociodemográficos e geopolíticos, com subnotificação sistemática comprometendo a real dimensão do problema. Iniciativas de eliminação têm obtido avanços expressivos, como a validação do Bangladesh como primeiro país a eliminar a LV como problema de saúde pública em 2023.

Palavras-chave: Leishmaniose. Epidemiologia. Incidência. Doenças Tropicais Negligenciadas. Flebotomíneos.

RESUMEN

La Leishmaniasis es una enfermedad tropical desatendida causada por protozoos del género *Leishmania*, transmitida por la picadura de flebótomos hembra infectados; endémica en 99 países, la enfermedad afecta a más de 12 millones de personas y representa un importante desafío de salud pública global, con estimaciones de la World Health Organization (WHO) de 30.000 nuevos casos de leishmaniasis visceral (LV) y más de 1 millón de casos de leishmaniasis cutánea (LC) anualmente; este estudio es una revisión narrativa cuyo objetivo es sintetizar la epidemiología global de la leishmaniasis, con énfasis en patrones de incidencia, prevalencia, mortalidad, distribución geográfica y determinantes socioeconómicos y ambientales de la transmisión; las bases de datos consultadas fueron PubMed, MedLine, LILACS, CAPES, PLOS y SciELO, además de datos oficiales de la WHO y la Pan American Health Organization (PAHO); en 2024, el 85% de los casos globales de LV se concentraron en siete países: Brasil, Etiopía, India, Kenia, Somalia, Sudán y Sudán del Sur; para la LC, Afganistán, Argelia, Brasil, Colombia, Irán, Perú y Siria representaron el 83% de la incidencia global; la distribución geoespacial de la enfermedad está determinada por factores ecológicos, sociodemográficos y geopolíticos, con un subregistro sistemático que compromete la verdadera magnitud del problema; las iniciativas de eliminación han logrado avances notables, como la validación de Bangladesh como el primer país en eliminar la LV como problema de salud pública en 2023.

Palabras clave: Leishmaniasis. Epidemiología. Incidencia. Enfermedades Tropicales Desatendidas. Flebótomos.

1 INTRODUCTION

Leishmaniasis belongs to the group of neglected tropical diseases (NTDs) and currently represents one of the leading public health problems on a global scale. Caused by several species of intracellular protozoa of the genus *Leishmania*, belonging to the family Trypanosomatidae, the disease is transmitted to humans and other mammals through the bite of infected female sandflies of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World) (WHO, 2025; Pace, 2014). The disease is endemic in 99 countries, with CL present in 90 and VL in 80 countries, with 71 countries presenting both forms concomitantly (PAHO, 2025).

In clinical terms, leishmaniasis manifests in three main forms: visceral leishmaniasis (VL), also known as kala-azar, the most severe and potentially fatal if untreated; cutaneous leishmaniasis (CL), the most prevalent form, characterized by ulcerative lesions on exposed areas of the body; and mucocutaneous leishmaniasis (MCL), the most disabling form, associated with progressive destruction of the nasal and oral mucosae (Grifferty et al., 2023; Pace, 2014). Beyond these classical forms, post-kala-azar dermal leishmaniasis (PKDL), a late complication of VL, accounted for 13,515 reported cases between 2012 and 2024, with greater concentration in East Africa and the Indian subcontinent (WHO, 2024).

The magnitude of the disease is considerable, as it is estimated that more than 12 million people are infected worldwide and more than 1 billion live in endemic areas at risk of infection (PAHO, 2025; WHO, 2025). The WHO estimates 30,000 new annual cases of VL and more than 1 million cases of CL per year (WHO, 2025). Analyses from the Global Burden of Disease (GBD) 1990–2021 indicate that leishmaniasis ranked as the fourth NTD in terms of "Disability-Adjusted Life Years" (DALYs) in 2010, with the tegumentary form recording the greatest DALY increase among all NTDs between 1999 and 2023 (GBD, 2021; Ruiz-Postigo et al., 2023). Systematic underreporting, estimated at only 25 to 45% of actual cases reported to the WHO, compromises understanding of the true epidemiological significance of the disease (Awoke et al., 2024; Sunyoto et al., 2018).

The geographic distribution of leishmaniasis is largely determined by the presence and abundance of sandfly vectors, whose survival depends on specific climatic conditions (Aversi-Ferreira et al., 2014; WHO, 2025), especially localities with temperatures between 16 and 44°C, high humidity and low wind speed (Knight et al., 2022). Beyond ecological factors, socioeconomic determinants such as poverty, accelerated urbanization, deforestation, forced migration due to armed conflicts and fragile health systems constitute the complex epidemiological landscape that favors transmission and perpetuates the endemic condition in vulnerable populations (GBD, 2021; Salam; Al-Shaqha; Azzi, 2014).

The present study aimed to synthesize and discuss the global epidemiology of leishmaniasis, with emphasis on incidence and prevalence patterns by region, geographic distribution determinants, and socioenvironmental risk factors that condition the burden of disease at the global and regional level.

2 MATERIALS AND METHODS

This is a narrative literature review. The bibliographic search was carried out in the electronic databases PubMed, MedLine, LILACS, CAPES, PLOS and SciELO, complemented with official epidemiological data from the World Health Organization (WHO), the Pan American Health Organization (PAHO) and the Global Burden of Disease Study (GBD). The descriptors used were: leishmaniasis, visceral leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, sandflies, epidemiology, incidence, prevalence and global burden.

The analytical framework for geographic and environmental variables related to leishmaniasis transmission was grounded in the review chapter by Aversi-Ferreira et al. (2014), which systematized the main evidence on global and regional determinants of disease distribution using the MEDLINE, PubMed, LILACS, CAPES, PLOS, SciELO and Google Scholar databases.

2.1 INCLUSION CRITERIA

Original articles and indexed reviews published between 2014 and 2025 addressing epidemiological aspects, geographic distribution, incidence, prevalence, mortality or DALYs of leishmaniasis were included, as well as technical documents and epidemiological bulletins from WHO and PAHO.

2.2 EXCLUSION CRITERIA

Studies prior to 2014 (except classic references without equivalent subsequent updates), studies focused exclusively on therapeutic, laboratory or molecular aspects without epidemiological interface, and works addressing the same content as more recent references already included were excluded.

3 GLOBAL EPIDEMIOLOGICAL OVERVIEW

Leishmaniasis is endemic in four major eco-epidemiological regions, namely the Americas, East Africa, North Africa, and Western and South Asia (WHO, 2025; PAHO, 2025). In 2024, 52 VL-endemic and 59 CL-endemic countries reported data to the WHO global

program, corresponding to 65% of endemic countries for each form. The 2024 global data confirm that the disease burden remains highly concentrated, i.e., 85% of VL cases were reported in only seven countries, namely Brazil, Ethiopia, India, Kenya, Somalia, Sudan and South Sudan, and 83% of CL cases were recorded in Afghanistan, Algeria, Brazil, Colombia, Iran, Peru and Syria (WHO, 2025).

The GBD 1990–2021 analysis demonstrated that the DALY burden of leishmaniasis is inversely proportional to the Socioeconomic Development Index (SDI), i.e., countries with lower SDI consistently presented the highest age-standardized DALY rates. The ten countries with the highest DALY rates in 2021 were Afghanistan, Suriname, Sudan, Djibouti, Nicaragua, Panama, Turkmenistan, Tunisia, Iraq and Brazil (GBD, 2021). The study also evidenced sexual dimorphism in disease burden: DALY rates for VL were substantially higher in men (7.31 per 100,000) than in women (3.36 per thousand), a difference partially explained by greater occupational exposure of males to sandfly habitats (GBD, 2021).

Underreporting represents a structural obstacle to epidemiological surveillance. Estimates indicate that only 25 to 45% of actual annual VL cases are effectively reported to the WHO, meaning that, in real terms, the burden may be two to four times higher than recorded (Awoke et al., 2024; Sunyoto et al., 2018). For CL in sub-Saharan Africa, the actual number of cases is estimated to be up to six times higher than reported (Sunyoto et al., 2018). In 2024, 133 imported CL cases and 73 imported VL cases were globally recorded, evidencing growing human mobility as a factor in disease dissemination to non-endemic regions (WHO, 2025).

Cutaneous leishmaniasis has shown global incidence growth since 2012, with the tegumentary form recording the greatest DALY increase among NTDs between 1999 and 2023 (Ruiz-Postigo et al., 2023). In contrast, VL showed a declining case trend in several regions following elimination initiatives, with Bangladesh becoming the first country validated by WHO in 2023 as free of VL as a public health problem, the result of an elimination program jointly launched in 2005 with India and Nepal (WHO, 2025). India reduced its VL burden from approximately 33,000 cases in 2005 to fewer than 6,000 in 2016, and from 77,000 cases in 1992 to fewer than 6,000 in 2016, following implementation of integrated indoor residual spraying strategies and active surveillance (Wilson et al., 2020; Dutta et al., 2023).

4 EPIDEMIOLOGY BY GEOGRAPHIC REGION

4.1 THE AMERICAS

In the Americas, leishmaniasis is a vector-borne zoonosis with a complex transmission cycle involving a wide diversity of parasite species, reservoirs and vectors. Of the 22

Leishmania species pathogenic to humans, 15 have been identified in the region, with approximately 54 vector species potentially involved in transmission (PAHO, 2025). Between 2001 and 2018, approximately 55,000 annual CL cases were recorded in 17 countries of the Americas, with 79.4% of cases concentrated in rural areas (Cossio et al., 2021). For VL, between 2001 and 2015, 52,000 cases were reported, with progressive reduction thereafter (Maia-Elkhoury et al., 2017). More than two-thirds of new CL cases in the Americas occur in six countries: Afghanistan, Algeria, Brazil, Colombia, Iran and Syria, with Colombia corresponding to the second highest continental CL incidence (Herrera et al., 2018).

Brazil is the country with the greatest diversity of *Leishmania* species causing CL in the Americas, with six belonging to the subgenus *Viannia* and prevalence of *L. (Viannia) braziliensis* (Saheki et al., 2017). More than 20,000 annual CL cases are recorded in the country, with more than 260 vector sandfly species identified (Meneguzzi et al., 2016). Between 2001 and 2020, 63,966 VL cases were notified, with a mean incidence rate of 1.68 cases per 100,000 inhabitants and a case fatality rate of 6.96% (Bruhn et al., 2024). Brazil accounts for 97% of VL cases in the Americas, with a case fatality rate of approximately 10% (Vieira-Duarte et al., 2024). The GBD 2016 analysis in Brazil demonstrated that the age-standardized incidence rate decreased by 48.5% between 1990 and 2016, but DALYs increased by 83.6% in the same period, reflecting increased case severity and aging of the affected population (Bezerra et al., 2018).

In terms of domestic distribution, the largest VL mortality clusters in Brazil are located in the Northeast and in the states of Tocantins and Roraima (Vieira-Duarte et al., 2024). Maranhão led VL incidence rates in children and adolescents over the past decade, and the impact of the COVID-19 pandemic was identified as a factor that altered incidence trends in several northeastern states between 2020 and 2022 (Fernandes et al., 2025). In Minas Gerais, cities surrounded by coffee plantations have recorded, since the 1960s, significant incidence of TL in rural workers; in Governador Valadares, 191 VL cases were reported between 2008 and 2017, with a case fatality rate of 14.7% (Silva et al., 2017).

In the municipality of Montes Claros, northern Minas Gerais, VL has become a consolidated urban endemic, with cases distributed across the entire urban area recorded between 2001 and 2007, with a reduction in incidence from 2005 onwards, although the disease has remained a serious public health problem in the region (Sousa et al., 2008).

Colombia has the second largest number of documented *Leishmania* species, with cases concentrated in rural and military areas. The prevalence of *L. braziliensis* in military personnel reaches 95.4%, directly related to exposure in vector habitats (Purse et al., 2017).

The Andean region accounts for more than 50% of Colombian CL cases (Posada-López et al., 2023).

The epidemiology of CL is complex, with intra- and interspecific variation in transmission cycles, reservoir hosts, vectors and clinical manifestations (Mubayi; Paredes; Ospina, 2018). In Peru, nearly 6,000 CL and MCL cases were recorded in 2015, with the Madre de Dios region being one of the most endemic in South America, with 4,000 cases between 2010 and 2015 (Zorrilla et al., 2017). Ecuador contributes to the dispersal of *L. lainsoni* in 21 of 24 provinces (Kato et al., 2016), and Paraguay recorded approximately 3,000 cases between 2006 and 2017, with predominance in San Pedro and Canindeyú (Benítez et al., 2020).

4.2 EAST AFRICA AND SUB-SAHARAN AFRICA

East Africa concentrates the second largest global number of VL cases, with Eritrea, Ethiopia, Kenya, Somalia, Sudan, South Sudan and Uganda as endemic countries (Awoke et al., 2024). An estimated 29,400 to 56,700 VL cases occur annually in the region, with only 8,560 cases effectively reported, evidencing one of the highest underreporting rates in the world (Awoke et al., 2024; Sunyoto et al., 2018). In Ethiopia, the annual VL incidence is estimated between 3,700 and 7,400 cases, with a population of more than 3.2 million people at risk. Approximately 60% of cases are concentrated in the northwestern plains, on the border with Sudan, while CL, caused mainly by *Leishmania aethiopica*, affects between 20,000 and 50,000 people annually, leaving approximately 30 million in a state of susceptibility (Awoke et al., 2024; Yohannes; Abebe; Boelee, 2019).

In Kenya, 900 new VL cases per year are estimated, with coexistence of cutaneous and visceral forms in locations such as the Rift Valley. The sandfly study in the Gilgil region identified *Phlebotomus guggisbergi* as a confirmed vector of *L. tropica* and *L. major*, with high infection rates detected (Owino et al., 2019; Hassaballa et al., 2021). The four forms of leishmaniasis present in Kenya put 1.6 billion people at risk globally, and the country is among the five African nations that bear the greatest proportion of the global VL burden (Grifferty et al., 2023).

In sub-Saharan Africa, the epidemiological burden of CL remains largely underestimated. A systematic review estimated that the actual number of cases may be six times higher than reported, with countries in Central, Western and Eastern Africa recording significant diagnostic gaps (Sunyoto et al., 2018). In Algeria, the largest endemic country in North Africa, 13,599 cases were reported in 2024, corresponding to 78% of all African CL cases notified that year, with incidence that nearly doubled between 2021 and 2024 (WHO,

2025). Case distribution is directly correlated with the distribution of the 24 sandfly species described in the Maghreb region (Benallal et al., 2022).

4.3 MIDDLE EAST AND CENTRAL ASIA

Leishmaniasis is considered the third most important vector-borne disease in the world, with a particularly severe impact in the Middle East (Knight et al., 2022). In 2016, 84% of globally notified CL cases were concentrated in ten countries, including Afghanistan, Algeria, Brazil, Colombia, Iraq, Pakistan, Peru, Syria, Tunisia and Yemen (Knight et al., 2022). Social factors, poverty, intense urbanization and violent conflicts, are critical determinants of the endemic condition in the region (Salam; Al-Shaqha; Azzi, 2014).

In Syria, the impact of war is exemplary: approximately 90,000 leishmaniasis records were notified in 2019, with more than 6,000 cases in the first month of 2020, with Deir-ez-Zor, Aleppo and Idleb as main foci, caused by *L. tropica* and *L. major* (Hussein et al., 2019). In Yemen, migration, the collapse of the health system, poverty and rubble serving as vector breeding sites determined more than 6,000 cases between 2019 and 2020, with MCL as the predominant form (Al-Bajalan et al., 2018). In Iraq, during the 2014–2015 civil war, a CL outbreak mainly affected the north and center of the country, with displacement of populations from endemic to non-endemic areas and deterioration of health services as the main factors (Al-Bajalan et al., 2018).

In India, VL is typically caused by *L. donovani*, with 90% of cases concentrated in Bihar, in the northwest of the country. National efforts reduced the burden from nearly 33,000 cases in 2005 to fewer than 6,000 in 2016 (Wilson et al., 2020). Saudi Arabia showed a significant decline in CL cases since the 1990s, with only 600 cases notified in 2021, while no VL case was recorded between 2019 and 2021, as a result of effective local epidemiological management (Knight et al., 2023). In Iran, Azerbaijan and Fars are VL foci for *L. infantum* and *L. major* (Adham et al., 2020; Behniafar et al., 2024).

Sri Lanka represents a singular case in Asia: CL caused by *L. donovani*, a species classically associated with the visceral form, is endemic in the country, with 2,217 cases in 2020 and 19,361 cases between 2001 and 2019 (Gunasekara et al., 2023). Projections for 2025 estimate more than 19,000 additional cases, evidencing an ascending trajectory without immediate control prospects (Karunaweera et al., 2021). China figures among the 14 countries with the highest global VL incidence, with distribution data in the northwest of the national territory (Chen et al., 2019).

4.4 EUROPE AND IMPORTED CASES

Southern Europe, especially Spain, Italy, France, Portugal and Mediterranean islands, is endemic for VL caused by *L. infantum*, while the central and eastern portions record cases due to *L. martiniquensis* (Maia et al., 2023). In 2022, 517 autochthonous cases were notified in metropolitan France and 1,725 imported cases between 1998 and 2020, with VL prevailing among autochthonous and CL among imported cases (Pasquier et al., 2022). The re-emergence of leishmaniasis in Spain between 2009 and 2012 alerted neighboring countries to the risk of expansion (Mubayi; Paredes; Ospina, 2018), and records of asymptomatic individuals for *L. infantum* exist in several European countries, including Italy, Spain, France and the Balearic Islands (Iatta et al., 2021).

In 2024, 133 imported CL cases and 73 imported VL cases were reported globally to WHO, reflecting the growing role of international mobility in disease dissemination (WHO, 2025). Austria recorded a change in the epidemiological profile of human leishmaniasis between 2000 and 2021, including a case of congenital transmission, a rare but documented route of infection (Riebenbauer et al., 2024). Studies in Barcelona demonstrated an increase in autochthonous and imported cases associated with a growing number of immunocompromised individuals and migrants from endemic areas (Knight et al., 2023). Furthermore, the geographic expansion of vector sandflies in the Mediterranean has been attributed to climate change and the geopolitical situation, facilitating parasite dispersal to previously non-endemic regions (Moriconi et al., 2017).

5 EPIDEMIOLOGICAL DETERMINANTS OF TRANSMISSION

5.1 SOCIOENVIRONMENTAL AND ECONOMIC DETERMINANTS

The association between leishmaniasis and poverty is widely documented and represents the main structural determinant of the endemic condition (GBD, 2021; Salam; Al-Shaqha; Azzi, 2014). Countries with lower HDI consistently present higher disease DALY rates, and spatial analyses in northeastern Brazil confirm that high leishmaniasis incidences are directly associated with unfavorable socioeconomic conditions and precarious infrastructure (GBD, 2021). VL is classically associated with malnutrition, a particularly grave risk situation: in Brazil, the highest rates of years of life lost (YLL) due to VL are observed in children under one year of age, with an increase of 131.2% between 1990 and 2016 (Bezerra et al., 2018).

Accelerated urbanization and deforestation with expansion of agricultural frontiers broaden human contact with sandflies (Aversi-Ferreira et al., 2014; Meneguzzi et al., 2016). In Espírito Santo, geographic expansion resulting from economic changes led to growth of

peripheral urban populations, increasing domestic CL reservoirs (Meneguzzi et al., 2016). In Maranhão, the wide spatial distribution of vectors, with a high degree of adaptation to domestic and anthropic environments, ensures transmission to both humans and dogs (Guimarães-e-Silva et al., 2017). Over the past 20 years, territorial expansion of the disease has been attributed to agricultural exploitation and forest destruction, which create favorable habitats for sandflies while simultaneously reducing the habitats of natural predators of these vectors (Glidden et al., 2023; Marinho-Júnior et al., 2023).

Seasonal migration of rural workers and human mobility in general function as disease dispersal vectors. The state of Rio de Janeiro, Brazil's main tourist destination, recorded 1,620 imported TL cases between 2001 and 2015, corresponding to 0.8% of national cases, associated with migratory flows from endemic areas (Miranda et al., 2019). Geopolitical conflict conditions exponentially amplify risk: mass population migration, collapse of health systems, precarious housing and rubble serving as vector breeding sites were identified as the main explanatory factors for outbreaks in Syria and Yemen (Du et al., 2016; Al-Bajalan et al., 2018).

The displacement of manual workers and migrants from rural to urban areas for work-related reasons has been identified as one of the most important risk factors for American tegumentary leishmaniasis (Bamorovat et al., 2021). Outdoor sleeping, proximity to animals and restricted public health systems additionally increase risks for populations living in disadvantaged conditions (Grifferty et al., 2023; Yohannes; Abebe; Boelee, 2019).

5.2 ECOLOGICAL AND CLIMATIC DETERMINANTS

The heterogeneity of leishmaniasis distribution is intrinsically associated with environmental and climatic conditions that determine the life cycle of the vector and the etiological agent (Aversi-Ferreira et al., 2014; Pace, 2014; Glidden et al., 2023). Sandflies survive across a wide temperature range, 16 to 44°C, with ideal activity on warm, clear nights with low wind speed (Knight et al., 2022). In the province of Sétif (Algeria), a correlation was demonstrated between the monthly number of sandflies and temperature, with low association with rainfall and humidity (Posada-López et al., 2023). Different habitat types, including forest areas, peridomicile and plantations, harbor distinct sandfly species compositions, with different ambient volatile chemistries that modulate vector selection (Hassaballa et al., 2021).

Global climate change represents a growing threat for the geographic expansion of sandflies to previously non-endemic regions, particularly at higher latitudes and altitudes (Riebenbauer et al., 2024; Sutrave; Richter, 2021). In the Mediterranean, vector expansion

has been attributed to climate change, and in India, high-altitude areas, classically unfavorable for vector proliferation, have recorded a progressive increase in cases (Thakur et al., 2018). Climate projections indicate that continued global warming should result in territorial expansion of the endemic, with disproportionately greater impact on already vulnerable populations (Riebenbauer et al., 2024).

The availability and variety of reservoir hosts constitutes a determining ecological variable. In the Americas, 60 animal species have been identified as *Leishmania* reservoirs, a number in continuous growth, including rodents and cats (Kato et al., 2021). Dogs are the main urban VL reservoirs, but other animals, such as hares, rodents, chickens and pigs, also contribute to parasite circulation (Guimarães-e-Silva et al., 2017). Rodents of the species *Rattus rattus*, present in peridomiliary environments, maintain high connectivity between rural areas and urban peripheries, sustaining high *Leishmania* infection rates at these interfaces (Marinho-Júnior et al., 2023). Periurban banana, pineapple and vegetable plantations were associated with higher densities of rodent hosts and, consequently, with higher relative risk of human infection at these sites (Marinho-Júnior et al., 2023; Bustos et al., 2015).

6 UNDERREPORTING, SURVEILLANCE AND CONTROL INITIATIVES

Underreporting is a structural phenomenon in leishmaniasis epidemiology and affects each endemic region differently. Global estimates indicate that only 25 to 45% of actual VL cases are annually reported to WHO (Awoke et al., 2024). For CL in sub-Saharan Africa, the actual number may be up to six times higher than reported (Sunyoto et al., 2018). The causes are multifaceted: fragility of epidemiological surveillance systems, difficult access of rural populations to health services, absence of mandatory reporting in some countries and diagnostic difficulties, especially for atypical forms and coinfections (Grifferty et al., 2023; Al-Bajalan et al., 2018).

International elimination initiatives have demonstrated expressive results when sustained by integrated strategies. The Kala-Azar Elimination Program in Southeast Asia, launched jointly by India, Bangladesh and Nepal in 2005, incorporated indoor residual spraying (IRS), active case detection and treatment, resulting in a reduction from more than 77,000 cases in 1992 to fewer than 6,000 in 2016 (Wilson et al., 2020). In 2023, Bangladesh became the first country in the world validated by WHO as having eliminated VL as a public health problem — a historic milestone demonstrating that elimination is achievable even in resource-limited settings (WHO, 2025).

Saudi Arabia represents an example of effective control in the Middle East: local epidemiological management significantly reduced CL cases since the 1990s (from hundreds per year to 600 cases in 2021), and no VL case was recorded between 2019 and 2021 (Knight et al., 2023). In contrast, conflict-affected countries such as Syria and Yemen illustrate how the disintegration of health systems and forced migration can rapidly reverse years of control progress, with a return to epidemic rates in a short time (Du et al., 2016; Hussein et al., 2019).

PAHO has been implementing since 2023 the Plan of Action for Strengthening Surveillance and Control of Leishmaniasis in the Americas 2023–2030, linked to the Communicable Disease Elimination Initiative and the WHO NTD Road Map (PAHO, 2025). The plan sets targets for incidence reduction, expansion of diagnostic and therapeutic coverage, and strengthening of entomological and reservoir surveillance. In this context, information systems such as SisLeish, a multinational standardized platform for monitoring leishmaniasis in the Americas, play a fundamental role in consolidating comparable epidemiological data among countries (Cossio et al., 2021).

7 CONCLUSION

Leishmaniasis remains one of the greatest global public health challenges, with a distribution that goes far beyond traditional climatic markers to reflect, in its essence, the distribution of poverty, social inequality and fragility of health systems worldwide. The 2024 data confirm that the concentration of disease burden in few countries, with Brazil, India, Ethiopia, Sudan and South Sudan accounting for a disproportionate fraction of global cases, is not a geographic accident, but the result of decades of underinvestment in surveillance, diagnosis and vector control in historically marginalized populations.

Systemic underreporting significantly compromises the formulation of evidence-based public policies. Estimates pointing to fewer than 50% of actual cases being reported to WHO indicate that the magnitude of the problem is substantially greater than official data suggest. Concurrently, the advances achieved in countries such as Bangladesh and India demonstrate that elimination is attainable when integrated, sustained and politically prioritized strategies exist.

The geographic expansion expected as a result of climate change, with displacement of sandfly habitable areas to higher latitudes and altitudes, adds a dimension of urgency to the problem. The combination of global warming, accelerated urbanization, growing human mobility and persistence of adverse socioeconomic conditions suggests that, without robust interventions, the global burden of leishmaniasis is likely to increase in the coming decades.

Full recognition of leishmaniasis as a priority public health problem, integrated with social equity policies, strengthened epidemiological surveillance and translational research in therapeutics and vaccines, is an indispensable condition for reversing this scenario.

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PHYSICAL VARIABLES OF LEISHMANIASIS TRANSMISSION
VARIÁVEIS FÍSICAS NA TRANSMISSÃO DA LEISHMANIOSE
VARIABLES FÍSICAS DE LA TRANSMISIÓN DE LA LEISHMANIASIS



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ABSTRACT

Leishmaniasis is a neglected tropical disease caused by protozoa of the genus *Leishmania*, transmitted by the bite of infected female sandflies. Endemic in 99 countries, the disease affects more than 12 million people and represents a major global public health challenge, with World Health Organization (WHO) estimates of 30,000 new cases of visceral leishmaniasis (VL) and more than 1 million cases of cutaneous leishmaniasis (CL) annually. This study is a narrative review aimed at synthesizing the global epidemiology of leishmaniasis, with emphasis on patterns of incidence, prevalence, mortality, geographic distribution, and socioeconomic and environmental determinants of transmission. The databases consulted were PubMed, MedLine, LILACS, CAPES, PLOS and SciELO, in addition to official data from WHO and PAHO. In 2024, 85% of global VL cases were concentrated in seven countries: Brazil, Ethiopia, India, Kenya, Somalia, Sudan and South Sudan. For CL, Afghanistan, Algeria, Brazil, Colombia, Iran, Peru and Syria accounted for 83% of global incidence. The geospatial distribution of the disease is determined by ecological, sociodemographic and geopolitical factors, with systematic underreporting compromising the true magnitude of the problem. Elimination initiatives have achieved notable progress, such as Bangladesh's validation as the first country to eliminate VL as a public health problem in 2023.

Keywords: Leishmaniasis. Epidemiology. Incidence. Neglected Tropical Diseases. Sandflies.

RESUMO

A leishmaniose é uma doença tropical negligenciada causada por protozoários do gênero *Leishmania*, transmitida pela picada de flebotomíneos fêmeas infectados. Endêmica em 99 países, a doença acomete mais de 12 milhões de pessoas e representa um dos principais desafios de saúde pública global, com estimativas da Organização Mundial da Saúde (OMS) de 30.000 novos casos de leishmaniose visceral (LV) e mais de 1 milhão de casos de leishmaniose cutânea (LC) anualmente. Este estudo trata-se de uma revisão narrativa que objetivou sintetizar a epidemiologia mundial da leishmaniose, com enfoque nos padrões de

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incidência, prevalência, mortalidade, distribuição geográfica e determinantes socioeconômicos e ambientais da transmissão. As bases de dados consultadas foram PubMed, MedLine, LILACS, CAPES, PLOS e SciELO, além de dados oficiais da OMS e da Organização Pan-Americana da Saúde (OPAS). Em 2024, 85% dos casos globais de LV concentraram-se em sete países: Brasil, Etiópia, Índia, Quênia, Somália, Sudão e Sudão do Sul. Para a LC, Afeganistão, Argélia, Brasil, Colômbia, Irã, Peru e Síria responderam por 83% da incidência global. A distribuição geoespacial da doença é determinada por fatores ecológicos, sociodemográficos e geopolíticos, com subnotificação sistemática comprometendo a real dimensão do problema. Iniciativas de eliminação têm obtido avanços expressivos, como a validação do Bangladesh como primeiro país a eliminar a LV como problema de saúde pública em 2023.

Palavras-chave: Leishmaniose. Epidemiologia. Incidência. Doenças Tropicais Negligenciadas. Flebotomíneos.

RESUMEN

La Leishmaniasis es una enfermedad tropical desatendida causada por protozoos del género *Leishmania*, transmitida por la picadura de flebótomos hembra infectados; endémica en 99 países, la enfermedad afecta a más de 12 millones de personas y representa un importante desafío de salud pública global, con estimaciones de la World Health Organization (WHO) de 30.000 nuevos casos de leishmaniasis visceral (LV) y más de 1 millón de casos de leishmaniasis cutánea (LC) anualmente; este estudio es una revisión narrativa cuyo objetivo es sintetizar la epidemiología global de la leishmaniasis, con énfasis en patrones de incidencia, prevalencia, mortalidad, distribución geográfica y determinantes socioeconómicos y ambientales de la transmisión; las bases de datos consultadas fueron PubMed, MedLine, LILACS, CAPES, PLOS y SciELO, además de datos oficiales de la WHO y la Pan American Health Organization (PAHO); en 2024, el 85% de los casos globales de LV se concentraron en siete países: Brasil, Etiópia, India, Kenia, Somalia, Sudán y Sudán del Sur; para la LC, Afganistán, Argelia, Brasil, Colombia, Irán, Perú y Siria representaron el 83% de la incidencia global; la distribución geoespacial de la enfermedad está determinada por factores ecológicos, sociodemográficos y geopolíticos, con un subregistro sistemático que compromete la verdadera magnitud del problema; las iniciativas de eliminación han logrado avances notables, como la validación de Bangladesh como el primer país en eliminar la LV como problema de salud pública en 2023.

Palabras clave: Leishmaniasis. Epidemiología. Incidencia. Enfermedades Tropicales Desatendidas. Flebótomos.

1 INTRODUCTION

Leishmaniasis is a non-contagious infectious disease belonging to the group of neglected tropical diseases (NTDs) [1, 2], chronically undervalued as an eradication priority. The WHO currently estimates 700,000 to 1 million new cases annually, with 20,000–30,000 deaths per year [51]. Recent analysis of the Global Burden of Disease Study 2021 (GBD 2021), covering 204 countries and territories, showed that the global age-standardized DALY rate for VL declined 92.9% between 1990 and 2021, while the DALY rate for CL and MCL increased 26.4%, particularly in low- and middle-SDI countries [49]. The disease can trigger intense epidemics primarily associated with nutritional and migratory factors [5, 6].

The disease most likely originated in East Africa, with records in ancient Egypt and Christian Nubia dating to approximately 4,000 B.C. [7]. As of 2022, 99 countries and territories are endemic for leishmaniasis, including 71 endemic for both VL and CL [51]. An estimated 200 million people are at risk of transmission [8]. The highest incidence is found in India, Bangladesh, Nepal, Sudan and Brazil [3]; in 2024, 85% of global VL cases were reported from just seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan [51].

The protozoan *Leishmania*, a unicellular flagellate, is the causative agent, transmitted to humans by female phlebotomine sandflies. Over 20 *Leishmania* species and more than 90 sandfly species are known to transmit the disease [51]. The main clinical forms are visceral (VL), cutaneous (CL) and mucocutaneous (MCL) [7, 53]. CL is endemic in almost 100 countries, affecting an estimated 12 million cumulative cases, with approximately 600,000 to 1 million new CL cases per year [53].

VL, also known as kala-azar, is fatal in over 95% of untreated cases [51]. It is caused by *Leishmania donovani* and *Leishmania infantum* (subspecies *L. infantum chagasi* in Brazil), both belonging to the family Trypanosomatidae. Clinical features include fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, anemia, weight loss and, in the absence of treatment, death [9, 54].

CL is the most common form worldwide, caused by approximately 20 different *Leishmania* species [51], known by various regional names such as Aleppo boil, Chiclero ulcer, Bauru ulcer, Oriental sore and Pian bois. MCL produces destructive and disfiguring lesions, especially on the face, caused primarily by *Leishmania braziliensis* [53].

Regardless of the type, transmission occurs through the bite of female phlebotomine sandflies, whose geographical distribution directly determines disease distribution. Sandflies inhabit mainly hot, wet tropical regions [10], although they also occur in dry and hot environments. Various natural reservoir hosts — canines, birds, cattle, equines, goats, swine

and felines [11-14] — share the same habitats as the vectors. Environmental disruptions such as climate change, deforestation, and urbanization significantly affect the distribution and abundance of sandfly vectors and their reservoir hosts [54].

Canine leishmaniasis is an important indirect indicator of human disease prevalence. The disease is broadly associated with tropical and equatorial zones, poor sanitary conditions and the proximity among parasites, vectors, reservoir hosts and humans.

In this context, it is possible to hypothesize that globalization and climate change may contribute to the expansion of leishmaniasis incidence worldwide. Therefore, this article aims to review the geographical and environmental variables associated with leishmaniasis transmission at global and regional scales.

2 MATERIALS AND METHODS

For this purpose, information was collated from an extensive literature search using the following electronic databases: MEDLINE, PLoS, PubMed, LILACS, CAPES Periodicals, Open Journal System, SciELO and Google Scholar. The search terms used were: leishmaniasis, visceral leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, phlebotomine sandflies, sandflies, geographical aspects of leishmaniasis and environmental aspects of leishmaniasis.

This paper is derivate from book chapter intitule “Geographical and Environmental Variables of Leishmaniasis Transmission” however with actualized literature and new data.

2.1 INCLUSION CRITERIA

Indexed papers published in the last 20 years; classic indexed papers on areas of highest endemicity. Selected textbooks and WHO technical reports were also used.

2.2 EXCLUSION CRITERIA

Papers that did not address the main topics reviewed here and texts with content equivalent to more recent publications already included.

3 GEOGRAPHICAL VARIABLES

3.1 WORLDWIDE VARIABLES

In terms of the biosphere, the geographical variables of leishmaniasis transmission are associated with the tropical zone and hot, wet climates with a regular rainfall index [10]. Underdeveloped and developing countries show the highest incidence. According to GBD 2021 data, from 1990 to 2021, global incident cases rose from 1.01 to 1.10 million and

prevalent cases nearly doubled from 3.18 to 6.21 million, with South Sudan, Syria, Afghanistan, Suriname and Sudan identified as persistent hotspots [50].

Both human VL and CL follow the geographical distribution of the insect vector [15]. VL is endemic in 80 countries with an annual global incidence of 50,000–90,000 cases [49]. CL and VL are found globally between the tropics but have also been detected in regions with relatively rigorous winters, such as France [16], Portugal, Russia and China [3].

In Africa, VL reports are sparse in the Sub-Saharan region. In East Africa, VL is endemic and cases have increased, accounting for 73% of global VL cases in 2022 [49]. The greatest concentrations are in Sudan [17, 18], Ethiopia [2, 9], South Sudan [3], Somalia, Uganda, Kenya [9] and Eritrea [3] (Table 1). VL total in Africa (8,571 cases) substantially exceeded CL (204 cases) in the reference period.

Table 1

Geographical distribution of VL and CL in Africa (based on reference [3]).

Country/Region	Visceral Leishmaniasis (VL)	Cutaneous Leishmaniasis (CL)
Sub-Saharan African Region		
Cameroon	0	55
Côte d'Ivoire	0	1
Ghana	0	27
Mali	0	58
Nigeria	1	5
Senegal	0	8
TOTAL	1	154
Eastern African Region		
Eritrea	100	50
Ethiopia	1,860	0
Kenya	145	0
Somalia	679	0
Sudan	3,742	0
South Sudan	1,756	0
Uganda	288	0
TOTAL	8,570	50

Source: Alvar et al. [3].

In Asia from the Middle East to Central Asia, significant VL prevalence is found mainly in Iraq (>1,000 cases). CL cases greatly exceed VL: 61,015 vs. 2,497, with Iran, Afghanistan, Pakistan, Saudi Arabia and Iraq among the highest CL-burden countries (Table 2). In the

Indian Subcontinent, India, Bangladesh and Nepal concentrate the majority of VL cases. Overall, Asia recorded 61,493 CL cases vs. 45,120 VL cases [3, 20, 21]. In 2024, Bangladesh became the first country validated by WHO for VL elimination as a public health problem [51].

Table 2

Geographical distribution of VL and CL in Asia (based on reference [3]).

Country/Region	VL	CL
<i>Middle East to Central Asia</i>		
Afghanistan	0	22,620
Armenia	7	0
Azerbaijan	28	17
China	378	0
Georgia	164	5
Iran	149	24,630
Iraq	1,711	1,655
Kazakhstan	1	15
Oman	1	5
Pakistan	0	7,752
Saudi Arabia	34	3,445
Tajikistan	15	25
Turkmenistan	0	99
Ukraine	2	2
Uzbekistan	7	142
Yemen	0	603
TOTAL	2,497	61,015
<i>Indian Subcontinent & SE Asia</i>		
Bangladesh	6,224	0
Bhutan	2	0
India	34,918	156
Nepal	1,477	0
Sri Lanka	0	322
Thailand	2	0
TOTAL	42,623	478

Source: Alvar et al. [3].

In the Mediterranean region, countries with more than 100 VL cases include Morocco, Italy, Spain, Albania and Algeria. For CL, more than 1,000 cases were reported in Algeria, Syria, Tunisia, Libya, Morocco and Turkey (Table 3). Overall, 85,886 CL cases were recorded

against 874 VL cases. In 2024, seven countries accounted for 83% of global CL incidence: Afghanistan, Algeria, Brazil, Colombia, Iran, Peru and Syria [51].

Table 3

Geographical distribution of VL and CL in the Mediterranean region (based on reference [3])

Country	VL	CL
Albania	114	6
Algeria	111	44,050
Bosnia-Herzegovina	2	0
Bulgaria	7	0
Croatia	5	2
Cyprus	2	1
Egypt	1	471
France	18	2
Greece	42	3
Israel	2	579
Italy	134	49
Jordan	0	227
Libya	3	3,540
Macedonia	7	0
Malta	2	0
Montenegro	3	0
Morocco	152	3,430
Palestine	5	218
Portugal	15	0
Spain	117	0
Syria	14	22,882
Tunisia	89	7,631
Turkey	29	2,465
TOTAL	874	85,556

Source: Alvar et al. [3].

In Latin America, VL cases have increased in northern Argentina [22], areas bordering Brazil and Paraguay, Colombia [23], Venezuela [24] and North America [25]; one case was recently recorded in Uruguay [19]. Brazil is the only country in the Americas with more than 1,000 VL cases. In 2023, Brazil accounted for 93.5% of reported VL cases in Latin America [57]. For CL, ten countries each report more than 1,000 cases. In 2001–2023, a total of 1,178,436 CL and MCL cases were reported to PAHO, with an annual average of 51,236 [57] (Table 4).

Table 4

Geographical distribution of VL and CL in the Americas (based on references [3], [19] and [25])

Country	VL	CL
Argentina	8	261
Bolivia	0	2,647
Brazil	3,481	26,008
Colombia	60	17,420
Costa Rica	0	1,249
Ecuador	0	1,724
French Guiana	0	233
Guatemala	15	684
Guyana	0	16
Honduras	6	1,159
Mexico	7	811
Nicaragua	3	3,222
Panama	0	2,188
Paraguay	48	431
Peru	0	6,405
Suriname	0	3
Venezuela	40	2,480
Uruguay	1	0
United States	0	42
TOTAL	3,668	66,983

Source: Alvar et al. [3]; Salomón et al. [19]; Gonzalez et al. [25]; PAHO [57].

The worldwide geographical distribution of leishmaniasis is shifting. Global climate change [25, 29] is expanding phlebotomine niches toward higher latitudes and altitudes. It is possible to hypothesize that globalization — through increased international travel, migration, and dog importation — together with climate change-driven expansion of sandfly habitats to higher latitudes and altitudes, is facilitating the spread of *Leishmania* vectors and parasites into previously non-endemic regions worldwide [54, 59, 60, 61]. Over the past decade, approximately 58,413 VL cases were reported globally (77.2% in Asia) and 214,082 CL cases. The higher CL burden may be explained by the greater diversity of CL parasites (over 20 species) compared to VL [3].

These worldwide patterns underscore the need for collaborative prevention among endemic countries to generate global solutions for disease eradication.

3.2 REGIONAL VARIABLES

Regional variables represent internal country areas where leishmaniasis probability has increased. In developing countries, the disease was historically rural but became associated with urbanization, expanding into urban peripheries in Brazil around the 1970s [31], driven by internal migration [30]. Deforestation and inadequate urban planning have been confirmed as major drivers of VL incidence increases in multiple Brazilian states [54, 58].

Migrants from rural zones typically settle in the urban periphery, adjacent to forest remnants — intertropical zones that maximize contact among humans, sandflies and reservoir hosts. This population often lacks access to basic sanitation, generating exclusionary urbanization [41]. A spatiotemporal analysis of VL in northeastern Brazil (2007–2022) confirmed a positive correlation between VL incidence and inadequate sewage systems, insufficient waste collection and deforestation [54].

The construction of risk maps for each endemic municipality — employing technologies such as Kernel density maps and spatial database analysis [32] — represents the primary strategy for targeting control efforts. Continuous monitoring of reported cases is essential, as dispersion can be amplified by internal migration into endemic areas and by crowded conditions [32].

Leishmaniasis is a complex multisystemic disease [33] requiring multidisciplinary effort from public health agencies, health professionals and scientists. Most causes of endemic outbreaks are associated with the natural environment and anthropogenic factors such as human migration, deforestation, urbanization and malnutrition [34].

4 ENVIRONMENTAL VARIABLES

4.1 WORLDWIDE VARIABLES

The maintenance of VL and CL is related to environmental variables favoring the simultaneous presence of vectors and vertebrate hosts at the same site [24]. The geographical distribution of leishmaniasis follows the distribution of sandfly niches, which depends on temperature, vegetation and humidity. Sandflies are thermophilic and cannot survive extended exposure to temperatures below 15°C [55]. In tropical and equatorial regions, warm and rainy climates [10, 35, 36] favor phlebotomine reproduction [37, 38].

Global climate change is reshaping the epidemiology of vector-borne diseases. Multiple studies using ecological niche models and climate projections indicate that sandfly habitat is expanding toward higher latitudes and altitudes. Under future climate scenarios (2050–2080), VL transmission risk in Nepal is expected to increase from 34% to 43% of land

area [55]. In Italy, six phlebotomine vector species are projected to expand both latitudinally and altitudinally by 2041–2060 and 2061–2080 [56]. In central-west Europe, northward expansion of *Phlebotomus* spp. has been documented, with the current northern border reaching Luxembourg [55].

Human travel and migration also contribute to the geographic expansion of leishmaniasis. The movement of people from temperate to tropical or equatorial climates — sometimes accompanied by pets [30] — facilitates disease spread beyond its traditional range. In 2024, 133 imported CL cases and 73 imported VL cases were reported globally [51].

Vegetation plays a complementary role in vector distribution. Although sandflies prefer forested areas, they can also be found in open and urban environments [35]. In summary, the global environmental variables favorable to sandfly niches are concentrated in Latin America and parts of Africa and Asia, in hot, wet climates with forest cover, although some species adapt to dry and open environments.

4.2 REGIONAL VARIABLES

At the regional level, the primary factor driving leishmaniasis dispersion is the presence of sandflies in specific areas. Since sandflies breed in soil or litter, they depend on water availability and moisture, and their small size enables them to inhabit various microhabitats [36]. Detailed analyses of sandfly breeding sites and larval development remain scarce [15].

Peri-urban areas represent significant risk factors for leishmaniasis transmission by maintaining niches for sandflies and natural reservoir hosts. A study in the Brazilian Legal Amazon (2007–2020) found a significant spatial dependence between VL cases and deforestation associated with agriculture, livestock and mining activities [58]. In São Paulo state, *Lutzomyia longipalpis* was detected in 32.4% of municipalities by 2022, with high-risk clusters strongly associated with elevated deforestation and higher temperatures [57].

Urban peripheries are frequently inhabited by low-income populations with limited access to sanitation and sewage treatment, generating exclusionary urbanization [41]. Deforestation linked to unplanned urbanization — producing dead tree trunks, decomposing organic material and increased soil microorganisms — positively affects the phlebotomine reproductive cycle [38, 42–45]. Poor housing and domestic sanitary conditions increase sandfly breeding and resting sites and facilitate their access to humans [51].

Reservoir hosts of *Leishmania* include rodents, marsupials, monkeys, wild canines [30], domestic dogs, chickens, cattle, equines, goats, swine and felines [11–14, 30]. The

presence of swine in the peridomicile represents an important contamination risk [40], and the presence of chickens attracts wild predators — potential reservoir hosts of *Leishmania* — intensifying the parasite cycle toward human and canine populations [39].

Current knowledge supports effective eradication strategies including sandfly control with insecticides, removal of organic material from peridomiciliary areas [47, 48] and elimination of contaminated reservoir hosts. A One Health approach — integrating vector control, host management and environmental sanitation — is essential for reducing the disease burden and achieving long-term control [54].

5 CONCLUSION

Leishmaniasis transmission depends on the association between contaminated sandflies, *Leishmania* reservoir hosts and humans. Geographically, this association is favored in intertropical regions where warm, wet climates and specific forest vegetation types predominate. At the regional level, the proximity of forest remnants or woodland to local peripheries increases sandfly density, creating favorable conditions for the *Leishmania* life cycle and its exposure to resident populations.

Recent global analyses confirm that, while VL burden has significantly declined since 1990, the burden of CL and MCL continues to rise, particularly in low- and middle-income countries [49, 50]. Climate change is expected to further expand sandfly habitats into previously non-endemic regions in Europe, North America and high-altitude areas of Asia [55, 56]. Deforestation, unplanned urbanization, rural-to-urban migration and inadequate sanitation remain the primary regional drivers of leishmaniasis expansion [54, 58].

Accurate public health policies, proper dissemination of relevant information to populations living in endemic areas, and rigorous epidemiological control and surveillance are essential for eliminating human contamination. A multidisciplinary, One Health approach integrating human, animal and environmental health is the most promising framework for combating this neglected disease in a changing world [54].

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USE OF ANABOLIC HORMONE THERAPIES IN SARCOPENIA IN OLDER ADULTS: CURRENT EVIDENCE AND PROGNOSIS

USO DE TERAPIAS HORMONAIAS ANABÓLICAS NA SARCOPENIA EM IDOSOS: EVIDÊNCIAS ATUAIS E PROGNÓSTICO

USO DE TERAPIAS CON HORMONAS ANABÓLICAS EN LA SARCOPENIA EN ANCIANOS: EVIDENCIA ACTUAL Y PRONÓSTICO



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ABSTRACT

Sarcopenia is a multifactorial condition associated with aging, characterized by the progressive loss of skeletal muscle mass and function, with significant impact on physical performance and quality of life in older adults. In this context, anabolic hormone therapies have been investigated as potential strategies to mitigate this process. This study aimed to critically analyze the current scientific evidence regarding the use of these therapies in the management of sarcopenia in older individuals. This is a narrative literature review conducted using PubMed, ScienceDirect, and SciELO databases, including publications from 2016 to 2026. A total of 17 studies were selected, addressing testosterone replacement therapy (TRT), selective androgen receptor modulators (SARMs), and other hormonal approaches. The findings indicate that TRT consistently improves lean body mass and body composition; however, its effects on physical function remain heterogeneous. SARMs show promising anabolic effects in experimental models, but clinical evidence is still limited. Additionally, relevant concerns persist regarding the safety of these interventions, particularly in relation to cardiovascular risk and long-term outcomes. In conclusion, despite favorable effects on structural parameters, anabolic hormone therapies do not yet have sufficient evidence to support their use as standard treatment for sarcopenia, highlighting the need for further studies focusing on functional outcomes and long-term safety.

Keywords: Sarcopenia. Hormone Therapy. Testosterone. Aging. Skeletal Muscle.

RESUMO

A sarcopenia é uma síndrome multifatorial associada ao envelhecimento, caracterizada pela perda progressiva de massa e função muscular, com impacto significativo na funcionalidade e na qualidade de vida de idosos. Nesse contexto, terapias hormonais anabólicas têm sido investigadas como estratégia potencial para atenuar esse processo. O presente estudo teve como objetivo analisar criticamente as evidências científicas acerca do uso dessas terapias na sarcopenia em idosos. Trata-se de uma revisão narrativa da literatura, realizada nas bases de dados PubMed, ScienceDirect e SciELO, contemplando publicações entre 2016 e 2026. Foram incluídos 17 estudos que abordaram a terapia de reposição de testosterona (TRT), os moduladores seletivos do receptor androgênico (SARMs) e outras abordagens hormonais. Os resultados demonstraram que a TRT apresenta efeitos consistentes sobre o aumento da massa muscular e melhora da composição corporal, embora seus impactos sobre a função física sejam heterogêneos. Os SARMs mostraram potencial promissor em modelos experimentais, porém com evidência clínica ainda limitada. Adicionalmente, persistem incertezas relevantes quanto à segurança dessas intervenções, especialmente em relação a riscos cardiovasculares e efeitos em longo prazo. Conclui-se que, apesar dos efeitos favoráveis sobre parâmetros estruturais, as terapias hormonais anabólicas ainda não apresentam evidência suficiente para sua utilização como tratamento padrão da sarcopenia, sendo necessárias investigações adicionais com foco em desfechos funcionais e segurança clínica.

Palavras-chave: Sarcopenia. Terapia Hormonal. Testosterona. Envelhecimento. Músculo Esquelético.

RESUMEN

La sarcopenia es un síndrome multifactorial asociado al envejecimiento, caracterizado por la pérdida progresiva de masa y función muscular, con un impacto significativo en la funcionalidad y la calidad de vida de los adultos mayores. En este contexto, se han investigado las terapias con hormonas anabólicas como una estrategia potencial para mitigar este proceso. Este estudio tuvo como objetivo analizar críticamente la evidencia científica sobre el uso de estas terapias en la sarcopenia en adultos mayores. Se trata de una revisión narrativa de la literatura, realizada en las bases de datos PubMed, ScienceDirect y SciELO,

que abarca publicaciones entre 2016 y 2026. Se incluyeron diecisiete estudios que abordaron la terapia de reemplazo de testosterona (TRT), los moduladores selectivos del receptor de andrógenos (SARMs) y otros enfoques hormonales. Los resultados demostraron que la TRT tiene efectos consistentes en el aumento de la masa muscular y la mejora de la composición corporal, aunque sus impactos en la función física son heterogéneos. Los SARMs mostraron un potencial prometedor en modelos experimentales, pero con evidencia clínica aún limitada. Además, persisten importantes incertidumbres con respecto a la seguridad de estas intervenciones, especialmente en lo que respecta a los riesgos cardiovasculares y los efectos a largo plazo. Se concluye que, a pesar de sus efectos favorables sobre los parámetros estructurales, las terapias con hormonas anabólicas aún carecen de evidencia suficiente para su uso como tratamiento estándar para la sarcopenia, y se requieren más investigaciones centradas en los resultados funcionales y la seguridad clínica.

Palabras clave: Sarcopenia. Terapia Hormonal. Testosterona. Envejecimiento. Músculo Esquelético.

1 INTRODUCTION

Sarcopenia is a complex geriatric syndrome, characterized by progressive loss of muscle mass and function, strongly associated with adverse clinical outcomes, including functional disability, frailty, and increased mortality. Although widely recognized as a multifactorial condition, recent literature emphasizes the central role of endocrine dysfunction in the imbalance between muscle anabolic and catabolic pathways (CHO et al., 2022; MINNETTI et al., 2026). In this scenario, the reduction of anabolic hormones such as testosterone, growth hormone, and IGF-1 has been consistently associated with deterioration in body composition. However, despite the biological plausibility, the magnitude and clinical relevance of these hormonal changes remain heterogeneous among studies, suggesting that their isolated contribution to sarcopenia may be overestimated in certain contexts (BATSIS; VILLAREAL, 2018; SHIN; JEON; KIM, 2018).

The progressive drop in testosterone levels in aging, often linked to late hypogonadism, has been pointed out as one of the main therapeutic targets in an attempt to reverse muscle loss. Although evidence indicates an association between low androgen levels and worsening muscle mass and strength, the causal relationship remains incompletely established, being influenced by multiple clinical and metabolic factors (TAKAYAMA, 2017; AMANO, 2025). In addition, observational studies and clinical interventions show inconsistent results regarding the direct impact of testosterone on physical functionality, suggesting that gains in muscle mass do not always translate into significant clinical improvement (SHIN; JEON; KIM, 2018).

In this context, testosterone replacement therapy (TRT) emerged as one of the main pharmacological strategies investigated. Although clinical trials demonstrate consistent increases in lean mass and improvement in body composition parameters, the effects on functional outcomes, such as mobility and physical performance, remain controversial (BHASIN et al., 2023; NIGHTINGALE et al., 2018). In addition, there are still relevant uncertainties regarding the long-term safety of TRT, especially with regard to cardiovascular risk and possible prostatic implications, which limits its clinical applicability in elderly populations (WANG; SWERDLOFF, 2022; KHODAMORADI et al., 2020). These inconsistencies highlight a critical gap between the observed physiological effects and the clinical benefits actually achieved.

At the same time, new pharmacological approaches, such as selective androgen receptor modulators (SARMs), have been proposed as potentially safer alternatives, due to their selective tissue action. Despite promising results in experimental models and initial studies, demonstrating increased muscle mass and favorable metabolic effects, the absence

of robust evidence in large-scale clinical trials significantly limits their incorporation into clinical practice (CHRISTIANSEN et al., 2020; BORECKI et al., 2025; MORIMOTO et al., 2020). In addition, the extrapolation of preclinical data to elderly populations with multiple comorbidities remains a substantial challenge, reinforcing the need for caution in the interpretation of these findings (SPRINGER; SPRINGER; ANKER, 2017).

Despite advances in the understanding of the hormonal mechanisms involved in sarcopenia, there is no consensus regarding the role of anabolic therapies in its management, especially with regard to its functional efficacy and long-term safety. While non-pharmacological interventions, such as resistance exercise and nutritional support, remain consolidated strategies (KILGORE, 2016; CHO, 2025), hormonal therapies still occupy an uncertain space between therapeutic promise and clinical limitation. In this context, there is a significant gap in the literature regarding the real applicability of these interventions in geriatric clinical practice. Thus, the present study aims to critically analyze the current evidence on the use of anabolic hormonal therapies in sarcopenia in the elderly, focusing on their efficacy, safety, and prognostic implications.

2 METHODOLOGY

This is a narrative review of the literature, with a qualitative approach, oriented to the critical analysis of scientific evidence on the use of anabolic hormonal therapies in the management of sarcopenia in the elderly. The bibliographic search was conducted in a structured manner in the PubMed, ScienceDirect and SciELO databases, including publications in the period from 2016 to 2026. English descriptors were used, combined by Boolean operators (AND, OR), including: *"sarcopenia"*, *"anabolic hormone therapy"*, *"testosterone replacement therapy"*, *"selective androgen receptor modulators"* and *"aging"*. The search strategy was designed to encompass studies that investigated both the pathophysiological mechanisms associated with sarcopenia and hormonal therapeutic interventions, prioritizing evidence with clinical applicability.

The eligibility criteria were previously defined. Original articles, reviews, and experimental or clinical studies with a direct relationship to the topic were included. The inclusion criteria included: (i) publications in the last ten years; (ii) availability of full text or structured abstract; and (iii) relevance to the use of anabolic hormonal therapies in sarcopenia in the elderly. Duplicate studies, non-peer-reviewed publications, articles with divergent thematic focus, and studies with no clinical relevance to the target population were excluded.

The study selection process was conducted in sequential stages. Initially, screening was performed by reading the titles and abstracts identified in the databases, excluding studies that did not meet the established criteria. Then, the eligible articles were read in full, when available, for further evaluation of methodological adequacy and scientific relevance. The final inclusion of the studies considered the consistency of the designs, the clarity of the outcomes analyzed, and the contribution to the understanding of the theme. At the end of this process, 17 articles were selected.

Data extraction and organization were carried out in a standardized manner, including information such as the type of study, the population investigated, the proposed intervention, the main outcomes related to muscle mass and function, as well as safety aspects associated with hormonal therapies. These elements supported the qualitative synthesis of the evidence.

The analysis of the studies was conducted from a descriptive-analytical perspective, with emphasis on the identification of patterns of evidence, convergences and divergences between the results, in addition to the critical evaluation of methodological limitations. Particular consideration was given to the efficacy of interventions on functional outcomes, the consistency of results between different designs, and uncertainties regarding long-term safety. The interpretation of the findings was oriented towards the integration of the available data and the problematization of the gaps in the literature, especially with regard to the clinical applicability of hormonal therapies in the elderly population.

3 RESULTS

We included 17 studies published between 2016 and 2026, covering narrative reviews, clinical and experimental studies, and mechanistic analyses. Overall, evidence focuses on evaluating the effects of anabolic hormone therapies on body composition, muscle function, and safety in elderly or hormone-deficient individuals.

Testosterone replacement therapy (TRT) was the most frequently investigated intervention, with consistent results regarding increased lean body mass and reduced fat mass, especially in individuals with hypogonadism (BHASIN et al., 2023; NIGHTINGALE et al., 2018). In addition, improvements in muscle strength parameters were observed, although the magnitude of these effects varies between studies. On the other hand, the outcomes related to physical function and functional performance were heterogeneous, with divergent evidence regarding their effectiveness in improving mobility and functional capacity (SHIN; JEON; KIM, 2018). With regard to safety, the studies point to relevant uncertainties, particularly related to cardiovascular risk and possible prostate implications, aspects that

remain inconclusive in the available literature (WANG; SWERDLOFF, 2022; KHODAMORADI et al., 2020).

Selective androgen receptor modulators (SARMs) emerge as a promising therapeutic approach, characterized by selective anabolic effects on muscle tissue. Evidence from experimental studies demonstrates an increase in muscle mass and improvement in metabolic parameters, with a potentially more favorable profile in terms of adverse effects when compared to traditional androgens (CHRISTIANSEN et al., 2020; MORIMOTO et al., 2020). In addition, recent reviews indicate the development of compounds in the clinical investigation phase, with preliminary results suggesting positive effects on lean mass (BORECKI et al., 2025). However, the literature still shows a predominance of preclinical data or initial studies, with limited evidence from robust clinical trials in elderly populations.

At the same time, other hormonal axes have been implicated in the pathophysiology and management of sarcopenia. Studies highlight the role of growth hormone (GH), insulin-like growth factor type 1 (IGF-1), and sex steroids in the regulation of muscle mass, showing that the decline of these hormones with aging contributes to the loss of muscle mass and function (MINNETTI et al., 2026; BATSIS; VILLAREAL, 2018). Additional therapeutic approaches, such as myostatin inhibitors, ghrelin analogues, and other hormone modulators, are in experimental stages, with still limited evidence regarding their clinical efficacy (CHO et al., 2022; CHO, 2025).

Regardless of the pharmacological approach, the studies analyzed consistently reinforce the central role of non-pharmacological interventions, particularly resistance exercise and nutritional support, as fundamental strategies in the management of sarcopenia (KILGORE, 2016).

In summary, the findings indicate that anabolic hormone therapies have more consistent effects on body composition parameters than on functional outcomes, while new approaches, such as SARMs, remain in the scientific consolidation phase.

4 DISCUSSION

The findings of this review show that, although anabolic hormone therapies have consistent effects on body composition parameters, their translation into relevant clinical benefits remains uncertain. Testosterone replacement therapy (TRT), for example, relatively uniformly demonstrates increased lean mass and reduced body fat (BHASIN et al., 2023; NIGHTINGALE et al., 2018). However, the heterogeneity of the results related to physical function suggests that structural gains do not necessarily translate into functional improvement, a central aspect in the clinical definition of sarcopenia. This dissociation raises

questions about the real effectiveness of TRT as an isolated therapeutic intervention, especially considering that functionality, and not only muscle mass, is the main prognostic determinant in the elderly (SHIN; JEON; KIM, 2018).

In addition, the absence of consensus regarding the safety of TRT represents a critical limitation for its clinical application. Although some studies indicate a relatively safe profile when used under controlled conditions, concerns persist regarding cardiovascular risk and possible prostatic repercussions, especially in elderly populations with multiple comorbidities (WANG; SWERDLOFF, 2022; KHODAMORADI et al., 2020). The lack of long-term clinical trials, with adequate statistical power to evaluate adverse events, makes it difficult to consolidate robust clinical recommendations, keeping TRT in a zone of therapeutic uncertainty.

Regarding selective androgen receptor modulators (SARMs), the available results reinforce their potential as a more specific and theoretically safer pharmacological alternative. Experimental studies demonstrate significant anabolic effects, with a positive impact on muscle mass and metabolic parameters (CHRISTIANSEN et al., 2020; MORIMOTO et al., 2020). However, the predominance of preclinical data and the scarcity of robust clinical trials substantially limit the extrapolation of these findings to clinical practice. In addition, the absence of consistent data on long-term safety and effects in frail elderly populations reinforces the need for caution, especially in view of the history of hormonal therapies whose risks only became evident after expanded use (BORECKI et al., 2025; SPRINGER; SPRINGER; ANKER, 2017).

Another relevant point refers to the complexity of the pathophysiology of sarcopenia, which cannot be attributed exclusively to hormonal decline. Although alterations in axes such as testosterone, GH, and IGF-1 play a relevant role, the interaction with inflammatory, metabolic, and functional factors suggests that isolated therapeutic approaches tend to have limited efficacy (MINNETTI et al., 2026; BATSIS; VILLAREAL, 2018). In this context, the literature analyzed consistently reinforces the central role of non-pharmacological interventions, particularly resistance exercise, as a fundamental strategy in the management of the disease (KILGORE, 2016). This indicates that hormonal therapies, when used, should be understood as adjuvants, and not as primary interventions.

The integrated analysis of the studies shows, therefore, a significant gap between the physiological effects of hormonal therapies and their effective clinical applicability. Although there are advances in the development of new approaches, such as SARMs and other hormone modulators, the absence of robust evidence, especially regarding relevant clinical outcomes and long-term safety, prevents the consolidation of these strategies as a

therapeutic standard. Thus, the current scenario is marked by consistent biological promises, but not yet fully translated into measurable clinical benefits.

Thus, the available literature does not support a consensus regarding the routine use of anabolic hormone therapies in the treatment of sarcopenia in the elderly, evidencing the need for more robust clinical studies, focusing on functional outcomes and long-term safety. The definition of the role of these interventions in clinical practice depends, therefore, on more consistent evidence that allows overcoming the current methodological limitations and reducing the uncertainties that still exist.

5 CONCLUSION

The evidence analyzed indicates that anabolic hormone therapies, particularly testosterone replacement therapy, have consistent effects on body composition parameters, such as increased muscle mass and reduced adiposity. However, these benefits do not translate uniformly into improved physical function, the main clinical outcome in sarcopenia, evidencing a relevant dissociation between structural and functional effects.

In addition, significant uncertainties persist regarding the safety of these interventions, especially in relation to cardiovascular risk and prostate implications, which limits their broad application in the elderly population. In the case of selective androgen receptor modulators, although initial results are promising, the predominance of preclinical evidence and the scarcity of robust clinical trials prevent their incorporation into clinical practice at the present time.

The multifactorial complexity of sarcopenia reinforces that isolated therapeutic approaches, based exclusively on hormonal modulation, have limited efficacy. In this context, non-pharmacological interventions, such as resistance exercise and nutritional support, remain fundamental strategies and supported by more consistent evidence.

Thus, anabolic hormonal therapies cannot yet be considered the therapeutic standard for sarcopenia in the elderly, currently occupying a potentially adjuvant role and restricted to specific clinical contexts. The consolidation of its use depends on the performance of high-quality clinical studies, focusing on functional outcomes and long-term safety, capable of reducing the uncertainties that are still present and guiding its applicability in clinical practice.

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DIGITAL TRANSFORMATION AND MULTIPROFESSIONAL INTEGRATION: NEW PATHWAYS TO PATIENT SAFETY AND SUSTAINABILITY OF HEALTH SYSTEMS

TRANSFORMAÇÃO DIGITAL E INTEGRAÇÃO MULTIPROFISSIONAL: NOVOS CAMINHOS PARA A SEGURANÇA DO PACIENTE E SUSTENTABILIDADE DOS SISTEMAS DE SAÚDE

TRANSFORMACIÓN DIGITAL E INTEGRACIÓN MULTIPROFESIONAL: NUEVAS VÍAS PARA LA SEGURIDAD DEL PACIENTE Y LA SOSTENIBILIDAD DE LOS SISTEMAS DE SALUD



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ABSTRACT

Digital transformation has significantly reshaped healthcare systems, influencing how care is delivered, managed, and evaluated. In this context, multiprofessional integration emerges as a key element to ensure safe, efficient, and patient-centered care. This study aims to discuss how the incorporation of digital technologies is redefining healthcare models and strengthening collaborative practices among health professionals, with direct implications for patient safety and health system sustainability. This is a qualitative study based on an integrative review of recent national and international scientific literature. The discussion will address key aspects such as telemedicine, remote monitoring, electronic health records, shared decision-making, and the role of different professional groups in delivering coordinated care. While digital transformation expands possibilities and improves care processes, it also presents challenges related to workforce training, system integration, and data security. It is concluded that digital transformation, when combined with effective multiprofessional collaboration, represents a promising pathway toward more resilient healthcare systems capable of delivering comprehensive, safe, and sustainable care.

Keywords: Digital Transformation. Digital Health. Multiprofessional Team. Patient Safety. Health Systems.

RESUMO

A transformação digital tem promovido mudanças profundas na organização dos serviços de saúde, influenciando diretamente a forma como o cuidado é planejado, executado e avaliado. Nesse cenário, a integração multiprofissional emerge como elemento central para garantir assistência segura, eficiente e centrada no paciente. Este estudo tem como objetivo discutir como a incorporação de tecnologias digitais vêm reconfigurando os modelos assistenciais e fortalecendo a atuação integrada das equipes de saúde, com impacto direto

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na segurança do paciente e na sustentabilidade dos sistemas de saúde. Trata-se de uma análise de natureza qualitativa, fundamentada em revisão integrativa da literatura científica recente, abrangendo evidências nacionais e internacionais. Ao longo da discussão, serão abordados aspectos como telemedicina, monitoramento remoto, prontuários eletrônicos, tomada de decisão compartilhada e o papel das diferentes categorias profissionais na construção de um cuidado mais coordenado. Destaca-se que, embora a digitalização amplie possibilidades e melhore fluxos assistenciais, também impõe desafios relacionados à qualificação profissional, à integração de sistemas e à garantia da segurança das informações. Conclui-se que a transformação digital, quando associada a uma atuação multiprofissional efetiva, representa um caminho promissor para a construção de sistemas de saúde mais resilientes, capazes de oferecer cuidado integral, seguro e sustentável.

Palavras-chave: Transformação Digital. Saúde Digital. Equipe Multiprofissional. Segurança do Paciente. Sistemas de Saúde.

RESUMEN

La transformación digital ha impulsado cambios profundos en la organización de los servicios de salud, influyendo directamente en la planificación, ejecución y evaluación de la atención. En este contexto, la integración multiprofesional se erige como un elemento central para garantizar una atención segura, eficiente y centrada en el paciente. Este estudio tiene como objetivo analizar cómo la incorporación de tecnologías digitales está reconfigurando los modelos de atención y fortaleciendo el desempeño integrado de los equipos de salud, con un impacto directo en la seguridad del paciente y la sostenibilidad de los sistemas de salud. Se trata de un análisis cualitativo, basado en una revisión integradora de la literatura científica reciente, que abarca evidencia nacional e internacional. A lo largo del análisis, se abordarán aspectos como la telemedicina, la monitorización remota, las historias clínicas electrónicas, la toma de decisiones compartida y el papel de las diferentes categorías profesionales en la construcción de una atención más coordinada. Cabe destacar que, si bien la digitalización amplía las posibilidades y mejora los flujos de atención, también plantea desafíos relacionados con la cualificación profesional, la integración de sistemas y la garantía de la seguridad de la información. Se concluye que la transformación digital, cuando se asocia con una acción multidisciplinaria eficaz, representa una vía prometedora para la construcción de sistemas de salud más resilientes, capaces de ofrecer una atención integral, segura y sostenible.

Palabras clave: Transformación Digital. Salud Digital. Equipo Multidisciplinario. Seguridad del Paciente. Sistemas de Salud.

1 INTRODUCTION

Digital transformation has promoted profound changes in the way health services are organized and offered, directly impacting care models and the dynamics of care. In recent years, the incorporation of technologies such as electronic medical records, telemedicine, clinical decision support systems, and remote monitoring has expanded the possibilities of intervention, while requiring a reorganization of professional practices. This movement does not occur in isolation, but is part of a broader context of modernization of health systems, driven by the need for greater efficiency, quality, and safety in care (WORLD HEALTH ORGANIZATION, 2021; SHAH et al., 2023).

In this scenario, multiprofessional integration stands out as one of the main pillars for the consolidation of more effective care models. The growing complexity of health demands requires the coordinated action of different professionals, such as doctors, nurses, pharmacists, physiotherapists, nutritionists and other team members, in order to ensure a more complete and patient-centered care. Recent studies show that interprofessional collaboration, when associated with the use of digital technologies, contributes to improving communication between teams, reducing care failures, and optimizing clinical outcomes (SAUTER et al., 2025; DELIMA; ALJABERI; DIOSO, 2025).

The evolution of care models is also directly related to the expansion of telemedicine and digital tools for remote monitoring. These technologies have enabled new forms of interaction between professionals and patients, breaking geographical barriers and expanding access to health services. In addition, they favor continuity of care and real-time monitoring, essential elements for preventing complications and improving the quality of care (MCVEY et al., 2024; LOW et al., 2025; GREENHALGH et al., 2021).

However, despite the advances, digital transformation also brings important challenges. The integration of systems, the training of professionals and the adaptation to new technologies still represent obstacles in many contexts. In addition, issues related to information security and data privacy have become increasingly relevant, requiring special attention from health institutions and managers (NAVARRO-MARTÍNEZ et al., 2025; KELLEHER et al., 2022).

Another aspect that deserves to be highlighted is the impact of digitalization on patient safety. The use of computerized systems has the potential to reduce errors related to prescription, communication, and clinical decision-making. However, when poorly implemented, these same systems can generate new types of failures, reinforcing the need for a critical and well-structured use of technologies (BATES; SINGH, 2020; DIXON-WOODS, 2019).

In addition, the literature points out that digital transformation can contribute significantly to the sustainability of health systems. Process optimization, reduction of operating costs, and improvement in resource management are some of the benefits associated with the adoption of digital technologies. However, these gains depend on proper implementation and integration between the different areas of care (BRAITHWAITE, 2018; WACHTER, 2015).

The performance of professionals such as pharmacists, for example, has been expanded in the digital context, especially in therapeutic monitoring and medication management in integrated environments. Likewise, nursing has played a central role in the coordination of care and in the use of technologies for monitoring and communication between teams (ALSHAHRANI, 2026; ZHANG et al., 2025).

Finally, it is important to highlight that digital transformation should not be understood only as the incorporation of new tools, but as a change in the way of thinking and organizing health care. The integration between technology and clinical practice requires a more humanized approach, which values the patient's experience and strengthens communication between professionals. In this sense, the combination of technological innovation and person-centered care represents one of the main challenges and, at the same time, one of the greatest opportunities for contemporary health systems (EFTHYMIU, 2025; KRUSE et al., 2020).

In this context, the present study aims to analyze how digital transformation, associated with multiprofessional integration, has been contributing to the reconfiguration of care models, with a focus on patient safety and the sustainability of health systems.

2 LITERATURE REVIEW

2.1 DIGITAL TRANSFORMATION IN HEALTHCARE

Digital transformation in health represents a structural change in the way services are organized, moving from being centered only on face-to-face processes to incorporating technological solutions capable of expanding access, qualifying care, and optimizing care flows. This movement has been driven by global strategies that encourage digitalization as an essential tool to improve the quality of health systems and strengthen data-driven decision-making (WORLD HEALTH ORGANIZATION, 2021).

In addition, the literature highlights that digitalization is not limited to the introduction of technologies, but involves a reconfiguration of work processes and relationships between professionals and patients. Digital systems have allowed greater integration of clinical information, facilitating the longitudinal follow-up of patients and contributing to more

coordinated care. In this sense, digital transformation is now understood as a strategic element for the evolution of contemporary health systems (SHAH et al., 2023; KELLEHER et al., 2022).

Another important point is that the adoption of these technologies also has a direct impact on the patient experience, allowing greater participation in care and easy access to health information. This new scenario requires professionals to develop digital skills and adapt their practices to new care demands.

2.2 CARE MODELS AND INTEGRATED CARE

Historically, health systems have been structured in a fragmented way, with little communication between the different levels of care and between the professionals involved in care. This model, although functional in certain contexts, has proven to be insufficient in the face of the growing complexity of health demands, especially in the management of chronic conditions and in the care of patients with multiple needs.

The transition to integrated care models emerges as a response to this limitation, proposing a patient-centered approach based on continuity of care. In this model, information circulates more fluidly among professionals, allowing for faster and more informed decisions. The integration of services, combined with the use of digital technologies, contributes to reducing communication failures and improving clinical outcomes (GREENHALGH et al., 2021; KRUSE et al., 2020).

In addition, integrated care favors a broader view of the patient, considering not only clinical aspects, but also social and behavioral factors. This approach has been associated with improved quality of care and the reduction of adverse events, reinforcing its importance in the current context.

2.3 MULTIPROFESSIONAL INTEGRATION IN HEALTH

Multiprofessional action is one of the fundamental pillars for the consolidation of more efficient care models. The complexity of health problems requires collaboration between different areas of knowledge, allowing for a more complete and problem-solving approach. In this context, communication between professionals becomes a central element for the success of interventions.

Studies indicate that the integration between multiprofessional teams is enhanced by the use of digital technologies, which facilitate the exchange of information and the coordination of care. Digital tools allow different professionals to monitor the same patient

simultaneously, contributing to safer and more effective care (SAUTER et al., 2025; DELIMA; ALJABERI; DIOSO, 2025).

In addition, integrated action strengthens shared decision-making, allowing different perspectives to be considered in care planning. This process contributes to the improvement of clinical outcomes and patient satisfaction.

2.4 DIGITAL TECHNOLOGIES IN HEALTH CARE

Digital technologies have played an increasingly relevant role in health care, offering new possibilities for care and expanding the reach of services. Telemedicine, for example, has been consolidated as an important tool for monitoring patients, especially in regions with difficult access to health services.

In addition, remote monitoring allows for the continuous collection of clinical data, enabling earlier interventions and reducing the risk of complications. These resources have been widely used in different contexts, contributing to the improvement of the quality of care and the optimization of care processes (MCVEY et al., 2024; LOW et al., 2025).

Another significant advance refers to clinical decision support systems, which help professionals in interpreting data and defining conducts. These systems, when well used, can reduce errors and increase the accuracy of interventions, reinforcing the importance of technology as an ally in health care.

2.5 PATIENT SAFETY IN THE DIGITAL AGE

Patient safety is one of the main challenges of health systems, and digital transformation has been pointed out as an important strategy to reduce risks and improve the quality of care. Computerized systems can minimize errors related to prescription, communication, and execution of procedures, contributing to safer care.

However, the literature also highlights that the introduction of new technologies can generate additional risks, especially when there is no adequate training or when systems are not well integrated. Thus, patient safety in the digital age depends not only on technology, but also on the way it is used by professionals (BATES; SINGH, 2020; NAVARRO-MARTÍNEZ et al., 2025).

In addition, building a culture of security is key to ensuring that the benefits of digitalization are fully realized. This involves the active participation of all professionals and the commitment to the continuous improvement of care processes.

2.6 CHALLENGES OF DIGITAL TRANSFORMATION

Despite the advances, digital transformation still faces several challenges that limit its potential. Among them, the resistance to change on the part of professionals, the need for continuous training and the difficulties in integrating information systems stand out.

Another relevant point is the issue of data security, which becomes increasingly complex with the increase in the volume of digital information. The protection of patient information is essential to ensure trust in health systems and avoid ethical and legal problems (KELLEHER et al., 2022).

In addition, inequality in access to technologies represents a major challenge, especially in developing countries. The lack of adequate infrastructure can limit the implementation of digital solutions, widening health disparities.

2.7 SUSTAINABILITY OF HEALTH SYSTEMS

The sustainability of healthcare systems has been a growing concern, especially in the face of rising costs and demand for services. In this context, digital transformation emerges as a promising strategy to improve efficiency and reduce waste.

The automation of processes, the improvement in resource management, and the reduction of avoidable hospitalizations are some of the benefits associated with digitalization. In addition, multiprofessional integration contributes to a more rational use of resources, avoiding unnecessary interventions and promoting more effective care (BRAITHWAITE, 2018; WACHTER, 2015).

Finally, it is highlighted that sustainability should not be understood only in economic terms, but also as the ability of health systems to offer quality care on an ongoing basis. In this sense, the combination of technology and multiprofessional action represents an important path to face current and future health challenges.

3 METHODOLOGY

3.1 STUDY DESIGN

This study was developed from a qualitative approach, of a theoretical-analytical nature, structured through an integrative literature review. The choice of this design allowed us to gather and analyze scientific evidence in a broad and critical way, making it possible to understand how digital transformation and multiprofessional integration have influenced care models, patient safety, and the sustainability of health systems. The integrative review was adopted because it allows the inclusion of different types of studies, favoring a more comprehensive analysis aligned with the complexity of the topic.

3.2 SEARCH STRATEGY AND DATABASES

The search for evidence was carried out in internationally recognized scientific databases, selected for their relevance in the area of digital health and organization of health systems. The following databases were used:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- Virtual Health Library (VHL)
- Google Scholar

In addition, institutional documents from international organizations, such as the World Health Organization (WHO), were included for their importance in the formulation of guidelines on digital health.

To construct the search strategy, descriptors in Portuguese and English were used, combined by Boolean operators (AND and OR), in order to increase the sensitivity and specificity of the results. Among the main terms used, the following stand out:

- Digital Transformation in Health
- Digital Health
- Multiprofessional integration
- Patient safety
- digital health
- Interprofessional Collaboration
- patient safety
- Health Systems

3.3 INCLUSION AND EXCLUSION CRITERIA

Scientific articles published in peer-reviewed journals, systematic reviews, observational studies, and institutional documents that addressed:

- Digital transformation applied to health
- Multiprofessional integration in care
- Digital technologies in care
- Patient safety in digital environments
- Organization and sustainability of health systems

Studies available in Portuguese, English, and Spanish, with access to the full text, were considered.

Duplicate studies, studies with an exclusively technical focus unrelated to care practice, publications without scientific rigor, and materials that did not adhere to the study's objective were excluded.

3.4 ANALYSIS PERIOD

Publications between 2020 and 2026 were prioritized, a period that concentrates recent advances related to digital transformation in health, especially after the intensification of the use of technologies during and after the COVID-19 pandemic. However, classic studies that are widely recognized in the literature were included when they were considered essential for the theoretical foundation of the theme, contributing to a more consistent analysis.

3.5 STUDY SELECTION PROCESS

Initially, the titles and abstracts of the identified studies were read, with the aim of selecting the most relevant ones. Then, the pre-selected articles were analyzed in full, allowing their contribution to the study to be evaluated.

At the end of the process, 20 scientific references were selected, which composed the theoretical basis of the article. The information extracted was organized in a thematic way, enabling the construction of a structured and coherent analysis.

3.6 DATA ANALYSIS AND SYNTHESIS

The data analysis was conducted in an interpretative way, seeking to identify patterns, convergences and gaps in the scientific literature. The synthesis of the evidence was carried out in a narrative manner, prioritizing clear, fluid writing that is close to health practice.

This approach allowed the integration of different perspectives, contemplating clinical, organizational and technological aspects, in addition to valuing multiprofessional action as a central element in the construction of more efficient care models.

3.7 METHODOLOGICAL RIGOR

Scientific rigor was ensured by the selection of studies from reliable databases, by the clear definition of inclusion and exclusion criteria, and by the critical analysis of the evidence. We sought to maintain fidelity to the information presented in the studies, avoiding undue generalizations and ensuring consistency in the interpretation of the data.

3.8 ETHICAL ASPECTS

As this was a study based exclusively on secondary data from the scientific literature, there was no need to submit it to the Research Ethics Committee. All sources used were duly cited throughout the text, ensuring transparency and respect for the ethical principles of scientific production.

4 RESULTS AND DISCUSSION

The analysis of the selected evidence demonstrates that digital transformation has promoted structural changes in care models, directly impacting the way care is organized, executed, and monitored. Studies indicate that the incorporation of digital technologies, such as telemedicine, computerized systems, and remote monitoring tools, has contributed to expanding access to health services and improving the continuity of care, especially in contexts of greater care complexity (WORLD HEALTH ORGANIZATION, 2021; SHAH et al., 2023; MCVEY et al., 2024).

One of the main results observed refers to the improvement in communication among health professionals. The use of shared digital systems allows different members of the multiprofessional team to access information in real time, reducing failures in data transmission and favoring safer decision-making. Studies show that digital integration between teams contributes significantly to care coordination, especially in services that involve multiple levels of care (SAUTER et al., 2025; DELIMA; ALJABERI; DIOSO, 2025; ZHANG et al., 2025).

In addition, telemedicine has stood out as a strategic tool to strengthen multiprofessional work. By enabling interaction between professionals from different areas, regardless of geographic location, this technology expands the possibilities of joint action and favors the construction of more complete therapeutic plans. Evidence shows that the use of digital platforms for remote monitoring has improved clinical indicators and reduced the need for unnecessary hospitalizations (LOW et al., 2025; GREENHALGH et al., 2021; KRUSE et al., 2020).

With regard to patient safety, the results indicate that the digitalization of care processes has the potential to reduce errors related to prescription, medication administration, and communication between teams. Clinical decision support systems, for example, help identify drug interactions and standardize conducts, contributing to safer care. However, the literature also shows that the introduction of these technologies can generate new types of failures, especially when there are limitations in the training of professionals or

failures in the integration of systems (BATES; SINGH, 2020; NAVARRO-MARTÍNEZ et al., 2025).

Another relevant aspect identified in the studies is the expanded role of different professional categories in the digital context. The performance of pharmacists, for example, has been strengthened in therapeutic monitoring and medication management in integrated digital environments, contributing to the reduction of adverse events and to the improvement of treatment adherence (ALSHAHRANI, 2026). Likewise, nursing has taken a leading role in the coordination of care and in the use of technologies for continuous monitoring of patients (ZHANG et al., 2025).

The analysis also shows that digital transformation contributes to the sustainability of health systems, by promoting greater efficiency in the use of resources. The automation of processes, the reduction of rework, and the improvement in information management are factors that directly impact care costs. Studies show that well-structured systems can reduce waste and improve the quality of care, as long as they are properly implemented and aligned with the needs of the services (BRAITHWAITE, 2018; WACHTER, 2015; KELLEHER et al., 2022).

However, the results also highlight important challenges that still need to be overcome. Resistance to the adoption of new technologies, the need for continuous training of professionals, and difficulties in integrating systems are barriers frequently reported in the literature. In addition, issues related to information security and data protection represent critical challenges in the context of digital health, requiring specific strategies to ensure the confidentiality and integrity of information (KELLEHER et al., 2022; NAVARRO-MARTÍNEZ et al., 2025).

Another highlight is the need for humanization of care in an increasingly technological context. The literature reinforces that, despite digital advances, health care must maintain its focus on the relationship between professional and patient. The integration between technology and a humanized approach is essential to ensure that the benefits of digitalization do not compromise the quality of care (EFTHYMIU, 2025; TOPOL, 2019).

In general, the findings indicate that digital transformation, when associated with multiprofessional integration, has the potential to promote significant changes in health systems, improving the quality of care, patient safety, and the efficiency of services. However, these benefits depend on a structured implementation, which considers not only the technological aspects, but also the human, organizational, and ethical dimensions involved in this process.

5 CONCLUSION

The analysis developed throughout this study shows that digital transformation, associated with multiprofessional integration, represents one of the main strategies for the reconfiguration of contemporary care models. It is not just about the incorporation of new technologies, but about a deeper change in the way care is thought of, organized and executed. The digitalization of health services has expanded possibilities, favored the continuity of care, and contributed to more coordinated and patient-centered care (WORLD HEALTH ORGANIZATION, 2021; SHAH et al., 2023).

The results demonstrate that the integration between different professionals, mediated by digital technologies, strengthens communication, reduces care failures and improves clinical decision-making. This movement reinforces the importance of effective multiprofessional action, in which doctors, nurses, pharmacists, physiotherapists, and other professionals act in an articulated way, sharing responsibilities and building more complete therapeutic plans (SAUTER et al., 2025; DELIMA; ALJABERI; DIOSO, 2025).

In addition, the use of tools such as telemedicine and remote monitoring has contributed significantly to expanding access to health services and improving clinical outcomes. These resources allow for earlier interventions and closer monitoring of patients, reducing the need for hospitalizations and optimizing the use of available resources (MCVEY et al., 2024; LOW et al., 2025; GREENHALGH et al., 2021).

In the field of patient safety, digital transformation has relevant potential for reducing errors and strengthening safer care practices. However, the benefits associated with technologies depend directly on how they are implemented and used by professionals. The presence of digital systems does not eliminate risks, but requires critical and qualified action to ensure that these resources are used appropriately (BATES; SINGH, 2020; NAVARRO-MARTÍNEZ et al., 2025).

Another important aspect refers to the sustainability of health systems. Digitalization, when well structured, contributes to the optimization of processes, cost reduction, and the improvement of resource management. Multiprofessional integration, in this context, enhances these results by promoting a more rational and efficient use of health services (BRAITHWAITE, 2018; WACHTER, 2015; KELLEHER et al., 2022).

However, the study also highlights challenges that still need to be faced, such as the need for training professionals, the integration of information systems, and ensuring data security. In addition, it is essential that technological advances do not compromise the humanization of care, and it is necessary to maintain the balance between innovation and patient-centered care (EFTHYMIU, 2025; TOPOL, 2019).

Thus, it is concluded that digital transformation, combined with multiprofessional integration, constitutes a promising path for strengthening health systems, contributing to safer, more efficient, and sustainable care. For this potential to be fully achieved, it is necessary to invest in professional qualification, technological infrastructure, and the construction of care models that value collaboration between different areas of health

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RATIONAL USE OF OPHTHALMIC MEDICATIONS IN PRIMARY CARE: AN APPROACH FOR GENERAL PRACTITIONERS ON PHARMACOKINETICS, IATROGENESIS, AND PRESCRIPTIVE SAFETY

USO RACIONAL DE MEDICAMENTOS OFTÁLMICOS NA ATENÇÃO PRIMÁRIA: UMA ABORDAGEM PARA O MÉDICO GENERALISTA SOBRE FARMACOCINÉTICA, IATROGENIA E SEGURANÇA PRESCRIPTIVA

USO RACIONAL DE MEDICAMENTOS OFTÁLMICOS EN LA ATENCIÓN PRIMARIA: UN ENFOQUE PARA EL MÉDICO GENERALISTA SOBRE FARMACOCINÉTICA, IATROGENIA Y SEGURIDAD PRESCRIPTIVA



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ABSTRACT

Introduction: Self-medication in Brazil represents an endemic public health problem, within which topical ophthalmic medications (eye drops) occupy a critical position. Frequently underestimated as mere visual hygiene solutions and widely marketed as over-the-counter products, eye drops are highly potent medications. Their route of administration allows rapid bypass of first-pass hepatic metabolism through nasolacrimal drainage, resulting in systemic bioavailability capable of inducing clinically relevant cardiovascular and respiratory effects in susceptible patients.

Objective: This chapter aims to deconstruct the fallacy of the harmlessness of eye drops and to equip the general practitioner, the principal gatekeeper of the healthcare system, for the prevention, identification, and management of ocular and systemic iatrogenic events resulting from the irrational use of these formulations. It also seeks to enable recognition of patients undergoing advanced ophthalmologic treatments (intravitreal injections, sustained-release implants, and prescribed therapies for dry eye disease) who may present to primary care with complications.

Development: The chapter details the pharmacokinetics of the ocular surface and examines the main therapeutic classes. It discusses the deleterious potential of indiscriminate corticosteroid use (inducing steroid-induced glaucoma and cataracts), topical vasoconstrictors, and empirical antibiotics. At the systemic level, it explores the inadvertent toxicity of ophthalmic beta-blockers. It further addresses in depth the toxicity of benzalkonium chloride (BAK) and the transition toward preservative-free formulations, while dedicating a specific section to patients undergoing highly complex ophthalmologic treatments and how the general practitioner should approach them.

Final Considerations: Mitigating morbidity associated with ophthalmic medications requires the general practitioner to adopt an active approach: rigorous inclusion of ophthalmic

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formulations in medication reconciliation, patient health literacy initiatives (including punctal occlusion technique), recognition of warning signs requiring immediate ophthalmologic referral, and pharmacovigilance reporting of detected systemic adverse reactions.

Keywords: Self-medication. Ophthalmic Preparations. Rational Use of Medicines. Pharmacokinetics. Primary Health Care. Glaucoma. Iatrogenic Disease.

RESUMO

Introdução: A automedicação no Brasil é um problema endêmico de saúde pública, cenário no qual os medicamentos oftálmicos tópicos (colírios) ocupam uma posição crítica. Frequentemente subestimados como meras soluções de higiene visual e amplamente comercializados isentos de prescrição, os colírios são fármacos de alta potência. Sua via de administração permite rápida evasão do metabolismo de primeira passagem hepática através da drenagem nasolacrimal, com biodisponibilidade sistêmica capaz de induzir efeitos cardiovasculares e respiratórios clinicamente relevantes em pacientes susceptíveis.

Objetivo: Este capítulo visa desconstruir a falácia da inocuidade dos colírios e instrumentalizar o médico generalista, principal gatekeeper do sistema de saúde, para a prevenção, identificação e manejo de iatrogenias oculares e sistêmicas decorrentes do uso irracional dessas formulações, bem como para reconhecer os pacientes em uso de tratamentos oftalmológicos avançados (injeções intravítreas, implantes de liberação prolongada, terapias para olho seco prescritas) que possam apresentar-se na atenção primária com complicações.

Desenvolvimento: A obra detalha a farmacocinética da superfície ocular e destrincha as principais classes terapêuticas. Discute o potencial deletério do uso indiscriminado de corticosteroides (indutores de glaucoma cortisônico e catarata), vasoconstritores tópicos e antibióticos empíricos. Em nível sistêmico, explora a toxicidade inadvertida de betabloqueadores oftálmicos. Aborda em profundidade a toxicidade do cloreto de benzalcônio (BAK) e a transição para formulações sem conservantes, e dedica seção própria ao paciente que faz tratamentos oftalmológicos de alta complexidade e como o generalista deve abordá-lo.

Considerações finais: A mitigação da morbidade associada aos medicamentos oftálmicos exige que o generalista adote postura ativa: inclusão rigorosa de formulações oftálmicas na reconciliação medicamentosa, letramento em saúde do paciente (técnica de oclusão do ponto lacrimal), reconhecimento de sinais de alarme para referenciamento oftalmológico imediato, e notificação farmacovigilante de reações adversas sistêmicas detectadas.

Palavras-chave: Automedicação. Preparações Oftálmicas. Uso Racional de Medicamentos. Farmacocinética. Atenção Primária à Saúde. Glaucoma. Doença iatrogênica.

RESUMEN

Introducción: La automedicación en Brasil constituye un problema endémico de salud pública, escenario en el cual los medicamentos oftálmicos tópicos (colirios) ocupan una posición crítica. Frecuentemente subestimados como meras soluciones de higiene visual y ampliamente comercializados sin prescripción médica, los colirios son fármacos de alta potencia. Su vía de administración permite una rápida evasión del metabolismo hepático de primer paso a través del drenaje nasolagrimal, con una biodisponibilidad sistémica capaz de inducir efectos cardiovasculares y respiratorios clínicamente relevantes en pacientes susceptibles.

Objetivo: Este capítulo tiene como finalidad deconstruir la falacia de la inocuidad de los colirios y capacitar al médico generalista, principal gatekeeper del sistema de salud, para la prevención, identificación y manejo de iatrogenias oculares y sistémicas derivadas del uso irracional de estas formulaciones. Asimismo, busca reconocer a los pacientes en tratamiento oftalmológico avanzado (inyecciones intravítreas, implantes de liberación prolongada y terapias prescritas para ojo seco) que puedan presentarse en la atención primaria con complicaciones.

Desarrollo: La obra detalla la farmacocinética de la superficie ocular y analiza las principales clases terapéuticas. Se discute el potencial deletéreo del uso indiscriminado de corticosteroides (inductores de glaucoma cortisónico y cataratas), vasoconstrictores tópicos y antibióticos empíricos. A nivel sistémico, se explora la toxicidad inadvertida de los betabloqueadores oftálmicos. También se aborda en profundidad la toxicidad del cloruro de benzalconio (BAK) y la transición hacia formulaciones sin conservantes, dedicando además una sección específica al paciente sometido a tratamientos oftalmológicos de alta complejidad y a la manera en que el médico generalista debe abordarlo.

Consideraciones finales: La mitigación de la morbilidad asociada a los medicamentos oftálmicos exige que el médico generalista adopte una postura activa: inclusión rigurosa de las formulaciones oftálmicas en la conciliación medicamentosa, alfabetización en salud del paciente (técnica de oclusión del punto lagrimal), reconocimiento de signos de alarma para derivación oftalmológica inmediata y notificación farmacovigilante de reacciones adversas sistémicas detectadas.

Palabras clave: Automedicación. Preparaciones Oftálmicas. Uso Racional de Medicamentos. Farmacocinética. Atención Primaria de Salud. Glaucoma. Enfermedad iatrogénica.

1 INTRODUCTION

Self-medication is a complex behavioral phenomenon and a public health challenge on a global scale, finding in Brazil a sociodemographic and regulatory ecosystem that catalyzes it. Data from the population-based survey of the National Survey on Access, Use and Promotion of the Rational Use of Medicines (PNAUM), as well as extensive systematic reviews, demonstrate the wide dissemination of this practice in the Brazilian adult population, especially for the management of acute diseases^[1, 2]. Although self-care is encouraged by the World Health Organization (WHO) when restricted to over-the-counter drugs (OTC) that are duly indicated, the national reality is marked by lack of control. The ease of access at the pharmacy counter, the scarcity of health literacy, aggressive advertising, and the asymmetry in access to primary and specialized care transform this practice into a silent generator of morbidity and mortality^[2, 3].

Within this vast and problematic panorama, topical ophthalmic medications, eye drops, occupy a peculiar and dangerous position. Historically, the false premise that eye drops are innocuous formulations, often equated with mere eye hygiene solutions, has been constructed in the popular imagination, and not infrequently in the perception of health professionals. The fact that they are administered in small vials, topically, creates the illusion that their action and toxicity are confined to the microenvironment of the eye. Consequently, the sharing of these medications among family members and the acquisition without professional guidance reach alarming prevalences, masking critical diagnoses and delaying appropriate therapeutic interventions.

However, this presumption of local confinement is a dangerous pharmacokinetic fallacy. The human eye interacts with tiny water volumes. Conjunctival fornix and tear film have physiological volumes of a maximum of 7 to 10 μL , while gout instilled in a standard commercial vial dispenses a volume between 30 and 50 μL ^[4]. This volumetric excess, associated with the eyelid reflex, directs approximately 80% of the drug to the nasolacrimal drainage system. When it reaches the nasal and pharyngeal mucous membranes, the active ingredient is absorbed by dense capillary beds, escaping hepatic first-pass metabolism^[4]. In terms of systemic bioavailability, a fraction of ophthalmic drop reaches the circulation with kinetics similar to that of an intravenous administration.

The underestimation of this absorption route triggers iatrogenic events on two fronts: local and systemic. In the ocular microenvironment, the chronic and unsupervised use of corticosteroids, often used to treat nonspecific complaints of red eye, induces alterations in the extracellular matrix of the trabecular meshwork, increasing the resistance to the flow of aqueous humor and culminating in cortisonic glaucoma, a silent and irreversible optic

neuropathy^[5, 6]. In addition, posterior subcapsular cataract and facilitation of fungal and herpetic ulcerative keratitis are added. From a systemic point of view, the impact is equally severe: topical vasoconstrictors (such as naphazoline) can trigger hypertensive crises and tachyarrhythmias, while ophthalmic beta-blockers (such as timolol), without proper tear point occlusion maneuvers, have been documented as a cause of profound bradycardia, atrioventricular blocks, and lethal bronchospasm in susceptible patients^[4, 7].

In view of the anatomical-pharmacological complexity and the high potential for serious adverse events, this chapter is justified as a critical instrument for general practitioners. In Primary Care, in Emergency Care Units and in clinical wards, the generalist is the gatekeeper: routinely the first evaluator of acute ophthalmologic complaints, and the one responsible for elucidating cardiovascular or respiratory decompensations that may, in fact, be adverse drug reactions of ocular origin. Understanding eye drops as a high-potency systemic drug, identifying the red flags of each class, and intervening in the prescriptive cascade are non-negotiable skills. The chapter also dedicates a specific section to patients using advanced ophthalmologic treatments (intravitreal injections, extended-release implants, therapies prescribed for dry eye), which are increasingly present in primary care.

2 RATIONAL USE OF MEDICINES: CONCEPTUAL FRAMEWORK

The transition from a scenario of harmful self-medication to a safe prescriptive practice requires the understanding that the drug is a critical input, whose therapeutic value is inseparable from its inherent risk. To structure this premise, the World Health Organization (WHO), at the Nairobi Conference in 1985, coined the classic definition of the Rational Use of Medicines (RMU): the patient receives the appropriate medicine for his clinical need, in the correct dose, for an adequate period of time and at the lowest possible cost to himself and the community^[8]. The application of this concept faces formidable barriers in fragmented health systems; It is estimated that more than half of the drugs prescribed, dispensed or sold globally are inadequate, and that half of patients fail to take them correctly^[9].

In Brazil, the institutionalization of this precept gained normative force through the National Medicines Policy (PNM) and the creation of the National Committee for the Promotion of the Rational Use of Medicines (CNPURM), linked to the Ministry of Health. The CNPURM acts as an articulating instance that transcends mere market regulation, proposing guidelines that range from the continuing education of health professionals to the population's health literacy^[10]. May 5 is established as the National Day for the Rational Use of Medicines, a time frame that serves as an annual alert on the impact of drug iatrogenesis, unmapped interactions, and antimicrobial resistance.

The technical-operational support for the guarantee of the URM rests on the National Health Surveillance Agency (Anvisa), whose role extends far beyond the registration of new molecules. The clinical approval phase (Phase III) occurs in tightly controlled environments, with homogeneous populations and often insufficient statistical power to detect rare or long-term adverse reactions. True safety validation occurs in Phase IV, in the real world, through pharmacovigilance. In Brazil, this activity is operated by the VigiMed system, Anvisa's platform for reporting adverse events by doctors, pharmacists and patients. The generalist is a central part of this ecosystem, as it often detects the first clinical sign of systemic toxicity not foreseen in the package insert.

By narrowing this conceptual framework to the reality of topical ocular formulations, a serious care gap is faced. Eye drops represent a real blind spot in URM promotion policies. During medication reconciliation, a critical step in hospital admission and primary care consultations, traditional anamnesis often fails to inquire about the use of ophthalmic solutions, and patients themselves omit this information because they do not categorize the eye drops as medication. This anamnestic silence prevents the identification of adverse events, underreports reactions to VigiMed, and perpetuates clinical myopia in relation to systemic risks. Promoting the rational use of eye drops requires, primarily, that the generalist rescues these medications from invisibility.

Clinical pearl

The question: Do you take any medication? it is insufficient. Replace in your anamnesis routine with: Do you use any eye drops, eye ointments, nose drops, patches or sprays? This simple reformulation detects omitted eye drops, nasal decongestants (with hypertensive risk analogous to that of ocular vasoconstrictor drops), nasal corticosteroids, and topical cutaneous with relevant systemic absorption.

3 OCULAR PHARMACOKINETICS AND SYSTEMIC ABSORPTION

To understand the magnitude of the systemic effects induced by eye drops, it is imperative to deconstruct the vision of the eye as an isolated compartment. The ocular surface is a highly specialized anatomical interface, designed to maintain homeostasis through a continuous renewal of the tear film and an extremely efficient drainage system. When a medicated drop is instilled, it abruptly subverts this fragile volumetric balance.

The inferior conjunctival fornix, the standard anatomical site for eye drop instillation, holds a maximum fluid volume between 7 and 10 μL . Due to physicochemical limitations of surface tension at the tip of commercial drippers, a standard droplet dispenses volume between 30 and 50 μL ^[4]. This immediate water surplus, which represents 3 to 5 times the

anatomical retention capacity, activates the eyelid reflex. During blinking, the contraction of the tear portion of the orbicularis muscle generates negative pressure in the tear sac, acting as a suction pump (tear pump).

Consequently, it is estimated that up to **80% of the volume of the administered drop** is rapidly pumped through the lacrimal canaliculi into the nasolacrimal duct, emptying into the lower meatus of the nasal cavity^[4, 7]. The nasal mucosa and nasopharynx have a dense and highly permeable capillary bed: the drugs absorbed in this region reach the systemic circulation directly, completely escaping the hepatic portal system and **first-pass metabolism**.

3.1 THE TIMOLOL PARADIGM

The most emblematic clinical example of this pharmacokinetic route is the use of non-selective topical beta-blockers, such as timolol maleate, which are widely prescribed for the treatment of open-angle glaucoma. Each 50 µL drop of 0.5% solution contains approximately 0.25 mg timolol; One drop in each eye delivers about 0.5 mg to the patient^[11]. Although the absolute amount is small when compared to the usual oral dose (10 to 20 mg), the fraction absorbed by the nasal mucosa reaches the systemic circulation in a manner analogous to an intravenous administration, escaping first-pass hepatic metabolism. Pharmacokinetic studies with topical timolol 0.5% document detectable plasma concentrations sufficient to induce clinically relevant systemic β -blocker effects in susceptible patients^[11].

For the general practitioner, the non-recognition of this absorption route can be catastrophic. Blockade of cardiac β_1 -adrenergic receptors can induce severe sinus bradycardia, atrioventricular blocks, and syncope, often investigated as primary cardiovascular events of obscure etiology. At the same time, antagonism of β_2 -adrenergic receptors in the respiratory tract can trigger refractory and potentially lethal bronchospasm attacks in patients with asthma or chronic obstructive pulmonary disease (COPD)^[7].

RED FLAG: investigate eye drops

Faced with any patient, especially the elderly, with unexplained bradycardia, syncope, new atrioventricular block, refractory bronchospasm, or COPD decompensation with no clear trigger, actively inquire about the use of glaucoma eye drops. Presentation may occur months or years after the start of treatment.

3.2 PRACTICAL GUIDANCE FOR RISK MITIGATION

The intervention of the non-ophthalmologist is based on simple but very high-impact prophylactic guidelines that radically alter the systemic bioavailability of the drug. Every

prescription or prescription renewal of eye drops must be accompanied by the teaching of the following techniques:

Lacrimal point occlusion (OPL). It is the most effective maneuver to prevent systemic toxicity. It consists of instructing the patient to, immediately after instillation of the droplet, lightly press the medial corner of the eye (over the lacrimal canaliculi) with the index finger for 2 to 3 minutes. Classic studies have shown that OPL substantially reduces systemic absorption, while increasing the contact time of the drug with the cornea, optimizing intraocular efficacy^[12].

Passive eyelid closure. In conjunction with the OPL, the patient should keep the eyes closed gently (without squeezing the eyelids, which would activate the tear pump) for 3 minutes.

Interval between eye drops. When multiple eye drops are prescribed, immediate sequential instillation causes the *washout effect*, where the second drop expels the first into the nasolacrimal duct prior to corneal absorption. The general practitioner should advise a minimum interval of 5 minutes between the application of different medications^[4].

4 CLASSES OF EYE DROPS: INDICATIONS, INAPPROPRIATE USE AND RISKS

Topical ophthalmic formulations encompass a broad pharmacological spectrum. For the general practitioner, the mastery of the primary indications of each class must invariably be accompanied by the understanding of its toxicity. The classes of most frequent use are detailed below, with emphasis on those most susceptible to irrational use. For the reader who wishes to delve deeper into drug-induced ocular toxicology, Fraunfelder's classic reference work brings together in consultation format the ocular and systemic toxicities associated with hundreds of ophthalmic and general-purpose molecules^[35].

4.1 EYE LUBRICANTS (ARTIFICIAL TEARS)

The premise that artificial tears are innocuous and can be used *ad libitum* is one of the most dangerous fallacies in the management of Dry Eye Syndrome. Although the active ingredients (sodium hyaluronate, carboxymethylcellulose, hydroxypropyl methylcellulose, propylene glycol) are biologically inert, the real toxicological villain in multidose formulations lies in the vehicle: preservatives^[13].

Benzalkonium chloride (BAK) is the most widely used preservative in the ophthalmic industry and is present in approximately **70% of topical formulations**^[13]. It is a quaternary ammonium compound with a detergent mechanism of action: at concentrations of 0.05 to 0.1% it induces cell necrosis; in 0.01% it induces apoptosis. Commercial formulations use

BAK at 0.004 to 0.02%. Chronic use of BAK-containing lubricants disrupts the lipid layer of the tear film, induces **apoptosis of the goblet cells** of the conjunctiva (responsible for mucin secretion), and causes desquamation of the corneal epithelium^[13]. A vicious cycle is thus created: the patient instills the eye drops to relieve dryness, but the preservative exacerbates the inflammation of the ocular surface, requiring increasingly frequent instillations, the **paradoxical iatrogenic dry eye**.

As an innovation and damage mitigation, the industry has transitioned to formulations with fast-dissipating oxidative preservatives (sodium perborate that breaks down into water and oxygen; stabilized oxychlor/Purite® complex that breaks down into chloride and oxygen; SofZia®, system with borates and zinc) or for vials with valved systems totally preservative-free (*preservative-free*), gold standard in chronic use^[13, 14].

4.2 CLINICAL PEARL

Patients who need lubricant more than 4 times a day, which includes most patients with moderate to severe Dry Eye Syndrome, should be prescribed a preservative-free formulation (single-dose vial or multidose vial with valve/COMOD®/ABAK® system). The cost is higher, but the tolerability over the months is unmatched and the grip increases.

It is worth noting that comparative evidence between specific formulations of artificial tears is limited. The most recent Cochrane review on the topic (43 randomised controlled trials, 3,497 participants) rated the overall quality of the evidence as low, with substantial publication bias (18 additional trials with 2,079 participants were registered without disclosure of results), and did not establish clear superiority between formulations^[15]. In practice, the choice is often based on individual tolerance, desired viscosity and, critically, the presence or absence of BAK.

4.3 VASOCONSTRICTORS

It is the most misused therapeutic class over the counter of Brazilian pharmacies. Topical vasoconstrictors (naphazoline, tetrahydrozoline, phenylephrine) are α -adrenergic agonists that promote rapid constriction of the conjunctival capillary network, resulting in immediate cosmetic whitening of red eye. The commercial appeal is based exclusively on the aesthetic effect, masking the underlying etiology, which can range from visual fatigue to acute uveitis^[16].

The central risk of this class is the induction of **tachyphylaxis** and **rebound hyperemia** (conjunctivitis medicamentosa). Continued use leads to desensitization and *downregulation* of postsynaptic α -adrenergic receptors. When the effect of the drug ceases,

severe paradoxical vasodilation occurs, and the patient, chronically reddened by the medication itself, becomes clinically dependent on shorter and shorter instillations^[16].

Systemic effects differ between agents. Imidazole derivatives (naphazoline, tetrahydrozoline, oxymetazoline) can cross the blood-brain barrier in children, causing severe central nervous system depression, bradycardia, hypothermia, and even coma; are formally contraindicated in pediatrics. Phenylephrine (pure α_1 -agonist) has hypertensive crisis and tachyarrhythmia as its main risk. Commercial combinations common in Brazil associate vasoconstrictor with antihistamine (e.g., nafazolin plus pheniramine), and their own package inserts carry explicit warnings for patients with narrow-angle glaucoma, cardiovascular disease, arterial hypertension and prostatic hyperplasia, comorbidities that are exactly prevalent in the elderly population that most consumes these products without guidance^[17].

4.4 ANTI-ALLERGY DRUGS

The topical treatment of allergic conjunctivitis has evolved significantly, but conceptual confusion in pharmacies often pushes the allergic patient to vasoconstrictors. Historically, the arsenal relied only on pure antihistamines (short-acting H1 blockers) or mast cell stabilizers (sodium cromoglycate, which requires weeks of prophylactic use to achieve effectiveness)^[18].

The class was revolutionized by dual-acting agents (olopatadine, ketotifen, alcaftadine, epinastin). These molecules act simultaneously as competitive H1 receptor antagonists (immediate relief of pruritus) and as mast cell membrane stabilisers (prevention of subsequent degranulation). For the generalist, identifying pruritus as a cardinal symptom of allergic etiology and directly prescribing a dual-action agent avoids the chronicity of the condition and keeps the patient away from iatrogenic self-medication with naphazoline^[18].

4.5 TOPICAL ANTIBIOTICS

The empirical and indiscriminate prescription of ophthalmic antibiotics (aminoglycosides such as tobramycin and gentamicin; fluoroquinolones such as ciprofloxacin, moxifloxacin, and besifloxacin) in an empirical and indiscriminate manner is one of the major failures in primary care screening. The vast majority of acute community-based infectious conjunctivitis is of viral etiology, predominantly adenovirus, presenting with aqueous/mucoid secretion, preauricular lymph node enlargement, and self-limiting status in 1 to 2 weeks^[19].

The differential diagnosis of conjunctivitis is feasible at the bedside and is summarized in Table 1.

Table 1

Differential diagnosis of acute conjunctivitis: clinical presentation, secretion, associated symptoms and initial management

Type	Typical presentation	Secretion	Associated symptoms	Initial conduct
Viral (adenovirus)	Unilateral onset, progresses to the second eye in 1 to 5 days; epidemic context; Recent VAT.	Aqueous or mucoid.	Palpable preauricular lymph node; feeling of sand; mild photophobia.	Cold compresses, preservative-free tears, strict hand hygiene. No antibiotic.
Bacterial	Bilateral from the beginning; eyelids glued in the morning.	Purulent, thick, abundant.	No lymph node; little pain; preserved vision.	Most are self-limited within 5 to 7 days; topical antibiotic (fluoroquinolone or polymyxin plus trimethoprim) accelerates resolution.
Hyperacute (gonococcal)	Evolution in 12 to 24 h; sexually active young people; newborns.	Profuse, frankly purulent, explosive.	Significant eyelid edema; corneal perforation may be present.	Ophthalmic emergency. Forward immediately; systemic antibiotic therapy (ceftriaxone).
Allergic	Seasonal or perennial; bilateral; atopic history.	Mucoid, scarce.	Pruritus is the cardinal symptom; chemosis; eyelid edema.	Topical dual-action antihistamine; avoid scratching; To ward off allergens.
Toxic/medicated	Prolonged use of eye drops (BAK, vasoconstrictors).	Variable.	Persistent hyperemia; burning; paradoxical worsening.	Suspend the offending agent; preservative-free lubricant; reassess prescription.

Source: prepared by the authors, based on references [19] and [32] and the AAO Preferred Practice Pattern for conjunctivitis (2024).

The irrational use of topical antibiotics not only exposes the ocular surface to direct toxicity (aminoglycosides are highly epitheliotoxic and slow corneal healing), but places ophthalmology at the center of the global breakdown of antimicrobial resistance. Surveillance studies such as ARMOR (Antibiotic Resistance Monitoring in Ocular Microorganisms) demonstrate alarming rates of *Staphylococcus aureus* strains (including MRSA) and *Staphylococcus epidermidis* of the periocular flora resistant to fourth-generation fluoroquinolones, making serious intraocular infections, such as post-surgical endophthalmitis or corneal ulcers, progressively untreatable^[20].

4.6 RED FLAG: NEVER TREAT AS CONJUNCTIVITIS

The following findings exclude the diagnosis of simple conjunctivitis and require urgent ophthalmologic referral: decreased visual acuity, profound eye pain (not just superficial burning), intense photophobia, colored halos around lights, anisocoria, ciliary hyperemia (hyperemia close to the limbus, rather than diffuse), recent contact lens use with a red eye, trauma or chemical exposure, and history of previous ocular surgery. In either of these scenarios, empirical topical antibiotic masks the diagnosis and delays the vision-saving treatment.

5 TOPICAL CORTICOSTEROIDS: THE HEART OF THE CONCERNS

As anticipated in the Introduction, the inadvertent use of topical corticosteroids is the most documented cause of severe and irreversible ocular morbidity due to self-medication or reckless empirical prescription. This section, absent in earlier versions of this chapter, now occupies the place the theme deserves.

5.1 WHY CORTICOSTEROIDS WORK, AND WHY IT'S PART OF THE PROBLEM

Topical corticosteroids (dexamethasone, prednisolone, fluorometholone, loteprednol, difluprednate) are potent anti-inflammatory drugs, indispensable in the treatment of uveitis, intraocular surgeries, sterile keratitis, refractory severe allergic conjunctivitis, and various segmental inflammations. Its anti-inflammatory effect is so clinically evident, the eye turns white and the patient is comfortable in a few days, that it creates a cognitive trap: both patients and non-specialist professionals tend to perpetuate automatic prescriptions and renewals, without reevaluation.

Corticosteroids differ in relative potency and ability to elevate intraocular pressure (IOP). In descending order of hypertensive risk: difluprednat, dexamethasone, prednisolone, loteprednol, and fluorometholone. In generalist practice, the first action is to assume that **any patient in chronic use of any topical corticosteroid is at risk**, and that this risk is greater the more potent the agent.

5.2 CORTISONIC GLAUCOMA: SILENT NEUROPATHY

The mechanism of **cortisone glaucoma** is distinct from primary open-angle glaucoma. Corticosteroids induce changes in the trabecular meshwork: increased deposition of extracellular matrix (fibronectin, IV collagen, glycosaminoglycans), formation of *cross-linked actin networks* (CLAN), and decreased expression of metalloproteinases. The result

is increased resistance to aqueous humor flow, with **progressive and silent elevation of IOP**^[5, 6].

The clinically decisive points for the generalist are: a) approximately 1/3 to 1/2 of the population is a responder to corticosteroids, with a significant increase in IOP with prolonged topical use; b) IOP elevation typically manifests between 2 and 6 weeks of continuous use, but may occur earlier in severe responders; c) cortisonic glaucoma is silent, the patient does not feel elevated IOP and the damage to the optic nerve, once installed, is irreversible; d) after corticosteroid discontinuation, IOP often normalizes within days to weeks, but the lost visual field does not return.

The package insert for prednisolone acetate 1%, the gold standard ophthalmic corticosteroid, is explicit in warning that prolonged use can result in glaucoma with damage to the optic nerve, visual acuity and visual field defects, and posterior subcapsular cataracts, and recommends that **if the product is used for 10 days or more, intraocular pressure should be routinely monitored**^[21]. This recommendation should be taken as dogma by the generalist: no topical corticosteroid is benign after 10 days.

5.3 POSTERIOR SUBCAPSULAR CATARACT

The second major ocular effect of chronic topical corticosteroids is posterior subcapsular cataract, a central opacity that affects vision early, particularly for reading and bright light. Unlike senile (nuclear) cataracts, posterior subcapsular cataracts can compromise visual acuity with a few weeks to months of prolonged corticosteroid use. It is dose-dependent and relatively independent of the relative potency of the agent.

5.4 INFECTION FACILITATION: THE PITFALL OF MISDIAGNOSIS

Corticosteroids locally suppress the immune response, and this converts self-limiting infections into severe conditions. Three scenarios are worth mentioning:

Herpetic keratitis. Ocular herpes simplex (dendritic epithelial keratitis) is one of the absolute contraindications to topical corticosteroids alone. Administration of corticosteroids in a patient with undiagnosed dendrite may progress to severe stromal keratitis, desemetocoele, and perforation. Herpetic keratitis presents as a red eye with a foreign body sensation, corneal hypoesthesia, and the classic dendritic tree figure seen with fluorescein^[21].

Fungal keratitis. In patients with a history of ocular trauma due to plant material (twig, leaf, soil) or contact lens wearers, corticosteroids without antifungals transform fungal

keratitis into a therapeutic disaster, with a prolonged clinical course and an outcome that is often blind.

Acanthamoeba. In contact lens wearers with poor hygiene, especially exposure to tap water or swimming pools, *Acanthamoeba keratitis* can be treated initially as bacterial with associated corticosteroids, with progressive worsening.

RED FLAG: never prescribe without an ophthalmologist

Commercial combinations that associate corticosteroids with antibiotics (dexamethasone plus tobramycin, dexamethasone plus neomycin and polymyxin, prednisolone plus sulfacetamide) are widely sold in Brazil and widely misused. The generalist should not prescribe them empirically for red eye. The presence of the antibiotic does not protect against herpes, fungus or amoeba; on the contrary, it can mask the clinical worsening. Any prescription of eye drops with corticosteroids must be made or authorized by an ophthalmologist, with a defined plan of duration and reevaluation.

5.5 THE PATIENT WHO SELF-MEDICATES WITH CORTICOSTEROIDS

A recurring scenario in Brazil: a patient who once received a combined eye drop (corticosteroid plus antibiotic) for conjunctivitis, thought it worked well, and started to buy and use it repeatedly, without guidance. Years later, he presents with slowly progressive visual loss. Examination reveals advanced optic disc cavitation and significant visual field loss: **irreversible cortisonic glaucoma**.

The general practitioner can stop this cascade by simply actively asking, at any visit of a patient with chronic ocular complaint, about the use of eye drops and, specifically, about **which bottles the patient keeps at home and uses on their own**. Corticosteroid review and discontinuation, referral to an ophthalmologist for IOP measurement, fundoscopy, and campimetry are interventions that can preserve useful vision for the rest of the patient's life.

6 SELF-MEDICATION WITH EYE DROPS IN BRAZIL: SOCIOCULTURAL CONTEXT

Ophthalmic self-medication in Brazil is rooted in sociocultural and economic determinants. Although the National Survey on Access, Use, and Promotion of Rational Use of Medicines (PNAUM) does not isolate eye drops as a primary category in its consolidated reports, it is observed in Brazilian clinical practice that two groups are especially vulnerable to the irrational use of eye drops.

The first group is young and middle-aged adults with occupational complaints related to prolonged use of screens (Computer Vision Syndrome), who present asthenopia and compensatory hyperemia and spontaneously resort to topical vasoconstrictors for the

cosmetic appeal of eye whitening. **The second group** is the geriatric population, in which the physiological Dry Eye Syndrome of aging and glaucoma overlap with systemic polypharmacy. In this age group, the sharing of vials, the lending of medicines between spouses, family members or neighbors, is a common practice, subjecting the elderly to risks of toxicity by beta-blockers or corticosteroids not prescribed for them.

There is specific literature on the misuse of over-the-counter drugs in the elderly. A North American study with the elderly showed that more than 1/3 use at least one IPM, and that concomitant use with prescriptions or supplements is frequent, creating potential for interactions. Adverse events related to OTCs are implicated in emergency hospitalizations in this population, and misuse was characterized into four categories: related to age, interaction with other medications, worsening of existing conditions, and deviation from package insert instructions^[22]. Although the study addresses MIPs in general, its conclusions apply directly to the ophthalmic setting, where lubricants, ocular decongestants, and antihistamine/vasoconstrictor combination products are classic examples of MIPs with the potential for misuse.

Two regulatory and commercial factors support this panorama in Brazil. The first is the classification of many ophthalmic formulations (simple lubricants and decongestants) as Over-the-Counter Drugs (OTC), according to Anvisa's Collegiate Board Resolution (RDC) No. 98/2016. The free disposal of these bottles on the shelves and counters of pharmacies, without a pharmacist barrier, creates a cognitive bias of zero risk. The second factor is advertising: advertising for eye decongestants aggressively focuses on whitening and immediate relief, omitting or minimizing the risks of rebound effect and systemic contraindications.

7 BENZALKONIUM CHLORIDE AND THE TRANSITION TO PRESERVATIVE-FREE FORMULATIONS

The topic of preservatives in eye drops deserves its own treatment in this chapter, given its specific relevance for patients with chronic use of ocular medication, especially glaucomatous medication, but also patients with Dry Eye Syndrome, who constitute a significant portion of elderly patients treated in primary care.

7.1 WHY BAK IS PROBLEMATIC

Benzalkonium chloride (BAK) is a quaternary ammonium molecule and the most widely used preservative in eye drops, present in **approximately 70% of topical formulations**^[13]. There is an uncomfortable rule of thumb in this field: *the antimicrobial*

efficacy of a preservative is inversely proportional to its safety for the ocular surface. BAK is a cationic detergent that acts by altering the permeability of the cell membrane: at concentrations of 0.05 to 0.1% it induces necrosis, and at 0.01% it induces apoptosis. Commercial formulations use BAK in concentrations between 0.004 and 0.02%.

Why is BAK still so widely used? It's not just inertia. BAK increases the penetration of the active ingredient into the anterior chamber precisely because of its detergent properties, compromising the corneal barrier in order to facilitate the delivery of the drug. But this same commitment is what generates chronic toxicity.

The toxicological mechanisms described are threefold: detergent effect on the tear film (altering the outer lipid layer); direct toxic effect on the corneal and conjunctival epithelium (loss of goblet cells, squamous metaplasia, apoptosis); and immunoallergic effect. There is also a deeper mechanistic axis, mitochondrial: due to its cationic nature, BAK selectively interacts with mitochondria (the only negatively charged intracellular compartment), induces mitochondrial fragmentation and oxidative stress, and can inhibit mitochondrial function by more than 90%^[13]. Mitochondrial dysfunction is now described as a contributor to ocular surface disease, age-associated corneal diseases, and normal corneal aging.

7.2 CLINICAL MAGNITUDE

The consistency of the literature is remarkable. The prevalence of ocular surface disease (OSD) among chronic glaucomatous patients on preserved topical therapy with BAK is reported to be between **30% and 70%**, compared with only 5% to 30% in adults of the same age without glaucoma^[13]. The total dose of BAK, number of medications, drops per day, duration of therapy, correlates with the prevalence and severity of OSD.

Clinical manifestations in glaucomatous patients under BAK include pain and discomfort (burning, pruritus, foreign body sensation), paradoxical tearing, increased corneal and conjunctival staining by fluorescein, reduced tear film breakdown time (BUT), reduced Schirmer tear film breakage, increased punctate keratitis, and worsening OSDI (Ocular Surface Disease Index) scores. There are also surgical consequences: BAK-induced subepithelial inflammation and conjunctival fibrosis reduce the success of trabeculectomy (filtering surgery for glaucoma) and there is a higher rate of cataract surgery in eyes under prolonged hypotensive therapy^[13].

7.3 THE SWITCH EVIDENCE: ODDONE STUDY 2024

A prospective, multicenter study conducted by Oddone et al. in 2024 provides the best recent evidence for the generalist. In 38 patients with open-angle glaucoma or ocular hypertension, using latanoprost with BAK and presenting with signs and symptoms of OSD, with uncontrolled IOP, switching to the fixed combination tafluprost plus timolol without preservative (PF-TTFC) resulted, after 3 months, in^[23]:

- a) reduction in mean 24-hour IOP from 17.8 mmHg (95% CI 17.1 to 18.6) to 15.3 mmHg (95% CI 14.6 to 16.1), $p < 0.001$;
- b) better night control (-2.9 mmHg) than day control (-2.3 mmHg);
- c) improvement of fluorescein corneal staining in 52.6% of the patients; worsening by only 10.5%;
- d) improvement of conjunctival hyperemia in 63.3%; worsening by only 5.3%;
- e) significant reduction in the mean size of corneal wing cells under in vivo confocal microscopy, with $p < 0.005$, suggesting recovery of the epithelium.

The study is particularly relevant because the effect combines additional pharmacological action (timolol) with the removal of BAK, and demonstrates that **the transition to PF does not compromise blood pressure control**, it may even improve it. Konstas et al., in a 2021 review, get straight to the point: ideally, future antiglaucomatous therapy should be 100% preservative-free, recognizing that cost, global availability, and the absence of long-term comparative studies limit this immediate transition^[24].

7.4 PRACTICAL IMPLICATIONS FOR THE GENERALIST

The generalist does not replace the ophthalmologist in the management of glaucoma, but can, and should, intervene in the following situations: a) patient on polytherapy for glaucoma (2 or more eye drops) reporting burning, dryness, persistent hyperemia or intolerance: discuss with the ophthalmologist the possibility of migration to formulations without preservatives; b) patient with pre-existing Dry Eye Syndrome (Sjögren's, elderly, contact lens wearer) starting glaucoma eye drops: guide preservative-free formulation from the beginning; c) patient in the preoperative period of filtering surgery or cataract: reducing the burden of BAK can improve surgical outcomes; d) patients in chronic use of any eye drops (including lubricants) more than 4 times a day: prescribe a formulation without preservatives.

It is worth noting that even the classic timolol has a preservative-free version available in a single-dose vial; the pharmaceutical infrastructure for PF exists, and the remaining bottleneck is more economical and logistical than pharmacological^[11, 31].

8 THE PATIENT USING ADVANCED OPHTHALMIC TREATMENTS

This section addresses a growing reality of primary care: patients who have specialized eye treatments, monthly intravitreal injections, extended-release implants, prescription dry eye therapies, frequently arrive at the generalist's office and the emergency room. The generalist does not need to be an expert in these treatments, but needs to recognize the patient, identify complications, conduct the initial approach, and refer appropriately.

8.1 THE PATIENT WHO HAS INTRAVITREAL INJECTIONS (ANTI-VEGF)

Intravitreal antiangiogenic agents (bevacizumab, ranibizumab, aflibercept, faricimab) have revolutionized the treatment of retinal diseases that until two decades ago were an important cause of blindness: age-related macular degeneration (AMD) in the neovascular form, diabetic macular edema, and retinal venous occlusion^[25]. These patients, typically elderly people with diabetes or vascular disease, receive intravitreal injections on a monthly or bi-monthly basis for consecutive months or years. The sustained efficacy of aflibercept in neovascular AMD was demonstrated with maintenance of visual gain at 96 weeks in the VIEW 1 and VIEW 2 studies^[34].

What the generalist needs to recognize

Infective endophthalmitis is the most devastating and most urgent complication of intravitreal injections. The reported incidence ranges from 0.01% to 0.26%, but the visual outcome is often catastrophic if treatment is delayed. The most common agents are coagulase-negative staphylococci (*S. epidermidis*) of the conjunctival flora and viridans streptococci of the oral flora^[25].

RED FLAG: Same-day forwarding

Patient who has received intravitreal injection within the last 7 to 14 days and presents with:

- a) decrease in visual acuity (even slight);
- b) deep eye pain (not just superficial burning);
- c) severe ocular hyperemia;
- d) hypopyum (yellowish liquid level in the anterior chamber, visible to inspection);

must be referred on the same day to the ophthalmologist on duty. Treatment is intravitreal antibiotic injection or vitrectomy within hours. Not prescribing topical antibiotics in the ER delays diagnosis without treating the intraocular infection.

Other relevant complications include **retinal detachment** (up to 0.6%; may manifest as sudden perception of floaters, flashes of light, or dark curtain in the visual field); **vitreous**

hemorrhage (0.02% to 4.5%; suddenly blurry or opaque vision); and **acute IOP elevation** (usually self-limited, resolves within hours of anti-VEGF injection)^[25].

Systemic effects: what we know

Intravitreal anti-VEGF targets the systemic circulation and reduces plasma VEGF. The literature on systemic effects is mixed: most large studies have not demonstrated a significant increase in cardiovascular events (infarction, stroke, thromboembolic events) in general populations, but signs of increased risk persist in subgroups, particularly in type 2 diabetics, in which a recent analysis associated anti-VEGF with a higher cumulative incidence of systemic adverse events at 5 years (37.0% vs 18.4%)^[25]. For the generalist, the recommendation is clinical surveillance of blood pressure, cardiovascular and renal control in these patients, without reflex alarm.

Clinical pearl

Do not discontinue anticoagulation or antiplatelet therapy for intravitreal injections without discussing with the ophthalmologist who is applying the treatment. The ocular hemorrhagic risk of the procedure is low and does not justify the interruption of the antithrombotic in patients with a firm cardiovascular indication, the interruption carries a substantial risk of thromboembolic event.

8.2 THE PATIENT WITH AN EXTENDED-RELEASE INTRAOCULAR IMPLANT

Several extended-release ocular implants are now in clinical use in Brazil and worldwide, offering sustained therapy for months to years with a single application. The main ones include Ozurdex® (biodegradable dexamethasone, 6 months clearance) for diabetic macular edema, venous occlusion edema, and uveitis; Iluvien® (non-biodegradable fluocinolone, 36 months) for chronic diabetic macular edema; Yutiq® (fluocinolone, 36 months) for posterior uveitis; and Durysta® (biodegradable intracameral bimatoprost, 3 to 4 months) for glaucoma^[26, 33].

For the generalist, two scenarios demand attention:

Implant migration from Ozurdex to the anterior chamber. In pseudophakic patients with compromised posterior capsule, the dexamethasone implant may migrate to the anterior chamber within the first few days after injection, causing acute corneal edema^[27]. The patient presents with red eye, pain, blurriness and, on examination, the implant cylinder can be seen in the anterior chamber. **Refer immediately: early removal reduces the risk of permanent corneal decompensation.**

Implant-induced cortisomic glaucoma. Patients with Ozurdex, Iluvien, and Yutiq are at substantial risk of IOP elevation, intravitreal triamcinolone, a similar agent, elevates IOP

in up to 2/3 of patients^[25]. IOP monitoring is the responsibility of the ophthalmologist, but the generalist who detects ocular hypertension in a patient with previous implantation must ensure that ophthalmologic follow-up is up to date.

8.3 THE PATIENT ON PRESCRIPTION DRY EYE THERAPY

Dry eye is a multifactorial ocular surface disease characterized by loss of tear film homeostasis, in which lacrimal hyperosmolarity, inflammation, ocular surface damage, and sensorineural abnormalities play etiological roles^[28, 30]. The overall prevalence, considering symptoms, varies between 5% and 50% depending on the population. The tear film is structured in three layers (lipid, aqueous, mucin), and the disease can be classified as aqueous deficient, evaporative (most common, linked to meibomian gland dysfunction) and mixed.

The patient with moderate to severe dry eye often receives staggered therapy that includes not only lubricants but also prescription anti-inflammatory agents such as cyclosporine 0.05% (Restasis®), cyclosporine 0.1% (Verkazia®/Ikervis®), and lifitegrast 0.5% (Xiidra®). These therapies need continuous use for months to achieve full effectiveness, and adherence is often compromised by burning sensation at the beginning of treatment, cost, and complexity of the regimen^[28].

Clinical pearl

When seeing a patient using cyclosporine or topical lifitegrast referring to not being noticeable. Reinforcing adhesion and ensuring adequate concomitant lubrication (preferably preservative-free) is more useful than suggesting treatment change on your own.

Other interventions for dry eye that the patient may mention include **punctal plugs** (occluders of the tear canaliculi to increase the permanence of natural tears and eye drops), whose evidence of benefit is, according to Cochrane, limited, and whose relevant adverse events include epiphora (excessive tearing) in up to 82% of patients in some studies and spontaneous loss in up to 30%^[29]; **warm compresses** and **intense pulsed light (IPL)** for meibomian dysfunction; and **autologous serum** in refractory cases.

9 STRATEGIES FOR RATIONAL USE AND THE ROLE OF THE GENERALIST

Reversing the irrationality in the use of eye drops requires a systemic approach, in which the general practitioner acts as the main *gatekeeper* of the patient's health. The strategies are divided into direct clinical actions and technological integrations.

9.1 MEDICATION RECONCILIATION AND HEALTH LITERACY

The most immediate change should occur in the anamnesis. The generalist should abandon the passive question (Do you take any medication?) and adopt active search: Do you use any eye drops, eye ointments, nose drops, patches or sprays?. When identifying the use, patient education should be incisive: explain the anatomy of nasolacrimal drainage and teach in person the Lacrimal Point Occlusion (OPL) technique and the need for a 5-minute interval between different vials.

9.2 PRESCRIPTIVE SECURITY

The prescription of eye drops does not allow for ambiguity. Generic prescriptions containing only 1 drop every 8 hours are unacceptable. The prescription must specify: a) laterality (OE, left eye; OD, right eye; AO, both eyes); b) the exact concentration of the solution; c) the duration of treatment, especially for antibiotics and corticosteroids, avoiding inadvertent continuous use; d) explicit guidelines on not touching the tip of the bottle on the eyelashes to avoid contamination of the reservoir.

9.3 TELEMEDICINE AS A SCREENING TOOL

The expansion of telemedicine in Primary Care offers a window of opportunity for red-eye complaints. Although fine diagnosis by slit lamp is impossible remotely, the physician can differentiate alarm signs that require immediate ophthalmological referral (sudden low visual acuity, profound eye pain, severe photophobia, colored halos, anisocoria, trauma, chemical exposure) from self-limited allergic or viral conditions that can be managed initially without antibiotics, preventing the patient from resorting to self-medication at the pharmacy.

9.4 ACTIVE PHARMACOVIGILANCE

The generalist is the front line of detection of systemic adverse drug reactions (ADRs) resulting from eye drops. In the face of refractory bradycardia in an elderly person (investigate the use of topical timolol), iatrogenic Cushing's syndrome (investigate abusive ocular corticosteroids) or herpetic keratitis in a patient with a history of previous use of combined corticosteroids, it is an ethical and epidemiological duty to notify Anvisa through the VigiMed platform. It is this data feed that allows the regulatory agency to issue health alerts and, eventually, reclassify the sales status of certain compounds.

Summary table: ophthalmic therapeutic classes

The following table consolidates, in a quick consultation format, the main classes of eye drops involved in irrational use, their predominant risks, and the expected conduct of the general practitioner.

Table 2

Summary table of ophthalmic therapeutic classes: examples, local risk, systemic risk and practical conduct of the general practitioner

Class	Common examples	Local (ocular) risk	Main systemic risk	Practical conduct of the generalist
Corticosteroids	Dexamethasone, prednisolone, fluorometholone, loteprednol, difluprednate.	Cortisonic glaucoma (irreversible); posterior subcapsular cataract; masking of herpetic, fungal, and amoebic keratitis.	Suppression of the hypothalamic-pituitary-adrenal axis (rare, in chronic abusive use).	Never prescribe empirically for red eye. Every prescription authorized by an ophthalmologist. Monitor IOP if use longer than 10 days.
Vasoconstrictors	Naphazoline, phenylephrine, tetrahydrozoline, oxymetazoline.	Severe rebound effect (chronic hyperemia); conjunctivitis, drug-related.	Hypertensive crises and tachyarrhythmias (all); CNS depression in children (particularly imidazoles, contraindicated).	Investigate the underlying cause (allergy, dryness, visual fatigue). Discourage purely cosmetic use.
Beta-blockers	Timolol (treatment of glaucoma).	Dry eye, hyperemia, contact allergy.	Severe bradycardia, atrioventricular blocks, lethal bronchospasm (asthma/COPD).	To investigate use in older people with syncope or unexplained bradycardia. Teach OPL technique.
Antibiotics	Tobramycin, ciprofloxacin, moxifloxacin, gentamicin.	Corneal epithelial toxicity, delayed healing.	Promotion of antimicrobial resistance (One Health concept).	Avoid empirical prescription for watery secretions (viral suspicion). Restrict to purulent frames with defined criteria.
Lubricants (with preservatives)	Benzalkonium chloride (BAK) formulas.	Tear film rupture, epithelial cell apoptosis, exacerbation of Dry Eye Syndrome.	Null systemic relevance.	For chronic use (more than 4 times/day), prescribe a preservative-free formulation (without preservatives).

Class	Common examples	Local (ocular) risk	Main systemic risk	Practical conduct of the generalist
Prostaglandin analogues	Latanoprost, bimatoprost, travoprost, tafluprost.	Irreversible darkening of the iris; eyelash growth; periorbital fat atrophy; conjunctival hyperemia.	Clinically minimal systemic relevance.	Reassure the patient about expected aesthetic changes, to avoid abandonment of glaucoma treatment.
Antihistamines/dual action	Olopatadine, ketotifen, alcaftadine, epinastin.	Well tolerated; Occasional initial irritation.	Minimum.	First-line for allergic conjunctivitis with pruritus. It adequately replaces vasoconstrictors in this indication.
Immunomodulators (for dry eye)	Cyclosporine 0.05% and 0.1%; lifitegrast 0.5%.	Frequent initial burning; intolerance in some patients.	Negligible systemic absorption.	Strengthen adherence: clinical effect requires 3 to 6 months. Follow up together with an ophthalmologist.

Source: prepared by the authors, based on the references cited throughout the chapter.

10 FINAL CONSIDERATIONS

The underestimation of topical ophthalmic drugs is a historical error that exacts an unacceptable price in terms of visual morbidity and systemic morbidity and mortality. As demonstrated throughout this chapter, a drop of eye drops carries real pharmacological potential: it crosses mucosal barriers, escapes hepatic metabolism, and interacts with systemic receptors.

The mitigation of cortisonic glaucoma, antimicrobial resistance on the ocular surface and cardiovascular crises by sympathomimetics and beta-blockers is not the exclusive task of the ophthalmologist. On the contrary, the change of this paradigm rests firmly in the hands of the general practitioner. It is in Primary Care, in the clinical ward and in the emergency room that medication reconciliation saves lives. And it is also in these spaces that the generalist must recognize the patient using advanced ophthalmological treatments (intravitreal injections, implants, therapies prescribed for dry eye) to identify complications in time, refer appropriately, and not interfere harmfully with specialized conducts.

The rational use of ophthalmic drugs requires, above all, the recovery of respect for ophthalmic drop: it is not a cosmetic, it is not an innocuous solution; It is a full-fledged drug that requires precise indication, exact dosage, and strict clinical surveillance. The integration between primary care and ophthalmology, via active communication, medication

reconciliation and timely referral, is the way for this therapeutic category to stop being a blind spot in the health system.

Editorial note on figures and images. *This chapter contains no pictures or images. All visual elements used are tables (Table 1 and Table 2), prepared by the author based on the references cited; Specific sources are indicated at the bottom of each table.*

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THE INFLUENCE OF THE THERAPEUTIC ALLIANCE ON ADHERENCE TO PSYCHOLOGICAL TREATMENT: A LITERATURE REVIEW

A INFLUÊNCIA DO VÍNCULO TERAPÊUTICO NA ADEÇÃO AO TRATAMENTO PSICOLÓGICO: UMA REVISÃO DA LITERATURA

LA INFLUENCIA DEL VÍNCULO TERAPÉUTICO EN LA ADHESIÓN AL TRATAMIENTO PSICOLÓGICO: UNA REVISIÓN DE LA LITERATURA



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ABSTRACT

Adherence to psychological treatment remains a significant challenge in clinical practice, particularly given the rates of premature dropout observed across different therapeutic contexts. In this scenario, the therapeutic bond has been consistently identified as a key factor associated with patient engagement and continuity in psychotherapy. This study aimed to understand, based on scientific literature, how the therapeutic bond influences adherence to psychological treatment. A narrative literature review was conducted using the Scielo and Google Scholar databases, including articles published between 2015 and 2025. Eligible studies were full-text, freely available articles written in Portuguese or English that addressed the therapeutic bond within the context of psychotherapy. After applying the inclusion and exclusion criteria, 14 articles were selected for analysis. The findings indicate convergence regarding the central role of the therapeutic bond in treatment adherence, highlighting elements such as empathy, trust, collaboration, and shared goal-setting as factors associated with patients' permanence in the psychotherapeutic process. The studies also show that a fragile therapeutic alliance is related to treatment dropout, particularly in institutional settings, psychotherapy with children and adolescents, and online modalities. It is concluded that the therapeutic bond is an essential component of psychotherapy effectiveness, functioning as a protective factor against dropout and should be understood as a dynamic relational process, sensitive to clinical contexts and patients' needs.

Keywords: Therapeutic Bond. Adherence to Psychological Treatment. Therapeutic Relationship. Psychotherapy.

RESUMO

A adesão ao tratamento psicológico constitui um desafio relevante na prática clínica, especialmente diante dos índices de abandono observados em diferentes contextos terapêuticos. Nesse cenário, o vínculo terapêutico tem sido apontado como um dos principais fatores associados à permanência e ao engajamento do paciente na psicoterapia.

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O presente estudo teve como objetivo compreender, a partir da literatura científica, como o vínculo terapêutico influencia a adesão ao tratamento psicológico. Trata-se de uma revisão narrativa da literatura, realizada nas bases Scielo e Google Acadêmico, contemplando artigos publicados entre 2015 e 2025. Foram incluídos estudos completos, disponíveis gratuitamente, em português ou inglês, que abordassem o vínculo terapêutico no contexto da psicoterapia. Após a aplicação dos critérios de inclusão e exclusão, 14 artigos compuseram o corpus da revisão. Os resultados indicam convergência quanto ao papel central do vínculo terapêutico na adesão ao tratamento psicológico, destacando elementos como empatia, confiança, colaboração e definição compartilhada de objetivos como fatores associados à permanência do paciente no processo psicoterapêutico. Os estudos também evidenciam que a fragilidade da aliança terapêutica está relacionada ao abandono, especialmente em contextos institucionais, atendimentos com crianças e adolescentes e modalidades online. Conclui-se que o vínculo terapêutico constitui um componente essencial da efetividade da psicoterapia, atuando como fator protetivo frente ao abandono e devendo ser compreendido como uma construção relacional dinâmica, sensível às características do contexto clínico e às necessidades do paciente.

Palavras-chave: Vínculo Terapêutico. Aliança Terapêutica. Adesão ao Tratamento Psicológico. Psicoterapia.

RESUMEN

La adhesión al tratamiento psicológico constituye un desafío relevante en la práctica clínica, especialmente ante los índices de abandono observados en diferentes contextos terapéuticos. En este escenario, el vínculo terapéutico ha sido señalado como uno de los principales factores asociados a la permanencia y al compromiso del paciente en la psicoterapia. El presente estudio tuvo como objetivo comprender, a partir de la literatura científica, cómo el vínculo terapéutico influye en la adhesión al tratamiento psicológico. Se trata de una revisión narrativa de la literatura, realizada en las bases de datos SciELO y Google Académico, incluyendo artículos publicados entre 2015 y 2025. Se incluyeron estudios completos, disponibles gratuitamente, en portugués o inglés, que abordaran el vínculo terapéutico en el contexto de la psicoterapia. Tras la aplicación de los criterios de inclusión y exclusión, 14 artículos conformaron el corpus de la revisión. Los resultados indican convergencia respecto al papel central del vínculo terapéutico en la adhesión al tratamiento psicológico, destacando elementos como empatía, confianza, colaboración y definición compartida de objetivos como factores asociados a la permanencia del paciente en el proceso psicoterapêutico. Los estudios también evidencian que la fragilidad de la alianza terapéutica está relacionada con el abandono, especialmente en contextos institucionales, atención a niños y adolescentes y modalidades en línea. Se concluye que el vínculo terapéutico constituye un componente esencial de la efectividad de la psicoterapia, actuando como un factor protector frente al abandono y debiendo comprenderse como una construcción relacional dinámica, sensible a las características del contexto clínico y a las necesidades del paciente.

Palabras clave: Vínculo Terapéutico. Alianza Terapéutica. Adhesión al Tratamiento Psicológico. Psicoterapia.

1 INTRODUCTION

Adherence to psychological treatment is one of the main challenges of contemporary clinical practice, especially in view of the high dropout rates observed in different care contexts. Studies indicate that a significant portion of patients interrupt psychotherapy early, often before achieving consistent clinical changes, which compromises the effectiveness of mental health care [1, 2]. In view of this scenario, it is essential to understand the factors that favor the patient's permanence in the therapeutic process and sustain engagement throughout the treatment.

Among the elements associated with adherence, the therapeutic bond, often called therapeutic alliance, is consistently pointed out as one of the main predictors of continuity and success of psychotherapy. Since Bordin's classic formulation [3], the therapeutic alliance is understood as a collaboration between therapist and patient, involving the establishment of shared goals, agreement on treatment tasks, and the construction of an affective bond based on trust and cooperation [3]. On the other hand, Gelso & An [4] prefer to name the phenomenon as a therapeutic relation, with the working alliance being one of the three components of this relation, which is also composed of the real relation and the transference-countertransference configuration). However, regardless of the theoretical approach adopted, reviews and meta-analyses reinforce that the quality of the therapeutic relationship is associated with better clinical outcomes and greater adherence to treatment [5, 6].

The literature points out that elements such as empathy, qualified listening, emotional validation, conscious collaboration, and joint goal setting are central components of the therapeutic bond and have a direct impact on patient engagement [7, 8]. In addition, studies indicate that the appropriate management of ruptures in the therapeutic relationship can strengthen the alliance and contribute to the continuity of treatment, instead of necessarily representing a factor of abandonment [9].

The relevance of the therapeutic bond becomes even more evident in specific contexts, such as psychotherapy with children and adolescents, care provided in school services, online modalities, and follow-up of patients with greater emotional vulnerability. In these scenarios, institutional, family, and contextual factors can interfere with adherence, increasing the risk of dropout [10, 11]. Even so, evidence suggests that a well-established therapeutic bond can act as a protective factor, minimizing the impact of these barriers and favoring the patient's permanence in the psychotherapeutic process [1, 2].

Despite the recognition of the centrality of the therapeutic link, it is observed that the scientific production on the subject is heterogeneous, involving different methodological designs, populations, and clinical contexts. In addition, there are still gaps related to the

systematization of the findings, especially with regard to the integrated understanding of how the therapeutic bond influences adherence to psychological treatment in different modalities of psychotherapy [5, 9]. In this sense, narrative reviews play an important role in allowing the critical articulation of evidence, favoring a broader understanding of complex and multifactorial phenomena, such as the therapeutic relationship.

Therefore, the present study aims to understand, based on the scientific literature, how the therapeutic bond influences adherence to psychological treatment. It seeks to review scientific productions published between 2015 and 2025 that address the role of the therapeutic bond in the engagement, permanence, and outcomes of psychotherapy, identifying convergences, theoretical contributions, and gaps in scientific production on the subject.

2 METHOD

The research is a narrative review of the literature, with a qualitative approach and descriptive character, whose objective was to gather, analyze and discuss scientific productions on the influence of the therapeutic bond on adherence to psychological treatment. The narrative review was chosen because it allows a broad and interpretative analysis of the theme, favoring the integration of different theoretical perspectives and clinical contexts [10].

The search for studies was carried out in the SciELO and Google Scholar databases, selected for their relevance to the area of Psychology and for the wide availability of open access articles. The following search strategy was used: ("therapeutic bond" OR "therapeutic alliance" OR "therapist-patient relationship") AND ("adherence to psychological treatment" OR "therapeutic engagement" OR "abandonment of psychotherapy"). Articles published between 2015 and 2025, written in Portuguese or English, were considered.

The inclusion criteria were: complete scientific articles, available free of charge, that directly addressed the therapeutic bond in the context of psychotherapy, regardless of the theoretical approach, modality of care (individual, group, face-to-face or online) or age group of the public studied. The exclusion criteria included: articles published before 2015; texts with restricted access; duplicate studies; productions that dealt with the professional-patient relationship in other areas of health; and studies that addressed adherence to psychological treatment without an explicit relationship with the therapeutic bond.

The selection of studies occurred in two stages: initially by reading the titles and abstracts and, later, by reading the eligible articles in full. At the end of the process, 14 studies met the established criteria and composed the corpus of the review.

The analysis of the articles was carried out in a qualitative and interpretative way, seeking to identify thematic convergences, theoretical contributions, main findings and gaps in scientific production on the therapeutic bond and adherence to psychological treatment. The results were organized in a descriptive way, with the support of a synthesis table for the systematization of the evidence.

3 RESULTS

The initial search resulted in the identification of 54 studies. After the removal of duplicates ($n = 8$), the exclusion of dissertations, theses, course completion papers, books, and materials without access to the full text ($n = 23$), as well as the elimination of studies that did not directly address the relationship between the therapeutic bond and adherence to psychological treatment ($n = 9$), 14 articles that met the established criteria were included.

The selected studies were analyzed in terms of their methodological characteristics, main findings, and relationship with the therapeutic bond and adherence to psychological treatment. The synthesis of this evidence is presented in Table 1, which brings together productions with different designs, including literature reviews, clinical case studies, experience reports and documentary research carried out in Psychology school services.

Table 1

Articles included in the narrative review

Author(s) and year	Type of study	Main results	Relationship with the therapeutic bond and adherence
Adami, Portella & Dias (2020)	Qualitative study of a clinical case with borderline patients; interviews to understand engagement and therapeutic prognosis.	They observe that the breach of trust in psychotherapy is a decisive factor for abandonment; When trust is established, the borderline patient can build a bond, but fears dependence and may give up so as not to be abandoned first.	They highlight that the construction of a secure therapeutic bond is central to keeping borderline patients in therapy, showing that the relationship of trust is a key component of adherence.
Andrade, Fernandes and Silveira (2025)	Experience report, clinical internship in a psychological clinic-school with direct observation of interactions and records in a reflective diary during supervision (Analytical-Behavioral Therapy).	They observe that the therapeutic alliance is built through the direct observation of interactions, supervised reflections and field diaries, which favors the development of therapeutic skills in the intern.	They highlight the importance of the therapeutic alliance in the training process, the bond with the client serves as a basis to improve interpersonal and professional skills, reinforcing the relevance of the therapeutic bond for the effectiveness and maintenance of interventions.
Benetti, Mattos, Silva &	Clinical case study in psychoanalytic psychotherapy;	They observed that the patient's lack of insight and an immature defensive style were	They highlight that individual factors of the patient and the development of the

Bittencourt (2017)	analysis of 20 sessions using the <i>Adolescent Psychotherapy Q-Set (APQ)</i> and therapist's clinical notes.	predictors of psychotherapy abandonment.	therapeutic bond directly influence adherence, evidencing the need for attention to the therapeutic alliance in adolescence.
Brito, Montezuma, Melo and Moreira (2020)	This is a qualitative study, based on interviews with psychologists in training, analyzed through a phenomenological and hermeneutic approach.	The authors identified that the training process crosses insecurities, the need for supervision and emotional challenges, with the therapeutic relationship being the main axis of support for clinical practice. The bond appears as a condition for clinical management and patient engagement.	It contributes by demonstrating that the therapeutic bond is structuring both for the development of the therapist and for the patient's permanence, reinforcing that the quality of the relationship favors adherence and reduces the risk of abandonment.
Château & Leugi (2025)	Qualitative research with 22 Brazilian ACT therapists, through semi-structured interviews.	They observe that Brazilian ACT therapists integrate theories (such as Analytical-Functional Psychotherapy and Analytical-Behavioral Therapy), and adapt interventions in an experiential and idiographic way for their clients.	They highlight that flexibility in therapeutic practice and individual adaptation (idiographic) reinforce the importance of the therapeutic bond and alliance for treatment adherence, especially in acceptance and commitment therapy.
Des Essarts, Brenner, Ffner & Ramires (2022)	Narrative review; The authors selected studies on abandonment of psychoanalytic psychotherapy by adolescents and analyzed sociodemographic, clinical, and behavioral factors.	They observe that factors such as age, gender, antisocial behavior and clinical variables influence the abandonment of psychotherapy by adolescents.	They highlight that the quality of the therapeutic alliance is decisive for the continuity or abandonment of treatment, reinforcing the importance of the therapeutic bond for adherence.
Fraga, Hack, Valentini, Brenner & Ramires, (2022)	Qualitative-exploratory study; Semi-structured interviews with 23 adolescents who were being followed up or who had abandoned psychoanalytic psychotherapy, data analysis by thematic analysis method.	They observe that central themes for those who remain include the "Therapeutic relationship" and "Changes resulting from psychotherapy", and for those who leave, "Therapeutic relationship", "Defenses and resistances of adolescents" and "Therapeutic alliance with those responsible" stand out.	They highlight that the therapeutic bond, both with the therapist and with those responsible for them, emerges as a key factor for adolescents' adherence to treatment, reinforcing the importance of strengthening the therapeutic alliance in psychotherapy contexts with this public.
Machado & Eizirik (2016)	Review of reviews and meta-analyses on therapeutic alliance; analyzed narrative reviews, systematic reviews and meta-analyses involving adults, children/adolescents, treatment dropout, attachment, cultural	Therapeutic alliance (TA) is consistently associated with treatment outcomes, but its effects are small, and other factors also strongly influence outcomes.	It reinforces the central importance of the therapeutic bond for the adherence and success of psychological treatment, in addition to pointing out gaps in the investigation of how the therapeutic alliance affects different types of patients and contexts.

	differences, among others.		
Maffini & Cassel (2020)	Single, systematic case study; adolescent attended at a university psychology school service, with an exploratory character.	They observe that the lack of availability of schedules compatible with the school service, low family adherence and a fragile therapeutic alliance contributed to the premature interruption of treatment.	They highlight that the therapeutic bond and the support of family members are crucial factors for adherence, reinforcing the importance of strategies to strengthen this alliance in psychotherapy with adolescents.
Paez, Nunes & Hirakata (2015)	Quantitative-retrospective study; analysis of 600 medical records of children undergoing psychoanalytic psychotherapy in Porto Alegre.	It found that 24.2% of the children were discharged; Predictors of discharge included prior neurological evaluation and longer duration of treatment.	They highlight that the construction of the therapeutic alliance and the parents' understanding of the need for psychotherapy can influence adherence and continuity of treatment.
Peixoto et al. (2016)	Single case study; brief psychodynamic psychotherapy with analysis of the therapist's verbal interventions and therapeutic alliance measures throughout the sessions.	They point out that the therapeutic alliance increased progressively throughout the process, especially when the therapist's interventions were adjusted according to the phase of psychotherapy, favoring greater patient engagement.	They highlight that the study shows how the modulation of therapeutic interventions strengthens the therapeutic alliance, directly contributing to the maintenance of the bond and favoring adherence to psychological treatment.
Pimentel, Fonte and Martins (2020)	Quantitative-retrospective study; Analysis of 68 adults attended at a psychology teaching clinic, considering sociodemographic, institutional and clinical variables.	They observed that participants who abandoned psychotherapy early were generally younger, had a lower frequency of sessions, shorter intervention time, and more institutional difficulties	It points out the need for special attention to institutional and clinical variables (such as payment modality, frequency, intervention time) that can interfere with the therapeutic bond and, consequently, with treatment adherence, reinforcing that bond and therapeutic relationship are important factors for the patient to remain.
Rocha & Ferraz (2023)	Experience report (cognitive-behavioral approach) in a service-school.	They observed that the patient, even abandoning after a few sessions, reported significant improvement, which suggests that abandonment may indicate therapeutic autonomy and not just a withdrawal.	They highlight that the therapeutic alliance continues to be central, even with interruption, reinforcing that bonding and autonomy are relevant to understanding adherence and outcomes in psychotherapy.
Sei & Colavin (2016)	This is a descriptive documentary study (survey research, analysis of medical records, screening and case closure forms of a psychology school service).	They note that, among those who started psychotherapy in 2013, 24% dropped out during treatment; identify several reasons for abandonment: problems with the therapeutic alliance, institutional difficulties, external issues and unjustified absences.	They highlight that the fragility of the therapeutic alliance, as well as institutional and personal barriers, contributes to patient evasion, reinforcing the importance of the therapeutic bond for treatment adherence.

Source: prepared by the authors based on cited authors.

In addition to the methodological diversity, the studies analyzed contemplated different audiences and clinical contexts, including care with children, adolescents and adults, as well as interventions carried out in school services and in face-to-face and online modalities. Despite these variations, convergence was observed regarding the relational elements associated with adherence to psychological treatment, with emphasis on empathy, trust, collaboration, and clarity regarding therapeutic objectives. These components were recurrent in the studies as factors related to the patient's permanence in the psychotherapeutic process, regardless of the theoretical approach adopted.

In a convergent way, studies indicate that the quality of the therapeutic bond is directly associated with adherence to psychological treatment, with the fragility of the alliance being a recurrent factor in cases of abandonment. On the other hand, the construction of a therapeutic relationship based on trust, empathy and collaboration was associated with the patient's permanence in the psychotherapeutic process, regardless of the theoretical approach or the context of care.

4 DISCUSSION

The findings of this narrative review confirm that the therapeutic bond is a central element for adherence to psychological treatment, sustaining patient engagement and directly influencing the continuity and effectiveness of psychotherapy. The literature analyzed converges by indicating that the quality of the relationship established between therapist and patient plays a more consistent role in adherence than specific technical factors of the approaches, corroborating evidence already pointed out in previous reviews and meta-analyses [5, 6].

The interpretation of the results suggests that relational elements such as empathy, trust, collaboration, and shared goal setting function as mediating mechanisms between the therapeutic process and its outcomes. These components not only favor the patient's permanence in treatment, but also expand their emotional availability to cope with difficult content, strengthening the commitment to the psychotherapeutic process. Thus, the therapeutic bond is not only configured as an initial condition of psychotherapy, but as a dynamic construction, which is updated and strengthened throughout the clinical course [9].

The studies also indicate that the influence of the therapeutic bond becomes even more relevant in contexts marked by greater vulnerability to dropout, such as in care provided in school services, in psychotherapy with children and adolescents and in online modalities. In these situations, institutional, family, and contextual factors tend to interfere with

adherence, increasing the risk of early interruption. However, the analysis of the articles reveals that a consistent therapeutic bond can act as a protective factor, attenuating the impact of these barriers and favoring the patient's permanence in psychological care [1, 11].

With regard to population specificities, the literature reviewed indicates that, in child and adolescent care, the therapeutic bond goes beyond the daily relationship between therapist and patient, also involving those responsible and the family context. The absence of a solid alliance with these actors can weaken the therapeutic process, while their integration favors adherence and continuity of treatment. These findings reinforce the need for interventions that are sensitive to the particularities of development and the demands of the broader relational context [12].

In the context of online psychotherapy, the studies analyzed indicate that the therapeutic bond remains a central element, even if it requires specific adaptations related to the virtual setting. Aspects such as security, clarity in communication and ethical management of the digital space emerge as necessary conditions for maintaining the therapeutic alliance at a distance, showing that the quality of the relationship continues to be decisive for adherence, regardless of the modality of care.

When comparing the findings of this review with the previous literature, it is observed that it is in line with studies that highlight the therapeutic alliance as a robust predictor of psychotherapeutic success. However, the analyzed studies expand this understanding by evidencing the role of institutional, formative and contextual variables, often little explored in classical studies. This broadening points to the need to understand the therapeutic bond as a situated phenomenon, crossed by organizational, cultural and socioeconomic conditions that influence the clinical experience.

Among the limitations identified in the scientific production analyzed, the predominance of theoretical, narrative or qualitative studies stands out, with a lack of empirical investigations that use standardized measures to assess the therapeutic bond and its relationship with treatment adherence. In addition, the methodological and population heterogeneity of the studies makes it difficult to generalize the findings and points to the need for future research that explores, in a more systematic way, the management of ruptures in the therapeutic alliance and specific strategies for different clinical contexts.

In summary, the discussion of the results shows that the therapeutic bond should be understood as a dynamic relational process, central to adherence to psychotherapy and sensitive to the characteristics of the context and the population served. These findings reinforce the importance of clinical practices that prioritize the construction and maintenance of the therapeutic relationship as a fundamental axis of psychological care.

5 FINAL CONSIDERATIONS

This study aimed to understand, based on the scientific literature, the influence of the therapeutic bond on adherence to psychological treatment, through a narrative review of articles published between 2015 and 2025. The analysis of the selected productions showed that the therapeutic bond is a central element for the patient's permanence in psychotherapy, regardless of the theoretical approach or the modality of care.

The findings indicate that relational components such as empathy, trust, collaboration, and shared goal setting are key to sustaining patient engagement and favoring the continuity of the therapeutic process. In addition, the literature points out that the appropriate management of ruptures in the therapeutic relationship can strengthen the alliance and contribute to adherence, reinforcing the dynamic and procedural character of the bond.

The review also showed that the impact of the therapeutic bond is particularly relevant in contexts that are more vulnerable to dropout, such as school services, psychotherapy with children and adolescents, and online consultations. In these scenarios, institutional, family, and contextual factors can interfere with adherence, but a consistent therapeutic bond tends to act as a protective factor, minimizing the risk of dropout.

Among the limitations of the present study, the exclusively bibliographic nature of the review stands out, restricted to articles published in certain databases and languages, which may have limited the scope of the evidence analyzed. In addition, the methodological heterogeneity of the included studies makes it difficult to generalize the findings.

As a contribution, this work reinforces the centrality of the therapeutic bond as a structuring axis of adherence to psychological treatment, offering theoretical subsidies for clinical practice and for the training of psychotherapists. It is recommended that future research advances in the empirical investigation of the therapeutic bond, with the use of standardized instruments, analysis of breaks in the alliance, and exploration of specific strategies for different contexts and clinical populations.

In summary, the results of this review confirm that the therapeutic bond not only favors adherence to psychological treatment, but is an essential component of the effectiveness of psychotherapy, and should be understood as a dynamic relational construction, sensitive to the singularities of the clinical context and the needs of the patient.

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NURSING CARE FOR HYPERTENSION CONTROL IN PRIMARY HEALTH CARE: EFFECTIVENESS AND STRATEGIES

CUIDADOS DE ENFERMAGEM PARA O CONTROLE DA HIPERTENSÃO NA ATENÇÃO PRIMÁRIA À SAÚDE: EFICÁCIA E ESTRATÉGIAS

CUIDADOS DE ENFERMERÍA PARA EL CONTROL DE LA HIPERTENSIÓN EN ATENCIÓN PRIMARIA: EFICACIA Y ESTRATEGIAS



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ABSTRACT

Objective: To synthesize and discuss the scientific evidence on the role and effectiveness of nursing care in the control of Systemic Arterial Hypertension in Primary Health Care settings.

Method: This is a narrative literature review. The search was conducted in the LILACS, SciELO, and PubMed/MEDLINE databases, encompassing publications between 2020 and 2025. Nineteen relevant studies were selected, including randomized clinical trials, systematic reviews, cohort studies, and qualitative research. The synthesis of knowledge was organized into thematic categories.

Results: The most effective nursing interventions include: health education strategies (with a reduction in systolic blood pressure of up to 5.8 mmHg); blood pressure monitoring (with reductions of 3.3 to 8.5 mmHg); support for medication adherence; lifestyle modification programs; and nurse-led care models, such as nursing clinics and case management, which demonstrated reductions in systolic blood pressure between 5.4 and 12.41 mmHg.

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Outcomes include improved blood pressure control, increased adherence rates, enhanced disease knowledge, and improved quality of life.

Conclusion: The evidence confirms that nursing care is fundamental and highly effective for the control of hypertension in primary health care. Nurse-led interventions, particularly when integrated into collaborative models, result in better clinical outcomes.

Keywords: Hypertension. Nursing Care. Primary Health Care. Review. Health Education.

RESUMO

Objetivo: Sintetizar e discutir as evidências científicas sobre o papel e a efetividade dos cuidados de enfermagem no controle da Hipertensão Arterial Sistêmica em contextos de Atenção Primária à Saúde.

Método: Trata-se de uma revisão narrativa da literatura, com busca nas bases de dados LILACS, SciELO e PubMed/MEDLINE, abrangendo publicações entre 2020 e 2025. Foram selecionados 19 estudos, incluindo ensaios clínicos randomizados, revisões sistemáticas, estudos de coorte e pesquisas qualitativas. A síntese do conhecimento foi organizada em categorias temáticas.

Resultados: As intervenções de enfermagem mais efetivas incluem: estratégias de educação em saúde (com redução da pressão arterial sistólica em até 5,8 mmHg); monitoramento da pressão arterial (com reduções de 3,3 a 8,5 mmHg); apoio à adesão medicamentosa; programas de modificação do estilo de vida; e modelos de cuidado liderados por enfermeiros, como clínicas de enfermagem e gerenciamento de casos, que demonstraram reduções de pressão arterial sistólica entre 5,4 e 12,41 mmHg. Os desfechos positivos abrangem melhora no controle pressórico, aumento das taxas de adesão, ampliação do conhecimento sobre a doença e elevação da qualidade de vida.

Conclusão: As evidências confirmam que os cuidados de enfermagem são fundamentais e altamente efetivos para o controle da HAS na APS. Intervenções conduzidas por enfermeiros, especialmente quando integradas a modelos colaborativos, resultam em melhores desfechos clínicos.

Palavras-chave: Hipertensão. Cuidados de Enfermagem. Atenção Primária à Saúde. Revisão. Educação em Saúde.

RESUMEN

Objetivo: Sintetizar y analizar la evidencia científica sobre el rol y la efectividad de los cuidados de enfermería en el control de la hipertensión arterial sistémica en entornos de atención primaria de salud.

Método: Se trata de una revisión narrativa de la literatura, con búsquedas en las bases de datos LILACS, SciELO y PubMed/MEDLINE, que abarca publicaciones entre 2020 y 2025. Se seleccionaron diecinueve estudios altamente relevantes, incluyendo ensayos clínicos aleatorizados, revisiones sistemáticas, estudios de cohortes e investigación cualitativa. La síntesis del conocimiento se organizó en categorías temáticas.

Resultados: Las intervenciones de enfermería más efectivas incluyen: estrategias de educación para la salud (con una reducción de la presión arterial sistólica de hasta 5,8 mmHg); monitorización de la presión arterial (con reducciones de 3,3 a 8,5 mmHg); apoyo para la adherencia a la medicación; programas de modificación del estilo de vida; y modelos de atención liderados por enfermeras, como clínicas de enfermería y gestión de casos, que

han demostrado reducciones en la presión arterial sistólica de entre 5,4 y 12,41 mmHg. Entre los resultados positivos se incluyen un mejor control de la presión arterial, mayores tasas de adherencia al tratamiento, un mayor conocimiento sobre la enfermedad y una mejor calidad de vida.

Conclusión: La evidencia confirma que la atención de enfermería es fundamental y altamente eficaz para el control de la hipertensión en la atención primaria. Las intervenciones realizadas por enfermeras, especialmente cuando se integran en modelos colaborativos, dan como resultado mejores resultados clínicos.

Palabras clave: Hipertensión. Cuidados de Enfermería. Atención Primaria de Salud. Revisión. Educación Para la Salud.

1 INTRODUCTION

Systemic arterial hypertension (SAH) persists as one of the main global public health challenges in the twenty-first century. Defined by the sustained elevation of blood pressure (≥ 140 mmHg and/or 90 mmHg), it is a multifactorial clinical condition that affects more than 1.3 billion people worldwide and contributes to more than 10 million deaths annually (Anand, 2023; American Heart Association, 2020). SAH is the main modifiable risk factor for atherosclerotic cardiovascular diseases, including Acute Myocardial Infarction (AMI) and Cerebrovascular Accident (CVA), in addition to being directly associated with chronic renal failure.

Despite the availability of effective pharmacological treatments and widely disseminated clinical guidelines, blood pressure control rates remain low on a global scale. It is estimated that only about a quarter of hypertensive patients achieve adequate blood pressure levels (Anand, 2023; Jafar et al., 2022). This persistent gap between evidence-based recommendations and observed clinical outcomes is not only due to deficits in medical knowledge, but reflects systemic weaknesses in the organization of care, especially with regard to the longitudinality of care, therapeutic adherence, and coping with the social determinants of health.

In low- and middle-income countries, the situation is particularly critical. The World Health Organization (2021) recorded a significant increase in the number of hypertensive adults in the last three decades, which went from 650 million to 1.28 billion. In these contexts, where health systems face structural and resource limitations, the burden of uncontrolled hypertension is disproportionately high, perpetuating a cycle of morbidity, premature mortality, and impoverishment.

In this scenario, Primary Health Care (PHC) occupies a strategic position for the effective confrontation of SAH. Due to its capillarity, bond with the community, and ability to offer continuous and coordinated care, PHC can detect the disease early, monitor patients longitudinally, and implement interventions that transcend drug prescription. It is in PHC that the chronic care model is implemented, based on the proactivity of the teams, on the support of self-management and on the multiprofessional approach.

In this context, nurses occupy a central position. As the most numerous and widely distributed professional category in health services, they work on the front line of care, establishing lasting bonds with patients and their families. Nursing training, which focuses on health education, behavioral counseling, therapeutic communication, and a holistic view of the human being, provides these professionals with specific skills to address the multifaceted nature of hypertension management (Silva et al., 2020a).

Nursing care in SAH transcends blood pressure measurement. It comprises comprehensive patient assessment, identification of modifiable risk factors, education about the disease and its treatment, support for medication adherence, counseling for lifestyle changes (diet, physical activity, smoking cessation), and coordination of care with other professionals. Innovative models, such as nurse-led hypertension clinics, case management, and community health interventions, have shown promising results in improving clinical outcomes (Stephen et al., 2022; Vay-Demouy et al., 2025).

Despite the growing body of evidence on the effectiveness of nursing interventions, challenges persist for their full implementation and recognition. Barriers related to the patient (low health literacy, cultural beliefs), the health system (fragmentation of care, scarcity of resources) and the provider itself (work overload, training gaps) still limit the potential of nursing to control SAH.

In view of this panorama, it is justified to carry out this narrative review, which critically synthesizes the available evidence on nursing care for the control of SAH in PHC, with the objective of offering subsidies for clinical practice, health management and the formulation of public policies. The review seeks to answer the following question: "What is the role and effectiveness of nursing interventions in the control of Systemic Arterial Hypertension in Primary Health Care contexts?"

2 METHODOLOGY

2.1 STUDY DESIGN

This is an exploratory narrative review of the literature, developed with the purpose of gathering, synthesizing and critically discussing scientific productions that address nursing interventions for the control of Systemic Arterial Hypertension (SAH) in Primary Health Care (PHC) or community contexts. This type of review was chosen because it allows a broad, interpretative and contextualized analysis of the literature, making it possible to identify consolidated contributions, persistent gaps and emerging trends related to nursing care in this field of knowledge, without the intention of exhausting all the existing scientific production on the subject (Rother, 2007). Unlike systematic reviews, which seek exhaustiveness and strict replicability, the narrative review favors the construction of a critical and reflective synthesis, particularly suitable for discussing the theoretical and practical development of evolving areas of knowledge, such as the role of nursing in the management of chronic conditions in primary care.

2.2 SEARCH STRATEGY AND SOURCES OF INFORMATION

The search for studies was conducted in January 2026 in three electronic databases of recognized relevance in the health area: the Scientific Electronic Library Online (SciELO), which covers Latin American and Caribbean scientific production; the Latin American and Caribbean Literature on Health Sciences (LILACS), which indexes regional publications that are often not available in international databases; and PUBMED/Medline, considered the world's leading biomedical database and a reference for nursing and public health research. To ensure the scope and sensitivity of the search, controlled descriptors recorded in the Health Sciences Descriptors (DeCS) were used for searches in Portuguese and in the Medical Subject Headings (MeSH) for searches in English, combined through Boolean operators (AND, OR), with specific adaptations for each database, respecting their syntactic and indexing particularities. The combinations of descriptors used were as follows: "Systemic Arterial Hypertension" AND "Nursing Care" AND "Primary Health Care"; "Nursing Care" AND "Nursing" AND "HAS"; and, for searches in international databases, "Hypertension" AND "Nursing Care" AND "Primary Health Care", as well as "Nurse-led interventions" AND "Hypertension management" AND "Primary care". The search was limited to the period from January 2020 to December 2025, with the objective of capturing the most current and relevant evidence produced in the last five years, a period that follows the main updates of the international guidelines for hypertension management.

2.3 ELIGIBILITY CRITERIA

Explicit inclusion and exclusion criteria were established to guide the selection of studies. Scientific articles that simultaneously met the following requirements were included: availability of the full text in the consulted databases; publication in Portuguese, English or, when available, with reliable translation into one of these languages; direct approach to nursing care through interventions aimed at controlling hypertension; and research development in primary health care, community care, or population-based programs.

Regarding the designs, studies with different methodological designs, including randomized clinical trials, systematic reviews with or without meta-analysis, prospective or retrospective cohort studies, qualitative studies, quality improvement projects, and quasi-experimental studies, were considered eligible, as long as they presented a substantial contribution to the understanding of the role of nursing in hypertension control.

On the other hand, the following were excluded from the analysis: duplicate studies identified in more than one database; incomplete texts, such as abstracts published in annals, editorials, letters to the editor and expert opinions; materials without a formal

scientific character, including theses, dissertations, books and book chapters; publications that did not have a direct relationship with the proposed theme, even if they tangentially mentioned hypertension; studies focused exclusively on other health professionals, without substantive discussion of the nurse's performance; and studies that addressed SAH only as a secondary comorbidity, without focusing on the specific management of the condition.

2.4 STUDY SELECTION PROCESS

The selection of studies was conducted in successive and systematic stages, following a predefined flow that ensured transparency and replicability to the process. In the first stage, called identification, all findings from the three databases were recorded, with the references stored in an electronic spreadsheet for tracking. The second stage consisted of the manual removal of duplicates, carried out through the systematic comparison between title, authorship, year of publication and journal of origin, ensuring that each study was counted only once. In the third stage, called screening, the titles and abstracts of all remaining records were independently read, with a preliminary application of the eligibility criteria to select potentially pertinent studies. The fourth and final stage involved the full reading of the pre-selected texts, with definitive confirmation of the adequacy of the inclusion and exclusion criteria, at which time the information for the qualitative synthesis was also extracted.

2.5 RESULTS OF THE SEARCH AND SELECTION PROCESS

The initial search in the three databases resulted in a total of 5,681 records, distributed as follows: 16 records in SciELO, 152 in LILACS and 5,513 in PUBMED/Medline. After the removal of duplicates, 72 records that appeared simultaneously in more than one database were excluded, leaving 5,609 unique references for screening. Subsequently, the initial filters related to the publication period (2020-2025), language (Portuguese, English, or with translation available), availability of the full text, and broad thematic relevance (i.e., studies that mentioned hypertension and primary care, regardless of whether they directly addressed nursing) were applied. After this stage, 102 publications were selected for the reading of titles and abstracts, distributed in 2 records in SciELO, 34 in LILACS and 36 in PUBMED, totaling 72 records after a new removal of interbase duplicates. The reading of the titles and abstracts of these 72 articles, followed by the rigorous application of the eligibility criteria, reduced the set to 32 publications considered potentially relevant. Finally, after the full reading of these 32 texts and the definitive confirmation of the inclusion criteria, 19 articles composed the final corpus of the present narrative review. The final distribution of the studies included by

database was as follows: 1 article from SciELO, 5 articles from LILACS and 13 articles from PUBMED/Medline, reflecting the greater concentration of scientific production on the subject in internationally indexed journals.

2.6 EXTRACTION, ORGANIZATION AND SYNTHESIS OF DATA

Data from the 19 selected studies were systematically extracted using a standardized form developed specifically for this review, which included the following information: authors and year of publication; methodological design; context and place of the study; characteristics of nursing intervention; main quantitative (blood pressure reductions, control rates, levels of statistical significance) and qualitative (patient and professional experiences, perceived barriers and facilitators) findings; and limitations reported by the original authors.

After extraction, the data were organized into thematic categories that emerged from the critical and interpretative reading of the material, in a process of inductive and recurrent analysis. The categories were not defined a priori, but were constructed from the identification of patterns, recurrences and natural groupings of the themes addressed in the analyzed publications. This process resulted in the definition of five categories of analysis, which guided the synthesis of the results and the structuring of the discussion: (1) strategies for patient education and counseling; (2) blood pressure monitoring and management; (3) support for medication adherence; (4) lifestyle modification programs; and (5) nurse-led models of care, including nursing clinics.

For each category, the types of intervention reported, the main effectiveness findings and the available evidence were synthesized, with special emphasis on quantitative data that would allow measuring the impact of nursing interventions. The discussion was developed in an integrative way, articulating the findings among themselves, contextualizing them in the light of the broader literature on the management of chronic diseases and pointing out consistent implications for clinical practice, for the management of health services, for the formulation of public policies and for the development of future research.

3 RESULTS

The analysis of the 19 selected studies revealed a robust body of evidence that confirms the effectiveness and centrality of nursing care in the management of SAH in PHC. Table 1 presents the detailed characterization of the included studies.

Table 1

Characterization of the studies included in the review on nursing interventions in the control of systemic arterial hypertension in primary health care (2020–2025)

No.	Authors (year)	Design	Nursing Intervention	Key Findings
01	Falcão et al. (2023)	Systematic review with meta-analysis	Structured health education (individual and group)	Mean reduction of 5.8 mmHg in SBP and 3.2 mmHg in DBP
02	Stephen et al. (2022)	Systematic review with meta-analysis	Nurse-led interventions in general practice	Mean reduction of 5.4 mmHg in SBP and 2.8 mmHg in DBP
03	Vay-Demouy et al. (2025)	Systematic review with meta-analysis	Nurse-led interventions with prescriptive authority	Reduction of 7.4 mmHg in SBP and 3.8 mmHg in DBP
04	Ito et al. (2024)	Systematic review with meta-analysis	BP self-monitoring supported by nurses	Reductions in SBP from 3.3 to 8.5 mmHg; Improvement in long-term control
05	Silva et al. (2020a)	Randomized controlled trial	Case management by nurses	Reduction of 12.41 mmHg in SBP and 7.21 mmHg in DBP; Improved adherence and quality of life
06	Jafar et al. (2022)	Cluster randomized clinical trial	Multicomponent model (training, protocols, nurses, HSE)	Blood pressure control increased from 58.2% to 74.9%
07	Yu et al. (2023)	Cohort study (5 years)	Risk assessment and management program (based on the Jafar model)	Significant reductions in cardiovascular complications and mortality
08	Miao et al. (2020)	Randomized controlled trial	Nurse-led hypertension clinic	Control rate: 68.3% vs. 45.7% in the control group
09	Anand (2023)	Quality improvement project	Team-based care with nurses	Significant reductions in SBP and DBP ($p < 0.001$); Increased knowledge
10	Arshad et al. (2022)	Quality improvement project	"Treat to goal" strategy with nurses	Mean reduction of 7.6–9.5 mmHg in SBP; 31% reduction in the number of consultations
11	Lumu et al. (2024)	Cluster randomized clinical trial	Nurse-led management in type 2 diabetes with SAH	Reduction of 13.75 mmHg in SBP and 7.20 mmHg in DBP;

No.	Authors (year)	Design	Nursing Intervention	Key Findings
				Improvement in cardiovascular risk
12	Duller et al. (2024)	Randomized controlled trial	Collaborative Advanced Nursing Practice	Significant improvement in BP, BMI, knowledge and adherence; Outcomes comparable to physicians
13	Vedanthan et al. (2020)	Retrospective study	Management of SAH by nurses vs. clinical officer	Equivalent reductions in BP; Challenge in retention (42% in 12 months)
14	Kaur et al. (2022)	Multicenter study (cohort)	India Hypertension Control Initiative (IHCI)	Clinical control of 43%; from 1.4% to 5.0%
15	Mantovanil et al. (2021)	Systematic review	Case management by nurses vs. usual care	Improved BP control and medication adherence
16	Silva et al. (2023)	Qualitative study	Health education by nurses	Personalized education and social support as facilitators of adherence
17	Figueiredo et al. (2023)	Community intervention	Group and individual education with nurses	70% monitored BP daily; 87% reduced salt; 63% practiced physical activity
18	Setyoadi et al. (2024)	Quasi-experimental study	Home visits by nurses	Improved knowledge (p=0.01), salt adherence, and BP reduction
19	Junior et al. (2022)	Review/reflection	Preventive education in at-risk populations	Emphasis on the importance of prevention before diagnosis of SAH

Legend: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; SAH = Systemic Arterial Hypertension; PHC = Primary Health Care; AMPA = Blood Pressure Self-Monitoring; DASH = Dietary Approaches to Stop Hypertension; IHCI = India Hypertension Control Initiative; BMI = Body Mass Index.
Source: Prepared by the authors.

The results were organized into five main thematic categories, detailed below.

3.1 PATIENT EDUCATION AND COUNSELING STRATEGIES

Patient education is the basis of nursing interventions for hypertension control. Studies with different designs, including systematic reviews with meta-analysis, consistently demonstrate that structured educational interventions, led by nurses, produce significant

improvements in knowledge, self-management behaviors, and blood pressure control. Falcão et al. (2023), in a systematic review with meta-analysis, examined the impact of educational interventions carried out by nurses. The programs addressed the pathophysiology of hypertension, medication adherence, dietary modifications (with an emphasis on sodium reduction and adoption of the DASH diet), physical activity, stress management, and self-monitoring of blood pressure. The results demonstrated clinically meaningful reductions in systolic (mean 5.8 mmHg) and diastolic (mean 3.2 mmHg) blood pressure in the groups that received the educational interventions compared to the control groups.

The reviewed studies also explored different formats of education delivery. According to Silva et al. (2023), individual education allows for the personalization of the approach, adapting content and language to specific needs, health literacy, and each patient's readiness for change. On the other hand, group education, in addition to being potentially more cost-effective, offers the advantage of social support, allowing patients to share experiences, challenges, and successes, which can reinforce motivation and adherence to behavioral changes. Hybrid approaches, which combine group sessions with one-on-one follow-up, have shown particular promise.

The effectiveness of health education also depends on the quality and adequacy of educational materials and methods. Successful interventions utilized a variety of resources, including printed pamphlets with accessible language, practical demonstrations of blood pressure measurement techniques and low-sodium meal preparation, audio-visual aids, mobile apps, and digital platforms, and culturally tailored materials for specific populations. Junior et al. (2022) reinforced the importance of starting preventive education even before the diagnosis of SAH, focusing on at-risk populations to promote healthy habits from an early age.

3.2 BLOOD PRESSURE MONITORING AND MANAGEMENT

Regular and accurate blood pressure monitoring is indispensable for effective control of SAH. Nurses play a critical role not only in the execution of the measurement, but also in the interpretation of the results, in the identification of patterns and in the timely adjustment of conducts.

Self-monitoring of blood pressure at home (AMPA), supported by nurses, emerged as a highly effective strategy. In a systematic review with meta-analysis, Ito et al. (2024) evaluated the impact of nurse-led interventions that incorporated AMPA. The results showed reductions in systolic blood pressure ranging from 3.3 to 8.5 mmHg in the short term (up to

6 months), with maintenance of efficacy in long-term follow-ups (over 6 months). Interventions typically included: training patients in the correct measurement technique (positioning, timing, recording); supply of validated monitors; periodic review of AMPA records by nurses during face-to-face consultations or by telemedicine; and adjustments in treatment based on the data, following pre-established protocols or in collaboration with the physician.

In addition to AMPA, monitoring carried out in health units, especially in the context of nurse-led hypertension clinics, proved to be highly effective. Miao et al. (2020), in a randomized clinical trial conducted in an urban community, evaluated a nurse-led hypertension management model. The intervention group participated in regular, structured consultations with nurses, which included standardized BP measurement, symptom review and adherence, and health education. The control group received the usual care. After the follow-up period, the intervention group had a significantly higher rate of hypertension control (68.3% versus 45.7%).

Home visits represent another important monitoring modality, particularly for patients with reduced mobility, who live in remote areas or who face barriers to accessing health services. Setyoadi et al. (2024) investigated the effect of home visits by nurses on the knowledge, adherence to the low-sodium diet, and blood pressure of hypertensive patients in primary care. The visits allowed nurses to assess the home environment, identify contextual barriers (such as availability of healthy foods and family stressors), provide personalized education, and involve family members in the care plan. The results showed significant improvements in all outcomes evaluated.

3.3 MEDICATION ADHERENCE SUPPORT

Non-adherence to antihypertensive drug therapy is one of the main causes of inadequate blood pressure control, affecting approximately 50% to 70% of patients. Nursing interventions focused on improving adherence have demonstrated substantial effectiveness and act on multiple fronts.

Medication management strategies implemented by nurses include: detailed education about the purpose, dosage, timings, and potential side effects of medications; simplification of regimens, where possible, in conjunction with the prescribing physician (prioritizing single-dose daily medications or fixed-dose combinations); provision of memory aids, such as pill organizer boxes, cell phone alarms and reminder apps; and proactive approach to barriers to adherence, such as cost, fear of side effects, negative beliefs about the need for treatment, and complexity of the regimen.

Regular contact and ongoing counseling are key to sustaining adherence. Mantovanil et al. (2021), in a systematic review, compared case management by nurses with usual care for BP control. Case management, which included intensive and personalized adherence support through regular telephone contacts, motivational interviewing, and close follow-up, resulted in better BP control and higher adherence rates compared with usual care.

Nurses also play a crucial role in addressing patients' beliefs and concerns about medications. Using therapeutic communication techniques, they explore patient perceptions, correct common misconceptions (such as the idea that medication can be stopped when BP is controlled), offer strategies for dealing with side effects, and consistently reinforce the long-term benefits of treatment in preventing serious complications such as heart attack and stroke.

3.4 LIFESTYLE MODIFICATION PROGRAMS

Nonpharmacological interventions are the mainstay of SAH treatment, recommended for all patients, regardless of the stage of the disease. Nurses are on the front lines of implementing and supporting these behavioural changes.

In the context of dietary counseling, nursing interventions focus on reducing sodium consumption, educating patients about the main food sources (processed foods, sausages, ready-made spices) and teaching practical strategies to reduce intake, such as reading labels, cooking at home and using herbs and spices instead of salt. Promoting the DASH (*Dietary Approaches to Stop Hypertension*) diet, rich in fruits, vegetables, whole grains, and low-fat dairy products, is another key intervention. Setyoadi et al. (2024) demonstrated that home visits by nurses significantly increased patients' adherence to the low-sodium diet.

The promotion of physical activity is another key area of action. Nurses assess patients' level of physical activity, identify barriers (lack of time, access to safe places, health conditions), and assist in setting realistic and progressive goals, in line with recommendations of at least 150 minutes of moderate aerobic activity per week. Counseling includes guidance on the type, intensity, duration and frequency of exercise, as well as monitoring progress.

For smokers, smoking cessation support is a high-impact intervention. Nurses perform assessment of smoking status and readiness to quit, offer brief or intensive counseling, educate on nicotine replacement therapy options, and refer to specialized programs when available. Stress management is also addressed, recognizing its role as a risk factor and as a barrier to the adoption of healthy habits, with guidance on relaxation techniques and coping strategies.

3.5 NURSE-LED MODELS OF CARE, INCLUDING NURSE CLINICS

Nurse-led models of care represent a structured and comprehensive approach to managing SAH, going beyond isolated interventions. These include nurse-led hypertension clinics, case management programs, and collaborative models.

Nurse-led hypertension clinics are dedicated spaces in PHC where hypertensive patients receive specialized, ongoing care. They are characterized by regular consultations with trained nurses, who follow standardized protocols for evaluation, treatment and follow-up. Depending on the scope of practice and local regulations, nurses may have the authority to initiate or adjust antihypertensive medications, following pre-defined algorithms and in collaboration with physicians. Stephen et al. (2022), in a systematic review with meta-analysis of 32 studies, demonstrated that nurse-led interventions reduced systolic BP by an average of 5.40 mmHg (95% CI: -7.30 to -3.49) and diastolic BP by 2.80 mmHg (95% CI: -4.09 to -1.51) compared with usual care. Vay-Demouy et al. (2025) went further, showing that nurse-led interventions with prescriptive authority achieved even greater reductions: -7.4 mmHg in systolic BP and -3.8 mmHg in diastolic BP.

Case management by nurses is a model of care coordination, particularly useful for patients with greater complexity or multiple comorbidities. It involves initial comprehensive assessment, development of an individualized care plan, coordination of services between different providers, regular monitoring, and patient advocacy within the care network. Silva et al. (2020a) conducted a randomized controlled trial that evaluated case management by nurses for people with hypertension in PHC. In addition to usual care, the intervention group received an initial evaluation visit, an individualized care plan, monthly telephone contact, and coordination with the team. After 12 months, the intervention group showed significantly greater reductions in systolic (-12.41 mmHg) and diastolic (-7.21 mmHg) BP, in addition to better medication adherence, greater knowledge, and better quality of life.

Collaborative care models, in which nurses and physicians work in close partnership, sharing protocols and responsibilities, have proven particularly effective. Jafar et al. (2022) evaluated a multicomponent intervention in Singapore that included PHC team training, standardized protocols, case management by nurses, and SMS reminders. The results showed a significant increase in BP control, from 58.2% in the control group to 74.9% in the intervention group. The 5-year follow-up study, conducted by Yu et al. (2023), demonstrated that these benefits translated into significant reductions in cardiovascular complications and mortality, evidencing the sustainable impact of these models.

Finally, community-based hypertension programs, such as those evaluated by Vedanthan et al. (2020) in rural Kenya and by Kaur et al. (2022) in India, demonstrate the

feasibility and effectiveness of nurse-led interventions in resource-limited settings. These programs, which involve community screening, medication initiation and titration by nurses, and regular follow-up, have been able to substantially improve SAH control rates, indicating potential for expansion of these strategies.

4 DISCUSSION

The present narrative review synthesized a broad and consistent body of evidence that attests to the effectiveness and centrality of nursing care in the management of Systemic Arterial Hypertension in Primary Health Care. The results, from dozens of studies with different designs and carried out in different global contexts, converge to the conclusion that nurse-led interventions produce clinically significant improvements in blood pressure control, treatment adherence and quality of life of hypertensive patients. However, before deepening the analysis of the findings, it is necessary to recognize an important limitation of this synthesis: because this is a narrative and not a systematic review, no formal assessment of the risk of bias of the included studies was carried out, which recommends caution in the absolute interpretation of efficacy figures, especially those of greater magnitude.

First, the reductions in blood pressure observed in the meta-analyses reviewed are remarkable and deserve contextualized analysis. While Stephen et al. (2022) reported a mean reduction of 5.4 mmHg in systolic BP for nurse-led interventions in general, Vay-Demouy et al. (2025) found a reduction of 7.4 mmHg when nurses had prescriptive authority. Even more impressive, Silva et al. (2020a) achieved a reduction of 12.41 mmHg with an intensive case management model. However, it is essential to interpret these numbers in light of the methodological differences between the studies: the greatest effects tend to occur in short-term trials, with intensive follow-up and selected samples; pragmatic and longer-term studies, such as the one by Yu et al. (2023), report more modest but sustained effects. Despite this variation, one finding remains robust: a 5 mmHg reduction in systolic BP is associated with an approximately 10% decrease in the risk of major cardiovascular events. Therefore, even the most conservative effects achieved by nursing interventions translate into tangible benefits for patients' health.

In addition, the effectiveness of nursing interventions can be attributed to multiple mechanisms that act synergistically, which deserve to be made explicit. The first of them is the focus on patient education and empowerment. Unlike a purely prescriptive approach, nurses invest in dialogue, active listening, and the construction of a shared understanding of the disease and its treatment, which enables the patient to take an active role in their own care. Secondly, nurses offer intensive and continuous support to adherence, identifying and

assisting in overcoming practical barriers (cost, forgetfulness, complexity of the regime) and psychological barriers (fears, negative beliefs). Regular follow-up – whether in person, by phone or through digital technologies – creates a commitment that sustains persistence in treatment. Thirdly, nurses have consolidated skills in counseling for behavior change, an area that is known to be challenging in the treatment of SAH. Finally, nurse-led models of care, especially case management and nurse clinics, introduce coordination and continuity that is often lacking in fragmented usual care.

Comparatively, the findings of this review are in line with the broader literature on the management of chronic diseases, which reiterates the importance of multidisciplinary teams, patient-centered care, and support for self-management. The Chronic Care Model, widely accepted as a reference for the organization of care for chronic conditions, places the prepared and proactive health team as one of its fundamental pillars. In this sense, the results presented here confirm that nurses, when adequately trained and inserted in a support system, personify this pillar. It is also noteworthy that the comparison between the different care models reveals important nuances: nursing clinics and case management were superior to isolated interventions, suggesting that the structured and continuous approach is more effective than the sum of specific actions. The study by Vay-Demouy et al. (2025) adds a crucial layer to this discussion by demonstrating that prescriptive authority for nurses significantly enhances the impact of interventions, as it eliminates delays and barriers in medication adjustment.

With regard to implementation in practice, it is necessary to recognize that, despite robust evidence of effectiveness, the generalization of these programs faces significant barriers at multiple levels. At the patient level, treatment abandonment, low health literacy, mistaken cultural beliefs, and socioeconomic factors stand out. At the level of the health system, the chronic scarcity of resources, the fragmentation of care, and restrictive policies that limit the scope of nursing practice are the main obstacles. At the provider level, gaps in knowledge, work overload, and sometimes resistance to expanding the professional role pose additional challenges. On the other hand, the enablers identified include the deliberate adoption of *task-shifting*, the development of simplified and standardized protocols, investment in telehealth, and, crucially, the expansion of the scope of practice with prescriptive authority for trained nurses.

Finally, it is necessary to point out the main gaps in evidence that persist and that should guide future research. While the short- and medium-term benefits are well established, there is a pressing need for more cost-effectiveness studies that rigorously assess the return on investment in nurse-led programs. In addition, more research is needed

to identify the optimal components of multicomponent interventions, as the most efficient and effective combination of elements (education, monitoring, adherence, lifestyle) for different patient profiles and settings is still unclear. It is also recommended that future studies directly compare nurse-led care with physician-led care for uncomplicated hypertension in order to more accurately establish the non-inferiority or superiority of each model. Finally, it is crucial to invest in implementation research that investigates how to adapt and incorporate these evidence-based models in low- and middle-income countries and in vulnerable populations, ensuring that advances in care reach those who need it most.

5 CONCLUSION

This narrative review of the literature, by synthesizing the most relevant evidence produced between 2020 and 2025, allows us to conclude, consistently, that nursing care is a critical and highly effective component for the control of Systemic Arterial Hypertension in Primary Health Care. Nurse-led interventions—ranging from health education and individualized counseling to systematic monitoring, intensive medication adherence support, and complex case management—produce clinically meaningful reductions in blood pressure. These benefits, as demonstrated, translate into a lower risk of cardiovascular events, improved quality of life, and greater patient satisfaction, and are particularly significant when nurses work autonomously and in collaborative models.

Among the organizational models evaluated, nurse-led hypertension clinics and collaborative care demonstrated the best results, especially when associated with prescriptive authority. Compared to usual care, these models achieved additional reductions in systolic blood pressure ranging from 5.4 to 12.4 mmHg, values that, at the population level, would represent a substantial decrease in cardiovascular morbidity and mortality. The effectiveness of nursing practice, therefore, does not lie in a single technical procedure, but in its holistic and patient-centered approach, in the ability to establish lasting bonds, in the competence to educate and empower, and in the ability to coordinate care longitudinally.

However, for all this potential to materialize on a large scale, systemic changes are needed that go beyond the individual will of professionals. Based on the synthesized evidence, it is recommended that health managers and policymakers: invest in continuing education to update PHC nurses; broaden the scope of practice by granting prescriptive authority backed by protocols and oversight; support the implementation of nursing clinics and case management programs; incorporate technologies such as telehealth and remote monitoring; and, fundamentally, value nursing with working conditions and professional recognition that are commensurate with its health impact.

In summary, in view of the solidity of the evidence presented, it is possible to affirm that strengthening the role of nursing in Primary Care is not only a matter of efficiency or optimization of the workforce. Rather, it is a fundamental strategy to improve the quality of care, reduce health inequities and advance in the control of one of the most challenging chronic epidemics of our time. Investing in nursing is investing in the health of the population, and the results of this review make it clear that it is no longer a question of whether nursing care works, but rather how to implement it sustainably and equitably in health systems.

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INSERTION OF INTRAUTERINE DEVICE (IUD) BY FAMILY AND COMMUNITY PHYSICIANS IN PRIMARY HEALTH CARE IN SANTA MARIA, RIO GRANDE DO SUL, BRAZIL

INSERÇÃO DE DISPOSITIVO INTRAUTERINO (DIU) POR MÉDICO DE FAMÍLIA E COMUNIDADE NA ATENÇÃO PRIMÁRIA EM SANTA MARIA-RS

INSERCIÓN DE DISPOSITIVO INTRAUTERINO (DIU) POR MÉDICOS DE FAMILIA Y COMUNIDAD EN LA ATENCIÓN PRIMARIA DE SALUD EN SANTA MARIA-RS, BRASIL



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ABSTRACT

Unplanned pregnancy accounts for 40% of all pregnancies and remains a worldwide reality. Regarding physical health, the lack of reproductive planning to prevent unintended pregnancy is among the factors that worsen maternal mortality rates in Brazil. Therefore, guidance and access to contraceptive methods such as the intrauterine device (IUD) ensure women's right to reproductive and sexual health care. The Intrauterine Device (IUD) is one of the highly effective and long-acting contraceptive methods offered by the Brazilian Unified Health System (SUS), although it is still underused. In this context, the present study aimed to expand IUD insertion among SUS users in the municipality of Santa Maria-RS within the primary health care network. Initially, a theoretical and practical training course on copper IUD insertion was provided to Family and Community Medicine resident physicians from the Universidade Federal de Santa Maria and Universidade Franciscana in order to increase the availability of IUDs in the municipality's primary health care network. Subsequently, the IUD was offered as a contraceptive method to women during routine clinical consultations at Family Health Strategy (FHS) units. The project included 45 women aged 18 to 45 years who were SUS users in the city of Santa Maria, as well as four Family and Community Medicine physicians. The mean age of participants was 27 years, with 74.5% aged between 19 and 35 years; 42% had completed high school and 19.1% had completed higher education; 59.6% had paid employment; most were married and/or in a stable relationship (61.7%); and 72.3% had one or more previous pregnancies. The resident physicians who received training in Copper T 380A IUD insertion identified the following barriers before training: lack of prior knowledge and difficulty performing the procedure. After the training, 100% of the

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professionals reported feeling equipped with the necessary knowledge and skills, considering insertion to be an easy procedure. None of the 45 users experienced complications after IUD insertion. This study provided positive results that may support and encourage IUD insertion by Family and Community Medicine professionals, expanding the availability of long-acting contraception for the population.

Keywords: Intrauterine Device. IUD. LARC. Family and Community Medicine. Family Health Strategy.

RESUMO

A gravidez não planejada corresponde a 40% de todas as gestações, sendo uma realidade mundial. No que se refere à saúde física, a falta de planejamento reprodutivo, para evitar a gravidez indesejada, está entre os fatores que agravam a situação da mortalidade materna no Brasil. Desta forma, a orientação e a disponibilização de métodos contraceptivos como o dispositivo intrauterino (DIU) garantem o direito ao atendimento à saúde reprodutiva e sexual das mulheres. O Dispositivo Intrauterino (DIU) é uma das opções de contraceptivos ofertadas no Sistema Único de Saúde (SUS) de alta eficácia e longa duração, embora ainda pouco utilizado. Nesse contexto, o presente estudo objetivou ampliar a inserção de DIU entre usuárias do SUS do município de Santa Maria-RS na rede de atenção primária. Inicialmente, foi realizado uma capacitação teórico-prática em inserção de DIUs de cobre aos médicos residentes de Medicina de Família e Comunidade da Universidade Federal de Santa Maria (UFSM) e da Universidade Franciscana (UFN), a fim de ampliar a oferta de DIU na rede básica de saúde do município. Posteriormente, foi ofertado o DIU como método contraceptivo às mulheres durante consultas clínicas de rotina junto às unidades de Estratégia de Saúde da Família (ESF). Participaram do projeto 45 mulheres de 18 a 45 anos de idade usuárias do SUS da cidade de Santa Maria e quatro médicos de Medicina da Família e Comunidade. A média de idade das participantes foi de 27 anos, sendo 74,5% delas entre 19 e 35 anos; 42% delas completaram o ensino médio e 19,1% o ensino superior; 59,6% possuíam trabalho remunerado; a maioria era casadas e/ou em união estável 61,7% e 72,3% tinham uma ou mais gestações prévias. Os médicos residentes, que receberam treinamento para inserção do DIU de cobre 380A, apontaram os seguintes fatores impeditivos ou prejudiciais pré-capacitação: falta de conhecimento prévio e dificuldade em realizar o procedimento anteriormente. Após o treinamento, 100% dos profissionais sentiram-se dotados de conhecimento e habilidades, referendo a inserção como um procedimento fácil. Das 45 usuárias, nenhuma apresentou complicações após a inserção de DIU. Essa pesquisa forneceu resultados positivos, que podem apoiar e incentivar a inserção de DIU por profissionais de Medicina da Família e Comunidade, ampliando a oferta de contracepção de longa duração para a população.

Palavras-chave: Dispositivo Intrauterino. DIU. LARC. Medicina de Família e Comunidade. Estratégia de Saúde da Família.

RESUMEN

El embarazo no planificado corresponde al 40% de todos los embarazos y constituye una realidad mundial. En lo que respecta a la salud física, la falta de planificación reproductiva para evitar embarazos no deseados se encuentra entre los factores que agravan la situación de la mortalidad materna en Brasil. De esta manera, la orientación y la disponibilidad de métodos anticonceptivos como el dispositivo intrauterino (DIU) garantizan el derecho a la atención de la salud reproductiva y sexual de las mujeres. El Dispositivo Intrauterino (DIU) es una de las opciones anticonceptivas ofrecidas por el Sistema Único de Salud (SUS) de alta eficacia y larga duración, aunque todavía es poco utilizado. En este contexto, el presente estudio tuvo como objetivo ampliar la inserción de DIU entre usuarias del SUS del municipio de Santa Maria-RS en la red de atención primaria. Inicialmente, se realizó una capacitación

teórico-práctica en inserción de DIU de cobre dirigida a médicos residentes de Medicina Familiar y Comunitaria de la Universidade Federal de Santa Maria y de la Universidade Franciscana, con el fin de ampliar la oferta de DIU en la red básica de salud del municipio. Posteriormente, el DIU fue ofrecido como método anticonceptivo a las mujeres durante consultas clínicas de rutina en las unidades de Estrategia de Salud de la Familia (ESF). Participaron en el proyecto 45 mujeres de entre 18 y 45 años usuarias del SUS de la ciudad de Santa Maria y cuatro médicos de Medicina Familiar y Comunitaria. La edad promedio de las participantes fue de 27 años, siendo el 74,5% de ellas de entre 19 y 35 años; el 42% había completado la educación secundaria y el 19,1% la educación superior; el 59,6% tenía trabajo remunerado; la mayoría estaba casada y/o en unión estable (61,7%); y el 72,3% tenía uno o más embarazos previos. Los médicos residentes que recibieron capacitación para la inserción del DIU de cobre 380A señalaron los siguientes factores limitantes antes de la capacitación: falta de conocimiento previo y dificultad para realizar el procedimiento. Después de la capacitación, el 100% de los profesionales se sintieron dotados de conocimientos y habilidades, considerando la inserción como un procedimiento fácil. Ninguna de las 45 usuarias presentó complicaciones después de la inserción del DIU. Esta investigación proporcionó resultados positivos que pueden apoyar e incentivar la inserción de DIU por profesionales de Medicina Familiar y Comunitaria, ampliando la oferta de anticoncepción de larga duración para la población.

Palabras clave: Dispositivo Intrauterino. DIU. LARC. Medicina Familiar y Comunitaria. Estrategia de Salud de la Familia.

1 INTRODUCTION

Currently, 160 million women of reproductive age do not have access to contraception despite the availability of a variety of contraceptive methods for people (Haakenstad *et al.*, 2022). According to a report carried out by the United Nations Population Fund (UN, 2022), 50% of pregnancies in the world are unplanned. In Brazil, fifty-five percent (55%) of pregnancies are unplanned, this percentage represents 1.47 million unwanted pregnancies per year in the country according to data from the Ministry of Health (2024).

Reproductive planning assistance should be part of the list of actions of health teams that work in Primary Health Care (PHC) aimed at the health of women, men, couples and families, in a vision of comprehensive health care, based on respect for sexual and reproductive rights (Carceneri *et al.*, 2013, UFSC, 2016). In the 2000s, Brazil signed the Millennium Declaration stipulated by the United Nations (UN), which included among the millennium development goals that countries prioritize sexual and reproductive health. In 2006, Brazil implemented the Pact for Health in the Unified Health System (SUS) and through the Ministry of Health's More Health: Right for All Program in 2007 there was an expansion in family planning care through the provision of methods and techniques for conception and contraception, information and follow-up (Fernandes *et al.*, 2016)

Among the contraceptive methods distributed to Brazilian municipalities by the Ministry of Health, the Intrauterine Device (IUD) with copper TCu 380A stands out for being a safe method, highly effective (pregnancy rates of less than 0.4% or four women per thousand in the first year, and in the following years the pregnancy rate is even lower) and practical, long-lasting, reversible and non-hormonal, in addition to being eligible, including in the postpartum period, post-abortion and as the most effective method in emergency contraception available for use after unprotected intercourse (BRASIL, 2018; Ali *et al.*, 2014, FEBRASGO, 2017).

Although the SUS offers free IUD insertion with PHC, through Family Health teams, IUD insertion is still far below what would be possible, in view of the coverage of the Family Health Strategy (FHS) in Brazil. Currently, there is a technical manual from the Ministry of Health that recommends the guidance of contraceptive methods in PHC care, including the DIU (MINISTRY OF HEALTH, 2018), whose insertion can be performed by resident physicians in Health and Community Medicine. However, this practice is not adopted in the study region, which denotes a possible barrier in the dissemination and insertion of the method by primary care professionals.

In this sense, this work aims to contribute to the expansion of care and access to reproductive planning for women in the municipality of Santa Maria-RS, through the training

of resident physicians in Family and Community Medicine. To this end, it is proposed to evaluate the epidemiological profile of patients who underwent intrauterine device (IUD) insertion with family and community physicians, to analyze the theoretical-practical training of residents in performing the procedure, and to compare the results of IUD insertions before and after training.

2 LITERATURE REVIEW

2.1 HISTORY OF REPRODUCTIVE PLANNING

Since the 1990s, several world conferences promoted by the UN have been strongly marked by intense participation and articulation of social movements that have put human rights on the agenda, emphasizing women's rights. The struggle for a free and autonomous reproductive and sexual life was present in conventions and putting into discussion the need for policies and programs that would guarantee such rights (Ventura, 2009; UN 2015).

In 1994, in the city of Cairo, the International Conference on Population and Development (ICPD) took place, which defined for the first time the concept of reproductive health as: "a state of complete physical, mental and social well-being and not the simple absence of disease without restriction of organs, functions and systems". This concept gives the right to all women to have a safe, satisfying sex life and free to deliberate how and when to reproduce (UNFPA, 1994).

In the late 1990s and early 2000s, other World Conferences on women's health reinforced the concept of sexual rights and reproductive health, which were considered human rights that should be safeguarded by governments through specific practices and policies. However, with the increase in population growth and social inequalities, in the year 2000, world leaders met at the UN headquarters and prepared a document based on Human Rights with the objectives of protecting vulnerable populations and ensuring sustainable development. Among the objectives were gender equality and women's autonomy, improving maternal health and reducing the fertility rate in order to control poverty and reduce social inequalities (WHO, 2018). Brazil managed to achieve only one of these goals, reducing poverty rates from 25.5% (1990) to 3.5% (2012). The other goals were not fully achieved. Even so, there was a 55% reduction in birth rates between 1990 and 2011 according to data from the Brazilian Institute of Geography and Statistics (IBGE, 2020).

In 2012, with the failure of the goals by the countries, especially underdeveloped countries, there was a need for a World Health Conference in the city of Rio de Janeiro (RIO+20) that affirmed the objectives previously proposed and added other goals aimed at Sustainable Development (SDGs) that must be achieved by the countries by 2030. Among

them, the following stand out: "ensuring well-being and a healthy life for all; ensure gender equality; access to education and health for all women with access to contraceptive methods" (UN, 2015).

In Brazil, reproductive planning actions were only regulated in 1996 after the establishment of Law 9.263, which established the Family Planning Program. According to Law 9.263, with regard to reproductive planning: "conception and contraception actions are offered as a duty of the State and a right of all citizens, and must be guided by preventive and educational actions, means, methods and techniques available for the regulation of fertility". In addition, "the quality of reproductive planning care must ensure high standards of health, guaranteeing human rights in the provision of contraceptive information and services based on respect for informed choice, autonomy, privacy and confidentiality" (BRASIL, 1996).

In 1962, the *Population Council*, at the suggestion of Alan Guttmacher, then president of the *Planned Parenthood Federation of America (PPFA)*, organized the first international conference on IUDs in New York City. It was at this conclave that Jack Lippes, from Buffalo, presented his experience with his device, which had a single filiform tail and became the most widely used IUD in the United States and in the world. From then on, more and more new models began to appear with stainless steel materials, with silver, nylon and polyurethane wires and spiral (OMS, 2018). In Brazil, the contraceptive pill and the IUD have been marketed without hindrance since the beginning of the 70s. However, only from 2017 onwards, the Ministry of Health announced the expansion of free access to the copper IUD, distributed by the Unified Health System (SUS) in the various family planning services (FEBRASGO, 2017).

2.2 UNWANTED PREGNANCIES AND CONTRACEPTIVE FAILURES

An indication of failure in family planning often results in an unwanted pregnancy, which can be caused by lack of information, or access to contraceptive methods or their unavailability in the most different socioeconomic segments (Gelaw *et al.*, 2023). The distribution of information and access to more effective contraceptive methods can help reduce the number of unwanted pregnancies, as well as the negative effects that these pregnancies cause in psychological, social, economic, and health terms for children, women, men, families, and society (Sedgh; Singh; Hussain, 2014).

It is known that in cases of unwanted pregnancy, there is a lower probability of early prenatal care, in addition to a greater probability of fetal exposure to harmful substances, such as tobacco and alcohol. Unwanted pregnancies increase the likelihood of low birth

weight, death in the first year of life, fetal distress, and developmental problems. The mother is more likely to suffer abuse and depression, and her relationship is more likely to fail. Parents may face financial difficulties, preventing them from achieving their academic and professional goals (Nogueira *et al.*, 2024).

Between February 2011 and October 2012, a large-scale survey was carried out in Brazil called Birth in Brazil, which was coordinated by the Oswaldo Cruz Foundation (FIOCRUZ). The research involved 23,940 women in 121 municipalities. According to the study, unplanned pregnancies in Brazil are 55.4% and 66% among adolescents, with a higher prevalence among low-income women (Viellas *et al.*, 2014).

2.3 EPIDEMIOLOGY OF IUD USE IN BRAZIL AND IN THE WORLD

The intrauterine device is a reversible, long-term, high-efficacy method of contraception that is among the most effective methods available today (FEBRASGO, 2018). It is estimated that the pregnancy rate in the first year of use is only 0.4 per thousand women, as has been reported by several studies (Savage; Lindsay, 2018).

A U.S. contraception project implemented between 2007 and 2011 called "*CHOICE*" was a prospective study of contraceptive failures in the United States that sought to encourage the use of long-acting reversible contraceptives (LARC) to reduce the number of unintended pregnancies. The study was conducted with 9,256 women in the Saint Louis region (USA), aged between 14 and 45 years. The failure rate in the LARC group (progesterone-releasing and copper-releasing IUD and subdermal implant) was lower (0.3, 0.6, and 0.9%) compared to participants who opted for pills, patches, and vaginal ring (cutouts at the end of each year of the study of 4.8%, 7.8%, and 9.4%, respectively) (Mcnicholas *et al.*, 2014).

A study conducted in the United States on women of reproductive age (15 and 49 years old) during the years 2014 to 2016 estimated that 88% used modern contraceptive methods. Among the users, 18% used long-acting reversible contraceptive methods (LARC) (Megan; Kavanaugh; Pliskin, 2020). However, 84% of women still have unmet contraceptive needs, that is, they want to avoid pregnancy, but do not use contraceptive methods (Guttmacher, 2017). One explanation for this, according to the WHO, may be related to limited access to contraceptive methods, low quality of services, cultural and religious oppositions, undesirable side effects, among others (WHO, 2018).

A study conducted by Araújo *et al.* (2023) reported that only 4.8% of Brazilian women use long-acting methods, such as copper IUDs, hormonal IUDs, and subdermal implants. While, about 70% of Brazilian women use modern short-acting contraceptives (*Short-Term*

Contraceptives Methods, such as the pill and condom). According to the National Survey of Demography and Health of Children and Women – PNDS, carried out in 2006, the IUD was considered a contraceptive method little used in Brazil, representing only 1.9% (BRASIL, 2018).

In Brazil, 77,286, 102,836, and 41,492 IUDs were inserted and registered by the SUS in the years 2022, 2023, and 2024 (until May), respectively. In Rio Grande do Sul, 2,489, 2,708 and 943 IUDs were inserted and registered by the SUS in the same period, respectively. (DATASUS, 2024). In Santa Maria-RS, in the same database, there is no record of any IUD inserted in the period. It is estimated that in Brazil, there is a current statistic of 3% of IUD users of childbearing age, although the expectation is to reach the rates of 10% (MINISTRY OF HEALTH, 2024) which undoubtedly, to be obtained or approach, requires a population education and awareness campaign, as well as a careful prior selection of those who will obtain contraceptive benefits with this method.

2.4 INTRAUTERINE DEVICES (IUDS)

Intrauterine devices (IUDs) are considered LARCs, that is, contraceptive methods that have a durability equal to or greater than three years and that can be reversible. In addition to IUDs, both copper and hormonal, contraceptive implants also fall into the LARC category. These methods are characterized by safety, as they eliminate the need for the woman to remember to use them every day, or any other reason that prevents her from using them properly (FEBRASGO, 2022).

The first IUD was designed by German gynecologist Richard Richter in 1909, and consisted of a ring with two braided silk strips covered with cellulose. From this first model, the IUD evolved into the most modern one. It was in the 1960s that the product was developed in a "T" shape, as it better adapted to the shape of the uterus (Hsia *et al.*, 2016).

The device was widely accepted until a new model, the Dalkon Shield, was introduced in the United States in the 1970s that was associated with miscarriages, pelvic inflammatory disease (PID), and even deaths, leading to its withdrawal in 1974. Subsequently, more models were introduced, but mistrust made it remain in use until the appearance of the first Intrauterine System, marketed under the name of Mirena® (Hsia *et al.*, 2016). Currently, intrauterine devices are one of the safest contraceptives known, and there are more than 150 million users worldwide who use them (Searle, 2014).

The IUD consists of a small, solid, flexible object of variable shape that is inserted through the cervix into the uterine cavity, with the aim of preventing pregnancy (Figure 1).

According to its characteristics, the IUD can be classified as: inert, copper-releasing or hormone-releasing (BRASIL, 2018).

Figure 1

Copper Intrauterine Device (IUD)



Source: (AUTHOR, 2024).

2.4.1 Copper IUDs

The TCu 380 A copper-covered IUD, a model made available in Brazil by the SUS, is T-shaped and is coated with 324 mm² of copper on the vertical stem and two 33 mm² copper rings on the horizontal stem (Figure 1). After being inserted into the uterine cavity, copper ions cause a thickening of the cervical mucus and an inflammatory action on the endometrium, in addition to being toxic to sperm. In this way, they interfere with sperm motility and quality, preventing sperm ascension to the fallopian tubes and consequently fertilization (FEBRASGO, 2022).

The copper IUD has an average duration of 10 years and a high efficacy rate (0.4% failure in the first year of use). In addition, it is a practical and safe method that can be used by women who want long-acting contraception, whether they are adolescents, young people, or perimenopausal. They can also be used by nulliparous women, women with previous cesarean sections, ovarian cysts or who are breastfeeding (Bahamondes; Bahamondes, 2021).

They are contraindicated for use in women with intrauterine abnormalities or fibroids. Similarly, women with vaginal bleeding with no known cause, sexually transmitted infection (STI), pelvic inflammatory disease, endometritis, purulent cervicitis, pelvic tuberculosis, or

with cervical, ovarian, or endometrial cancer can use it only after appropriate treatment (FEBRASGO, 2022).

Copper IUD users may experience changes in menstrual pattern and flow, especially in the first three months of use. Between the first and sixth month after insertion, menstrual cramps may appear or worsen, with greater frequency or duration, improving as the months go by. Uterine perforation during insertion or spontaneous expulsion include rare events although of medical risk (BRASIL, 2018).

2.4.2 Intrauterine Hormone-Releasing Devices

Hormone-releasing IUDs are considered methods with a high efficacy rate of this IUD (99.7%), being one of the most effective contraceptive methods. In addition, it has the advantage of being a reversible method and rapid return to fertility after removal (FEBRASGO, 2017).

Hormone-releasing IUDs are also T-shaped and release Levonorgestrel (LNG-IUS). They have a reservoir with 52 mg of levonorgestrel, measures 32 mm in length and releases 20 µg of levonorgestrel per day. Through the control membrane, the system is able to release levonorgestrel, which in 15 minutes after insertion is already circulating in the plasma. The release rate of 20 µg/day decreases over the course of use, stabilizing at around 12 µg/day to 14 µg/day and finally reaches 11 µg/day at the end of five years, which is the recommended time of use of the LNG-IUS. It is a contraceptive with fewer side effects and exceptional effectiveness, for five years of use. The main mechanisms of action of this model are: thick cervical mucus that is hostile to sperm penetration, inhibiting its motility in the cervix, endometrium and fallopian tubes, preventing fertilization; high concentration of levonorgestrel in the endometrium, preventing response to circulating estradiol; strong antiproliferative effect on the endometrium; inhibition of mitotic activity of the endometrium (FEBRASGO, 2017).

Absolute contraindications include confirmed or suspected pregnancy, severe distortion of the uterine cavity (such as septa, endometrial polyps, or submucosal fibroids), acute or recent (within three months) or recurrent infection (including STI, postpartum infection, or postabortion), untreated cervicitis, known allergy to levonorgestrel, acute liver disease, or liver tumor. Among the relative contraindications are important risk factors for STI (non-monogamous relationships, history of STD), previous history of problems with intrauterine contraception (perforation or severe pain), undiagnosed abnormal uterine bleeding, immunosuppression, previous history of vasovagal reflex, previous history of

progesterone intolerance (important depression), women who do not accept developing oligomenorrhea or amenorrhea (FEBRASGO, 2017).

2.5 INDICATION REGARDING THE USE OF COPPER IUD

Guidance on contraceptive methods and IUD supply according to the Technical Manual for Health Professionals - IUD with copper TCu 380^a can be provided at any time in the woman's reproductive life, when the professional contacts the user, in clinical consultations, educational groups, preventive activities or home visits, whether or not mediated by the use of informative materials (MINISTRY OF HEALTH, 2018).

In the absence of contraindications, the IUD can be indicated for any woman who is looking for a reliable, reversible, independent of coitus and long-term contraceptive method. In addition, for women who have contraindications to estrogen or women who breastfeed, the use of the IUD with copper may be a good candidate. During the lactation period, it proves to be an advantageous method because it does not interfere with the quality and quantity of breast milk (FEBRASGO, 2022).

As for perimenopausal women, initially the IUD is a good option, especially in those who have relative or absolute contraindications to combined hormonal contraception, such as smokers, obese, hypertensive and diabetic women, as these associated factors lead to greater cardiovascular risk. In those who use the IUD with copper and under 50 years of age, it is recommended to remove it two years after the last menstrual period (menopause). In women over 50 years of age, one year of amenorrhea is expected to be removed (FEBRASGO, 2022).

2.6 ADVANTAGES AND DISADVANTAGES OF THE INTRAUTERINE DEVICE

The IUD stands out from other contraceptive methods due to the following advantages: i. rapid return to fertility after its removal; ii, there is no need for additional tests (laboratory, ultrasound, Pap smear) before its insertion iii. it only requires an anamnesis, pelvic examination and STI risk assessment (level of evidence A) for its insertion; iv. non-hormonal; v. long duration (BRASIL, 2018; Bahamondes *et al.*, 2019).

In addition, the IUD was considered by the World Health Organization to be a financially advantageous method for both public health agencies and users (WHO, 2018). Bongaarts and Johansson (2002) conducted a review of current methods for projecting future trends in contraception with the aim of alerting policymakers and program managers to the supplies and services needed to meet needs. They concluded that the copper IUD is the

most affordable long-acting reversible method that has ever been developed and that a lower-cost alternative LARC is unlikely to be developed (Bongaarts; Johansson, 2002)

Complications are considered rare and include the possibility of perforation of the uterine wall during insertion; however, they can evolve benignly, resulting in miscarriage, premature birth, or infection if a woman becomes pregnant while using the IUD. In addition, pelvic inflammatory disease (PID) is another occurrence when in cases of chlamydia or gonorrhea at the time the IUD is placed (Foran *et al.*, 2018; WHO, 2018).

Foran and colleagues (2018) found that there were reports of pain to varying degrees during device insertion, which may hinder the acceptance of the method as more reports of pain were moderate or severe in nulliparous women. Although, there are several options to relieve this pain, including the use of misoprostol prior to insertion, cervical local anesthesia, and the use of non-steroidal anti-inflammatory drugs prior to insertion, but there is no evidence that either technique is better (Foran *et al.*, 2018).

Changes in menstrual patterns, such as prolonged and heavy bleeding, irregular bleeding and more cramping during menstruation, especially in the first six months, are the most common complaints, which may be the cause of discontinuation of use (WHO, 2018).

There are few absolute contraindications to the method, namely: uterine abnormalities such as bicornuate uterus, septate or intense cervical stenosis; submucosal uterine fibroids with relevant distortion of the endometrial cavity; presence of STIs, such as chlamydia, gonorrhea and AIDS in clinical stages 3 and 4; presence of acute or chronic pelvic inflammatory disease, endometritis, mucopurulent cervicitis and pelvic tuberculosis; in the immediate postpartum period when fever is present during the labor or rupture of membranes for more than 24 hours, hypotonia or atonia after delivery, or placental retention; in the post-abortion period in cases of infected abortion; cervical cancer (BRASIL, 2018; WHO, 2018). The WHO medical eligibility criteria also consider contraindications to unexplained vaginal bleeding, malignant gestational trophoblastic disease, or elevated human chorionic gonadotropin (BhCG) levels (WHO, 2018). Due to the potential increase in menstrual flow observed in these cases, the use of copper IUDs will not be advantageous for women who use anticoagulants or have coagulation disorders (BRASIL, 2018; WHO, 2018). It can be offered to women who have had a previous ectopic pregnancy (Level B of evidence – by the American College of Gynecology and Obstetrics (ACOG) (Elgemark *et al.*, 2022).

2.7 KNOWLEDGE AND PROFESSIONAL PRACTICE IN IUD PLACEMENT

IUD insertion requires specialized training from professionals. Festin (2020) drew attention to the interest in promoting family planning programs, emphasizing the use of more effective, highly efficient, and safer contraceptives.

A survey that conducted 1,862 *online interviews* in 15 countries examined the knowledge and practice of professionals (gynecologists/obstetricians - GO, general practitioners and nurses) on IUD insertion in nulliparous women. The results showed differences between health professionals' opinions about the IUD and the available evidence (Black *et al.*, 2013). The professionals mentioned the following difficulties: difficulty in insertion, concerns about PID, pain during insertion and infertility. The authors come to the conclusion that more professional education is needed.

Carty *et al.* (2019) conducted a descriptive, cross-sectional study that used a structured questionnaire for attending physicians in the U.S. Army, most of whom worked in the primary care setting. The study revealed that of the physicians who reported having received training, the proportion was 10% in copper IUD insertion, 17% in progesterone IUD insertion and 33% in subdermal implants (LARCs). With regard to the copper IUD, only ten percent of the professionals trained in insertion said they had had the procedure in the twelve months prior to the survey. About 45% of respondents said they did not feel comfortable talking about IUD insertion with users, and 45% said they did not feel comfortable talking about the method (they felt more comfortable discussing less effective methods). Some also said that there were no materials needed for the procedure. The study found that professionals did not receive training in LARC and that they did not use the method either. Implementation can be hampered by lack of availability or information about the supplies needed to insert the device. They recommend training and evaluation of materials needed in the workplace.

A research conducted by Rubin *et al.* (2011), in which they sent a self-administered questionnaire to 3,500 FCMs, a random sample, with a response rate of 25%. Among the respondents, 61.5% had inserted at least one water infusion device (IUD) during medical residency, and 23.3% stated that they had inserted at least one IUD in the last 12 months of work. The only factor that indicated insertion in clinical practice was having inserted the IUD during residency (31.5% of the participants in the training during residency continued to insert the device, while 10.2% of the participants in the training during residency performed the procedure).

Compared to MFCs who did not use IUDs in daily practice, Rubin *et al.* (2011) found that MFCs who used IUDs in daily practice were more likely to recommend IUDs to women,

had greater knowledge about the method, considered it safe and effective, felt safe when talking about the method, and were more receptive to dialogues about the method. with a statistically significant difference In the previous twelve months, an average of 9 IUD devices were inserted in one year, and only 22.6% of MFCs inserted more than 10. Graduates with shorter undergraduate degrees in this study inserted IUDs more frequently than graduates with longer undergraduate degrees. This may indicate that there is better training in IUD insertion during residency. The authors argue that instruction and training in IUD insertion during medical residency can increase the number of women who can use the method.

2.8 GUIDELINES AFTER THE INSERTION OF THE COPPER IUD

It is important to guide the woman so that she knows how to identify the type of IUD she is using and its shape, in addition to understanding the importance of scheduled return appointments to monitor use; to know when to return to remove or change the IUD. The patient must be provided with a form in which the data on the insertion of the IUD are recorded, including month and year, and the date for removal. The woman should be instructed to inform the use of the IUD whenever she goes to any appointment, even if she is not asked.

In addition, a follow-up visit is recommended after your first period or three to six weeks after IUD insertion. After this visit, the IUD user should have an annual routine. The post-insertion visit allows for infection exclusion, assessment of bleeding patterns, assessment of patient and partner satisfaction, and a booster opportunity for condom use to protect against STIs (FEBRASGO, 2022).

The ideal positioning of the copper IUD aims to be closer to the uterine fundus. Therefore, a transvaginal ultrasound (TVUS) should be performed when there is doubt as to whether the IUD is correctly positioned and in the management of cases with suspected or present complications (Bartz, 2018; BRAZIL, 2018).

Requesting an ultrasound is recommended in the following cases, according to the Ministry of Health, if: suspected expulsion of the IUD; non-visualization of the IUD threads in the vagina or cervical canal, woman does not know if the IUD has been expelled; suspicion of perforation; obstruction of the canal preventing the placement of the IUD, or difficult insertion (when due to obstruction, fibroids, adenomyosis, retroverted positions, obesity) (BRAZIL, 2018).

2.9 SIDE EFFECTS AND COMPLICATIONS AND THEIR MANAGEMENT

Irregular bleeding or an increase in the amount of menstrual bleeding are the most common side effects in the first few months after IUD insertion. Change in menstrual flow in users when compared to non-users of copper IUDs can increase by up to 65%. The use of nonsteroidal anti-inflammatory drugs or tranexamic acid can help reduce menstrual loss. The average number of days of bleeding or "*spotting*" appears to decrease over time. Copper IUD users have an average of 13 days of bleeding or *spotting* in the first month after insertion, decreasing to an average of six days after 12 months of insertion. The cumulative rates of withdrawal due to menstrual problems after five years of use are up to 20% for copper IUDs. Pre-insertion counseling should include menstrual modifications, which will make acceptance easier (Harper *et al.*, 2012; FEBRASGO, 2022).

Pain or dysmenorrhea are causes of discontinuity in up to 6% of copper IUDs in five years. These may be a physiological response to the presence of the device, but the possibility of infection, malposition (including perforation), and pregnancy should be excluded. Lost hairs can be associated with several causes: perforation, expulsion, malposition, associated or not with pregnancy, but increasing its risk (FEBRASGO, 2022).

In these cases, a long forceps can be used inside the cervical canal in order to make the wire visible. If this is not possible, ultrasound should be considered. If the device is well positioned, it can be maintained and, at the time of its removal/replacement, if it was not possible to remove it by exploring the cervical canal with long forceps, it should be done by hysteroscopy. If perforation is detected, laparoscopy should be considered for removal. If TVUS is not available or the IUD is not noticed, X-ray of the pelvis should be considered. The copper IUD is radiopaque (FEBRASGO, 2022).

At the time of insertion, moderate to severe pain may occur. In some women, this triggers the vagovagal reflex and produces syncope. Symptoms such as hypotension, pallor, bradycardia, tachycardia, sweating may occur.

Perforation is the most severe complication of IUD insertion, which can occur through the uterine wall reaching the peritoneal cavity. It is directly proportional to the skill of the physician. Its incidence is estimated at 0-8.7 perforations per 1,000 insertions. One of the main reasons for its occurrence is the failure to determine uterine size and orientation, which is particularly important in uteruses with large anteversoflexion or retroversion. If chlamydia or gonococcal cervicitis is suspected, appropriate antibiotic therapy should be initiated for the user (and her sexual contacts). If PID is suspected, the IUD should be removed after antibiotic treatment. The use of barrier contraceptive methods for the prevention of STIs should be advised.

3 METHODOLOGY

This research consisted of two stages. Initially, residents in selected FCMs were trained to perform the procedure of inserting the copper IUD in the research participants. After training the team, a questionnaire was applied in order to evaluate the results and learning curve in IUD insertion by resident physicians of Family and Community Medicine in the city of Santa Maria-RS.

3.1 TRAINING OF FAMILY AND COMMUNITY PHYSICIANS FOR THE INSERTION OF THE COPPER IUD

At first, the resident in Family and Community Medicine responsible for the study underwent training for IUD insertion at the Family Planning Outpatient Clinic of the University Hospital of Santa Maria (HUSM), for a period corresponding to 2 months. This training, which is part of the Medical Residency Program in Family and Community Medicine at the Federal University of Santa Maria (UFSM), was carried out in a theoretical-practical way. The theoretical part addressed the IUD insertion technique and its possible complications, based on a protocol of the Ministry of Health (2018). The practical part consisted of the execution of the IUD insertion technique in 15 women under the supervision of the outpatient clinic's preceptor. After insertion, a TVUS was requested in order to verify the proper positioning of the IUD, the result of which was seen in a follow-up consultation for review of the case.

After being qualified for IUD insertion, the author of this study selected 3 resident physicians of Family and Community Medicine, upon expression of interest in participating in the project. The interested resident physicians participated in training supervised by the author of the study, for IUD insertion, in order to verify their previous theoretical/practical skills. In a second moment, they were presented with the POP IUD Insertion and Removal previously approved by the Secretary of Health of the municipality of Santa Maria-RS. After a careful study of the SOP, the resident physicians began the insertion of IUDs in the São José FHS, under the supervision of a Community Family Physician qualified for this purpose.

3.2 STUDY DESIGN

The present study was a qualitative and quantitative study, carried out at the FHS São José, São José neighborhood, city of Santa Maria, Rio Grande do Sul State, Brazil. Women of childbearing age (18-45 years) who were interested in using IUDs as a contraceptive method were invited to participate in this study.

The study included 47 women and 3 resident physicians in Family and Community Medicine, two of whom were second-year residents at the Franciscan University (UFN), one

assigned to the ESF Passo das Tropas and the other assigned to the ESF Parque Pinheiro Machado, and 1 first-year resident from UFSM, assigned to the ESF São José.

For this study, women assisted by FCM at the FHS São José, Camobi neighborhood, Santa Maria, RS, were selected. Patients with clinical indication for long-acting contraception were offered the copper IUD as a contraceptive method, which lasts for 10 years.

After clinical evaluation, respecting the indications and contraindications of the method, the insertion of the IUD was offered by resident physicians in Family and Community Medicine of the ESF São José. The women who agreed to participate in the study signed the Informed Consent Form (ICF). approved by the Research Ethics Committee under CAAE: 62388122.0.0000.5346; Opinion Number: 5.639.348.

Healthy women aged 18 to 45 years with desire and clinical indication for long-acting contraception were included in the study. Patients who are pregnant or have excessive vaginal bleeding, vaginitis, cervicitis, acute or chronic pelvic inflammatory disease, uterine malformations, pelvic tumors, or genital cancer were excluded from the study.

The information collected was used exclusively by the researchers in order to provide components for the realization of this research, the articles and publications that resulted from it. Data confidentiality was maintained during all stages of the research. In order to ensure confidentiality and privacy, the interviewers were instructed about the entire data collection process and instructed to be aware of signs of discomfort, both verbal and non-verbal on the part of the participants.

The research offered a medium risk, due to the probability of some complication or pain occurring during the IUD insertion process. In addition, there was minimal risk due to the likelihood of embarrassment, fatigue, or annoyance when answering the sociodemographic questionnaire, the time spent answering the questionnaire, and the risk of revealing confidential information.

3.3 APPLICATION OF QUESTIONNAIRES

Before the training for IUD insertion, a questionnaire containing five questions was applied to the resident physicians in Family and Community Medicine, in order to verify their knowledge and previous experiences. After the training, they answered seven others in order to check their experience and skills after learning about SOP Insertion and Removal of the Copper Intrauterine Device (IUD) approved by the Secretary of Health of the Municipality of Santa Maria-RS.

The study participants answered a questionnaire before IUD insertion containing seven questions in order to compute sociodemographic data of the target population of this study.

3.4 PRE-CONSULTATION AND IUD INSERTION

A pre-consultation with patients interested in IUD insertion was carried out by a Family and Community doctor at the ESF São José. In the consultation, the patients received guidance on the indications, contraindications, risks and benefits of inserting non-hormonal IUDs. In addition, in this consultation, a pregnancy test was requested to be performed the day before the date of scheduling for IUD insertion and a non-steroidal anti-inflammatory drug was provided to be used prior to IUD insertion.

The IUD model used during the research was the TCU 380 A copper IUD (Figure 1). This model lasts 10 years, has a T shape and is coated with 324 mm² of copper on the vertical rod and 33 mm² distributed in two copper rings on the horizontal rod. The IUDs used in the São José FHS were made available by the Municipal Health Department of Santa Maria-RS for the research.

The IUD insertion was performed, according to the technique described in Appendix I, by FCM working with the ESF São José and by resident physicians in Family and Community Medicine from UFSM and UFN, under the supervision of the former, with the support, when necessary, of the gynecologist and project advisor Dr. Cristine Kolling Konopka.

Guidance regarding the most prevalent clinical manifestations caused by IUD insertion was given to the patients, such as increased menstrual flow, dysmenorrhea, and pelvic pain. These symptoms are more frequent in the first months after the procedure and, for their relief, a non-steroidal anti-inflammatory drug was prescribed.

3.5 POST-IUD INSERTION FOLLOW-UP

After the insertion of the IUD, the patients were referred for TVUS at the ultrasound service of the city of Santa Maria (Women's Health Care Center), in order to verify the correct positioning of the IUD. In a follow-up visit, the result was evaluated by the FCM. Cases of IUD malposition were submitted to the removal of the device and these women were given the opportunity to perform a new IUD insertion at the same time.

3.6 STATISTICAL ANALYSIS OF THE DATA

Qualitative variables were presented through graphs and tables, with absolute and relative frequencies. Quantitative variables were represented by arithmetic mean ($\pm$ standard deviation). The software used was Statistica 14.0.

4 RESULTS

The patients who participated in the research through the insertion of the copper IUD by the FCM had a mean age of 27 years, and 74.5% of them were between 19 and 35 years old. The majority declared to be married and/or in a stable union 61.7%. In addition, 72.3% had one or more previous pregnancies (Table 1). Maternal age, marital status, and previous parity may be related to a greater need for LARC and knowledge about the benefits of the IUD may be decisive in the choice of contraceptive method.

Of the sample studied, the majority (66%) declared themselves white; had completed higher education (19.1%) and completed high school or incomplete higher education (51.1%); and engaged in some paid activity (59.6%). These indices may be related to the neighborhood in which the participating women belong, since it is an area where purchasing power is higher compared to other neighborhoods in the municipality. This same relationship can be seen in the question of having health insurance, since 44.7% stated that they had some health insurance.

Table 1

Sociodemographic characteristics of women who had IUDs placed

Features	n	%
Age - mean ($\pm$standard deviation)	28.2 ($\pm$ 6.4)	
$\leq$ 19 years old	02	4,2
From 19 to 34 years old	35	74,5
$\geq$ 35 years	10	21,3
Religion		
Catholic	14	29,8
Evangelical	10	21,3
Spiritist/Afro-Brazilian	03	6,3
None	20	42,5
Color		
White	31	66,0
Black	06	12,8
Brown	10	21,3
Education		
Incomplete elementary school	06	12,8
Complete elementary school/incomplete high school	08	17,0
Complete high school/ Incomplete higher education	24	51,1
Complete higher education	09	19,1
Has a paid activity		

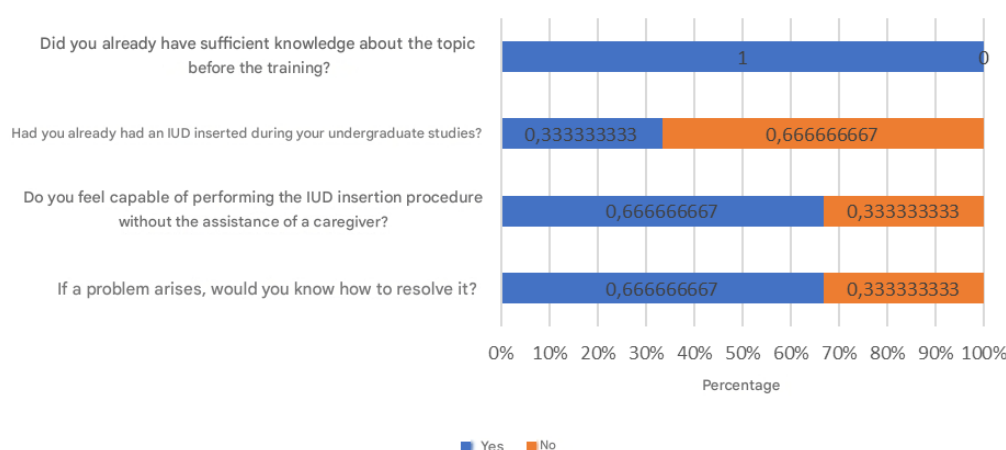
Yes	28	59,6
No	19	40,4
Married or Stable Union		
Yes	29	61,7
No	18	38,3
Health Plan		
Yes	21	44,7
No	26	55,3
How many pregnancies – average ($\pm$standard deviation)		
0	13	27,7
1	14	29,8
2	12	25,5
3 or +	08	17,0

Source: (AUTHOR, 2024).

The resident physicians in Family and Community Medicine who participated in the research answered a questionnaire, in which some items related to technical capacity and knowledge related to IUD insertion before and after training were evaluated. Figure 2 shows the answers to the questions asked in the pre-training (Annex V – Part 1). All resident physicians reported that they already had sufficient knowledge on the subject before the training and 66.7% of them considered the procedure as difficult before the training. Although only 33.3% of them had an IUD inserted during their undergraduate studies; 66.7% felt capable of performing the procedure without the help of a tutor and would know how to solve complications related to the insertion of the device.

Figure 2

Responses of resident physicians in Family and Community Medicine to the pre-training questionnaire



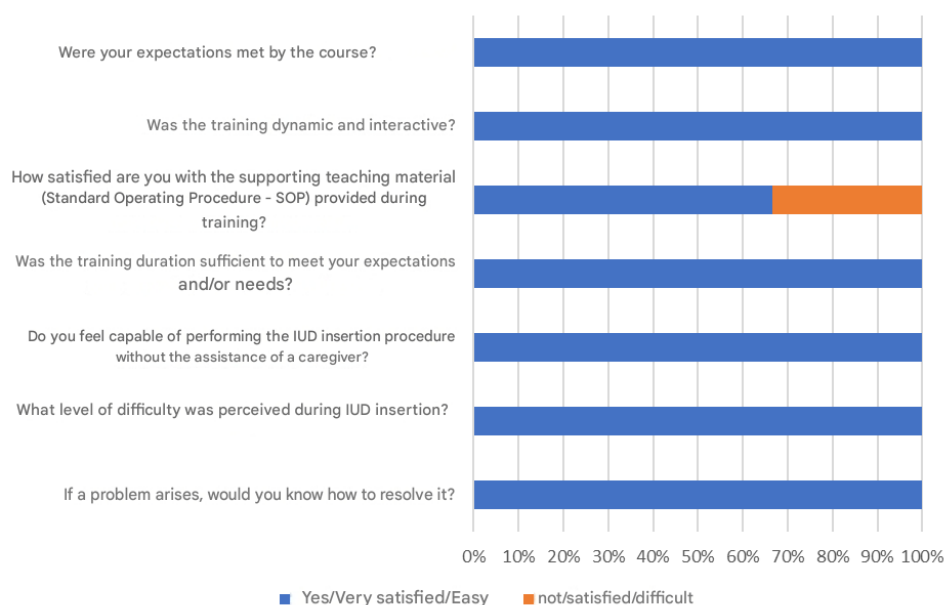
Source: (AUTHOR, 2024).

After training for IUD insertion, the same resident physicians answered the questions in Annex V, Part 2. The results are presented in figure 3. All of them considered that their expectations were met with the course, reported that the training was dynamic and

interactive, were satisfied with the didactic support material and considered that the duration of the training was sufficient to meet their expectations and/or needs. After the training, all of them stated that the insertion of the IUD is an easy procedure and they would know how to solve any complications, if it occurred, during the insertion.

Figure 3

Responses of resident physicians in Family and Community Medicine to the post-training questionnaire



Source: (AUTHOR, 2024).

Regarding the number of IUD insertions by the Family and Community physician, responsible for the development of the study, 34 IUD insertions were totaled, 15 of which during training at the Family Planning Outpatient Clinic of the HUSM, during the period of medical residency in Family and Community Medicine, under the supervision of Dr. Fernanda Lang, gynecologist and obstetrician; and another 19 IUDs at the ESF São José, post-training. On the other hand, 2 of the residents (UFN) performed 8 IUD insertions (entitled residents 1 and 3 in the order of citation), 4 pre-training IUD insertions and 4 post-training IUDs, while 1 of the residents (UFSM) performed 10 IUD insertions (entitled resident 2), 5 pre-training IUD insertions and 5 post-training IUDs, as shown in Figure 4.

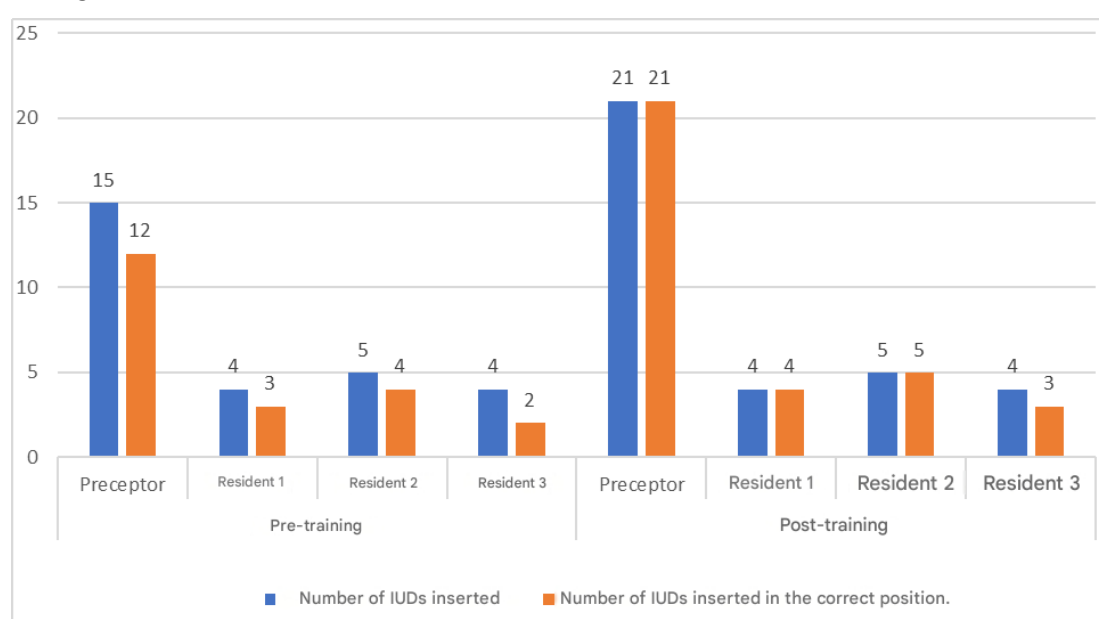
Regarding the correct position of the IUDs before and after training, of the 62 IUDs inserted, 54 (87.1%) were placed in the correct position. 28 and 34 IUDs were inserted, 21 (75%) and 33 (97%) in the correct position, respectively, in the pre- and post-training.

Of the 15 IUDs inserted during training at the Family Planning Outpatient Clinic of the HUSM carried out by the Family and Community physician (preceptor), 12/15 (80%) IUDs

were in the correct position, and of the 19 IUDs inserted post-training, 21/21 (100%) IUDs were in the correct position. As for the residents, the resident titled 1, of the 4 IUDs inserted, 3 (75%) IUDs were in the correct pre-training position and 4 (100%) IUDs in the correct post-training position, the resident titled 2, of the 10 IUDs inserted, 4 (75%) IUDs were in the correct pre-training position and 5 (100%) IUDs in the correct post-training position, while the resident entitled 3 of the 4 IUDs inserted, 2 (50%) IUDs were in the correct pre-training position and 3 (75%) IUDs in the correct position post-training (Figure 4).

Figure 4

Number of IUD insertions and number of IUDs inserted in the correct position in the pre- and post-training



Source: (AUTHOR, 2024).

In addition, when we evaluate the amount of IUDs inserted in the municipality, it is noted that at the beginning of the project that started in September 2022, only ESF São José inserted 24.1% of the IUDs in the municipality, the rest was centralized in the Women's Health Clinic, being performed by a gynecologist, and in all of 2023 there was a drop to 14.4%, this drop is due to the fact that in the Family and Community Medicine residency, in which one of the practical pillars is the insertion of the IUD, there was an increase in insertion in other ESFs after the training, in addition the municipality inaugurated a polyclinic where small procedures are performed, including the insertion of IUDs, but in the polyclinic the insertion is performed by MFCs. So the insertion of IUDs in the municipality remained, basically, with 3 fixed IUD insertion sites, and even so, the ESF São José managed to maintain a considerable percentage since Santa Maria has 26 basic health units.

5 DISCUSSION

Copper T Cu 380A IUDs were inserted in 47 women, aged 19 to 34 years (74.5%), with no religion (42.5%), white (66.0%), with complete high school or incomplete higher education (51.1%), who had a paid activity (61.7%), had no health insurance (55.3%) and were nulliparous (27.7%). In a similar study by Morais *et al.* (2021) found that women who underwent copper IUD insertion in Primary Health Care (PHC) in municipalities in Paraíba were between 20 and 29 years old, at least completed high school, had some paid activity, were nulliparous, and/or had at least one child. According to Dias *et al.* (2021) marital status, level of education, color/race, participation in a family planning group, and having already been pregnant are significant variables for reproductive autonomy.

The three resident physicians in Family and Community Medicine were trained, because according to Thompson *et al.* (2016), training is essential to ensure the quality and uniformity of all processes involved, including expanding the offer of LARCs. In addition, IUD training for healthcare professionals contributes to improved knowledge and attitudes towards IUD delivery, high rates of successful insertions with low complication rates, and increased supply of IUDs to women (Ouyang *et al.*, 2019).

In a study of 45 *Harvard Medical School* students who completed their OB and GYNECOLOGY internships at Brigham and Women's Hospital, Bartz *et al.* (2016) found that more than half of the participants (54%) had learned about IUDs in a previous medical school lecture, however, only a minority (26%) had previous or during college experience in IUD insertion. In addition, Bartz *et al.* (2016), found that among the interviewees (49%) chose "participating in practical activities" as a way to improve learning, suggesting that training increases scores such as skill, confidence and clinical performance. The resident physicians participating in our research answered the questionnaire regarding their technical capacity and knowledge related to IUD insertion before and after training. Here, the results showed that only 33.3% of the resident physicians who participated in this study performed IUD insertion during their undergraduate studies, but 100% stated that they already had sufficient knowledge about the subject before the training. After the training, 100% of the resident physicians answered that the duration of the training was sufficient to meet their expectations and/or needs and that the training was dynamic and interactive.

When the duration of the training, number of IUDs inserted, ability to insert the IUD without tutoring, difficulty in insertion, and dealing with possible complications were determined, all the professionals in our research reacted positively.

Another relevant data was related to the degree of difficulty, which 66.7% stated as a difficult procedure before training, and after training 100% of them reported as easy to insert

IUDs. This may be related to the answer regarding the degree of knowledge about IUD insertion, in which 66.7% stated that they did not have sufficient knowledge for this procedure before the training. Other data that bring the need for more training like this is the *feedback* reported by resident physicians, in which 100% of them declared that in addition to the training being dynamic and interactive, it can meet all the expectations set for it.

In a similar survey conducted in Australia (Stewart *et al.*, 2016), 87.5% of physicians working in PHC, both public and private, answered a questionnaire before and after IUD insertion training with the aim of identifying and understanding the results of the training on their knowledge and skills, as well as the obstacles to the method. Prior to the training, none of them had performed the procedure in their clinical practice. Among the twenty-two physicians who answered the follow-up questionnaire, which was conducted one year after the training, 298 IUD insertions were performed, with an 89% success rate. Compared to our study, training increased the number of IUDs placed in the correct position, because pre-training 75% of the IUDs were placed in the correct position and after training this percentage increased to 97%.

In the same Australian study, only 24% of trained physicians said they felt confident and skilled to insert copper IUDs in multiparous women, while 64% said they felt the same confidence for the procedure in nulliparous women. In total, only a few complications were reported (11% of the total), including problems with hysterometry, problems with IUD technology, vasovagal reactions, a poorly positioned IUD, and expulsion. There were no infections or perforations.

In a study to train PHC professionals for the insertion of the copper IUD in the municipality of Betim - Minas Gerais, it was revealed that at least 8 IUD insertions were able to fully enable the physician to perform such a procedure without tutoring (De Souza *et al.*, 2021). In addition, interventions with training, according to Thompson *et al.* (2018) were able to change the attitudes, knowledge and counseling practices of professionals related to IUD insertion, showing impactful, lasting work and encouraging continuing education.

In our context, the resident physicians participating in the training had a large gap between having received training and actually performing the procedure. In addition, it is added to the fact that when IUD providers during residency, they end up performing the procedure during the last year of residency in Family and Community Medicine without follow-up and continuity due to turnover, high demand for care and lack of public stimulus. All these factors, which we have pointed out here, corroborate the low adherence of contraception through IUDs by patients.

Although the IUD can be inserted at any time and is a simple and easy procedure, many of the users we serve reported having received mistaken information such as: i. not be menstruating; II. Be up to date with a preventive cervical exam; iii. not be nulliparous. Examples like this are even reported by the Ministry of Health as reasons for low adherence to the use of IUDs by users (BRASIL, 2018). According to the Ministry of Health, in addition to this information not being adequate, it can also hinder or postpone the use of contraceptive methods, which can result in unwanted pregnancies (BRASIL, 2018).

One way to give women access to the benefits of this method is to increase the supply of copper IUDs in Primary Care. As already reported by Gonzaga *et al.*, (2017), this is considered a necessary and significant effort to expand people's access to this contraceptive method. The approval of the SOP linked to the theoretical-practical training with resident physicians of Family and Community Medicine in this study, indirectly allowed not only to improve the technical quality of the procedures in the municipality, but also to bring the reality and conditions of the municipality closer, allowing all professionals to follow the same standard, even in the face of intrinsic disparities and realities. Thus, the research provided results that may support the indication of the copper intrauterine device, which is still very much involved in myths and unnecessary obstacles caused by the lack of knowledge and training of most professionals.

It is estimated that 1 health unit in Santa Maria - RS out of 26 perform the procedure continuously and routinely, and that another 5 units have professionals qualified to insert IUDs, but they do not perform it continuously due to lack of interest or job change.

Another important point of working more effectively is the concept of decentralization of service supply, sensitizing contracted Family and Community Doctors and PHC managers, through continuing education activities with theoretical and practical training, perhaps with a reduction in the demand for clinical care and a better financial appreciation.

The research reinforces the importance of medical residency, but also suggests that as the insertion of IUDs is part of the curricular matrices of residencies, the training of these Family and Community Medicine residents should be removed from the Family Planning sector of the University Hospital of Santa Maria (HUSM), where the training is currently carried out, and distribute it in health units that already have trained MFCs, thus making these units maintain the offer of IUD insertion in a routine way and not intermittently. With this there would be a much greater coverage of the entire city, including poorer regions where the number of unwanted pregnancies is high.

6 CONCLUSIONS

The training carried out with the residents of Family and Community Medicine was well received by the physicians, who considered the training adequate for their qualification and technical performance. This training model in the ESF allows a greater coverage of professionals who can promote contraception with LARC, consequently reducing the cases of unplanned pregnancies in the community. The epidemiological profile of the participating patients showed a majority of women with one or more pregnancies, with a profile for the use of LARC. The increase in the number of well-positioned IUD cases after training allows us to recommend the IUD training model by FCM residents under preceptorship supervision.

Thus, through this study it was possible to conclude that training for IUD insertion by family and community physicians in the UBS and with the ESFs is a plausible reality in the city of Santa Maria-RS. In addition, the wide supply of IUDs will automatically increase the number of IUD insertions in a short period of time in the municipality of Santa Maria-RS, decentralizing the supply and ensuring greater universality to women's right to reproductive health.

It is expected and suggested that there will be greater appreciation on the part of public health management regarding the insertion of IUDs in the UBS, and that there will be greater encouragement for Family and Community Medicine physicians to implement such a procedure as a routine.

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PHARMACOTHERAPY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (2015-2025)

FARMACOTERAPIA DO TRANSTORNO DO DÉFICIT DE ATENÇÃO/HIPERATIVIDADE EM ADULTOS: REVISÃO SISTEMÁTICA COM METANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS (2015-2025)

FARMACOTERAPIA DEL TRASTORNO POR DÉFICIT DE ATENCIÓN CON HIPERACTIVIDAD EN ADULTOS: UNA REVISIÓN SISTEMÁTICA CON METAANÁLISIS DE ENSAYOS CLÍNICOS ALEATORIZADOS (2015-2025)



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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) affects approximately 2.5% of the adult population globally. Multiple pharmacological agents are available, yet comparative efficacy and safety data remain limited. Objective: To systematically review and meta-analyze the efficacy, safety, and tolerability of pharmacological treatments for adults with ADHD using randomized controlled trials (RCTs) published between 2015 and 2025. Methods: Systematic searches were conducted in PubMed/MEDLINE, Embase, and Cochrane Library for double-blind, placebo-controlled RCTs in adults (≥ 18 years) with ADHD diagnosed according to DSM-IV, DSM-5, or ICD-10/11 criteria. Primary outcome was symptom reduction measured by validated scales (ADHD-RS, Conners, SNAP-IV). Secondary outcomes included adverse events, discontinuation rates, and functional improvement. Risk of bias was assessed using Cochrane RoB 2.0. Meta-analysis employed random-effects models with standardized mean differences (SMD) and 95% confidence intervals (CI).

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Heterogeneity was evaluated using I^2 statistics. GRADE methodology was applied to assess evidence quality. Results: Thirty-seven RCTs ($n=2,289$ adults) were included. Methylphenidate extended-release demonstrated the largest effect size (SMD: -0.92 ; 95% CI: -1.08 to -0.76), followed by lisdexamfetamine (SMD: -0.96 ; 95% CI: -1.17 to -0.76), mixed amphetamine salts (SMD: -0.81 ; 95% CI: -0.95 to -0.67), and atomoxetine (SMD: -0.48 ; 95% CI: -0.64 to -0.33). Guanfacine showed moderate efficacy (SMD: -0.66 ; 95% CI: -0.94 to -0.38). Stimulants demonstrated superior acceptability compared to non-stimulants. Adverse events were generally mild and dose-dependent. Heterogeneity was moderate (I^2 : 30–50%). Conclusion: Stimulant medications, particularly methylphenidate and lisdexamfetamine, represent first-line pharmacological treatments for adults with ADHD, with large effect sizes and favorable tolerability profiles. Non-stimulants offer alternatives for patients with contraindications or comorbidities. Evidence quality ranges from moderate to high for stimulants and low to moderate for non-stimulants.

Keywords: ADHD. Adults. Methylphenidate. Lisdexamfetamine. Atomoxetine. Guanfacine. Meta-Analysis. Randomized Controlled Trial.

RESUMO

Introdução: O transtorno do déficit de atenção/hiperatividade (TDAH) afeta aproximadamente 2,5% da população adulta globalmente. Múltiplos agentes farmacológicos estão disponíveis, porém dados comparativos de eficácia e segurança permanecem limitados. **Objetivo:** Revisar sistematicamente e realizar metanálise da eficácia, segurança e tolerabilidade de tratamentos farmacológicos para TDAH em adultos utilizando ensaios clínicos randomizados (ECR) publicados entre 2015 e 2025. **Métodos:** Buscas sistemáticas foram conduzidas em PubMed/MEDLINE, Embase e Cochrane Library para ECR duplo-cegos, controlados por placebo, em adultos (≥ 18 anos) com TDAH diagnosticado conforme DSM-IV, DSM-5 ou CID-10/11. **Desfecho primário** foi redução de sintomas medida por escalas validadas (ADHD-RS, Conners, SNAP-IV). **Desfechos secundários** incluíram eventos adversos, taxas de descontinuação e melhora funcional. Risco de viés foi avaliado usando Cochrane RoB 2.0. Metanálise utilizou modelos de efeitos aleatórios com diferenças de médias padronizadas (DMP) e intervalos de confiança 95% (IC 95%). Heterogeneidade foi avaliada usando estatística I^2 . Metodologia GRADE foi aplicada para avaliar qualidade de evidência. **Resultados:** Trinta e sete ECR ($n=2.289$ adultos) foram incluídos. Metilfenidato de liberação prolongada demonstrou o maior tamanho de efeito (DMP: $-0,92$; IC 95%: $-1,08$ a $-0,76$), seguido por lisdexanfetamina (DMP: $-0,96$; IC 95%: $-1,17$ a $-0,76$), sais de amfetamina mista (DMP: $-0,81$; IC 95%: $-0,95$ a $-0,67$) e atomoxetina (DMP: $-0,48$; IC 95%: $-0,64$ a $-0,33$). Guanfacina mostrou eficácia moderada (DMP: $-0,66$; IC 95%: $-0,94$ a $-0,38$). Estimulantes demonstraram aceitabilidade superior comparado a não-estimulantes. Eventos adversos foram geralmente leves e dose-dependentes. Heterogeneidade foi moderada (I^2 : 30–50%). **Conclusão:** Medicamentos estimulantes, particularmente metilfenidato e lisdexanfetamina, representam tratamentos farmacológicos de primeira linha para TDAH em adultos, com grandes tamanhos de efeito e perfis de tolerabilidade favoráveis. Não-estimulantes oferecem alternativas para pacientes com contraindicações ou comorbidades. Qualidade de evidência varia de moderada a alta para estimulantes e baixa a moderada para não-estimulantes.

Palavras-chave: TDAH. Adultos. Metilfenidato. Lisdexanfetamina. Atomoxetina. Guanfacina. Metanálise. Ensaio Clínico Randomizado.

RESUMEN

Introducción: El trastorno por déficit de atención con hiperactividad (TDAH) afecta aproximadamente al 2,5 % de la población adulta mundial. Existen múltiples agentes farmacológicos disponibles, pero los datos comparativos de eficacia y seguridad siguen

siendo limitados. **Objetivo:** Revisar sistemáticamente y realizar un metaanálisis de la eficacia, seguridad y tolerabilidad de los tratamientos farmacológicos para el TDAH en adultos utilizando ensayos controlados aleatorizados (ECA) publicados entre 2015 y 2025. **Métodos:** Se realizaron búsquedas sistemáticas en PubMed/MEDLINE, Embase y la Biblioteca Cochrane de ECA doble ciego, controlados con placebo en adultos (≥ 18 años) con TDAH diagnosticado según DSM-IV, DSM-5 o CIE-10/11. El resultado primario fue la reducción de los síntomas medida por escalas validadas (ADHD-RS, Conners, SNAP-IV). Los resultados secundarios incluyeron eventos adversos, tasas de interrupción y mejora funcional. El riesgo de sesgo se evaluó utilizando Cochrane RoB 2.0. El metaanálisis empleó modelos de efectos aleatorios con diferencias de medias estandarizadas (DME) e intervalos de confianza del 95 % (IC del 95 %). La heterogeneidad se evaluó mediante el estadístico I^2 . Se aplicó la metodología GRADE para evaluar la calidad de la evidencia. **Resultados:** Se incluyeron treinta y siete ECA ($n = 2289$ adultos). El metilfenidato de liberación prolongada demostró el mayor tamaño del efecto (DME: -0,92; IC del 95%: -1,08 a -0,76), seguido de la lisdexanfetamina (DME: -0,96; IC del 95%: -1,17 a -0,76), las sales mixtas de anfetamina (DME: -0,81; IC del 95%: -0,95 a -0,67) y la atomoxetina (DME: -0,48; IC del 95%: -0,64 a -0,33). La guanfacina mostró una eficacia moderada (DME: -0,66; IC del 95%: -0,94 a -0,38). Los estimulantes demostraron una aceptabilidad superior en comparación con los no estimulantes. Los eventos adversos fueron generalmente leves y dependientes de la dosis. La heterogeneidad fue moderada (I^2 : 30-50%). **Conclusión:** Los medicamentos estimulantes, en particular el metilfenidato y la lisdexanfetamina, representan los tratamientos farmacológicos de primera línea para el TDAH en adultos, con efectos de gran magnitud y perfiles de tolerabilidad favorables. Los fármacos no estimulantes ofrecen alternativas para pacientes con contraindicaciones o comorbilidades. La calidad de la evidencia varía de moderada a alta para los estimulantes y de baja a moderada para los no estimulantes.

Palabras clave: TDAH. Adultos. Metilfenidato. Lisdexanfetamina. Atomoxetina. Guanfacina. Metaanálisis. Ensayo Clínico Aleatorizado.

1 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent patterns of inattention and/or hyperactivity-impulsivity that interfere with functioning or development (1). According to the DSM-5, the diagnosis requires evidence of symptoms present before 12 years of age, manifestation in multiple contexts (school, occupational, social), and clinically significant functional impairment (1). The ICD-11 classifies ADHD under the category of neurodevelopmental disorders, with similar diagnostic criteria (2). The prevalence of ADHD in adults varies between 2.5% and 6.8% depending on the study methodology and the population investigated (3).

Meta-analysis studies indicate that approximately 2.58% of the adult population has persistent ADHD since childhood, while 6.76% report ADHD symptoms in adulthood regardless of age of onset (3). The prevalence is consistently higher in males compared to females, with an approximate ratio of 1.5:1 to 2:1 (3).

ADHD in adults is associated with significant impairments in occupational functioning, interpersonal relationships, quality of life, and increased risk for psychiatric and behavioral comorbidities (4). ADHD involves dysfunction in monoaminergic neurotransmission systems, particularly dopamine and norepinephrine (5). Functional neuroimaging studies demonstrate alterations in neural networks involved in attention, inhibitory control, and reward processing, including the dorsolateral prefrontal cortex, anterior cingulate cortex, and striatum (5).

Deficits in dopamine in the prefrontal cortex result in impaired executive functions, while dopaminergic dysfunction in the limbic system contributes to emotional dysregulation and impulsivity (5). Genetic polymorphisms in genes encoding dopamine transporters (DAT1) and dopamine receptors (DRD4, DRD5) are associated with increased risk of ADHD (6).

Stimulants such as methylphenidate and amphetamines are monoamine reuptake inhibitors that increase synaptic concentrations of dopamine and norepinephrine through blockade of the dopamine transporter (DAT) and noradrenaline transporter (NET) (7). Lisdexamfetamine is a prodrug that requires hepatic metabolism for conversion to active d-amphetamine, conferring a longer pharmacokinetic profile and lower potential for abuse (7).

Stimulants with tomoxetine are a selective noradrenaline reuptake inhibitor that increases prefrontal noradrenaline concentrations without direct effects on dopamine (8). Guanfacine and clonidine are alpha-2 adrenergic agonists that modulate noradrenergic activity in the prefrontal cortex, improving executive functions and inhibitory control (8). Although stimulants are considered first-line, approximately 30% of adult patients do not respond adequately or have unacceptable adverse effects (9). Direct comparisons between

pharmacological agents are essential to optimize treatment selection based on individual efficacy profile, tolerability, and safety. Recent meta-analyses allow quantitative synthesis of data from multiple RCTs, providing comparative effect estimates and identifying heterogeneity in therapeutic response (9).

Although multiple systematic reviews address ADHD pharmacotherapy in children and adolescents, data specific to the adult population remain fragmented (10). Few studies directly compare multiple pharmacological classes in a homogeneous adult population. Data on long-term efficacy (>6 months) are limited. Information on predictors of therapeutic response and dose optimization strategies remains insufficient (10).

This systematic review with meta-analysis aims to synthesize evidence from randomized controlled trials published between 2015 and 2025 comparing efficacy, safety, and tolerability of methylphenidate, lisdexamfetamine, mixed amphetamine salts, atomoxetine, guanfacine, and clonidine in adults with ADHD, using validated symptom rating scales as the primary outcome.

2 METHODOLOGY

2.1 TYPE OF STUDY AND REGISTRATION

This is a systematic review with meta-analysis of double-blind, placebo-controlled randomized controlled trials (RCTs). The report of this review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (11). The detailed protocol of this review was prospectively registered in the international database PROSPERO (International Prospective Register of Systematic Reviews) under registration number CRDxxxxxx (2.2).

2.2 SEARCH STRATEGY AND DATA SOURCES

The literature search was carried out in three electronic databases: PubMed/MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL). The search was limited to studies published between January 1, 2015 and December 31, 2025, and restricted to English and Portuguese.

The complete search strategies, using MeSH and DeCS terms, were adapted to each database, as detailed below:

PubMed: (ADHD OR "attention deficit hyperactivity disorder") AND (adult* OR adult) AND (methylphenidate OR amphetamine OR lisdexamfetamine OR atomoxetine OR guanfacine OR clonidine) AND (randomized OR randomised OR RCT OR "clinical trial") AND (2015:2025[pdat])

Embase: 'attention deficit hyperactivity disorder'/exp OR ADHD AND adult* AND (methylphenidate OR amphetamine OR lisdexamfetamine OR atomoxetine OR guanfacine OR clonidine) AND (randomized OR randomised OR 'clinical trial') AND [2015-2025]/py

Cochrane: ADHD AND adult* AND (methylphenidate OR amphetamine OR lisdexamfetamine OR atomoxetine OR guanfacine OR clonidine)

2.3 ELIGIBILITY CRITERIA (PEAK)

Eligibility criteria were defined based on the PICO framework (Population, Intervention, Comparator, Outcome):

Category

Inclusion Criteria

Exclusion Criteria

Population (P)

Adults (≥ 18 years old) with a diagnosis of ADHD (DSM-IV, DSM-5 or ICD-10/11).

Studies in children or adolescents exclusively.

Intervention (I)

Methylphenidate (immediate- or extended-release), lisdexamfetamine, mixed amphetamine salts, atomoxetine, guanfacine, clonidine.

Studies lasting < 1 week.

Comparator (C)

Placebo.

Active control studies in the placebo arm.

Drawing(s)

Randomized controlled trials (RCTs), double-blind, placebo-controlled. Minimum duration of 1 week.

Observational, quasi-experimental or open-label studies.

Primary Outcome (O)

ADHD symptom reduction as measured by validated scales (ADHD-RS, Conners, SNAP-IV).

Studies with very low methodological quality (Cochrane RoB 2.0 with high risk in ≥ 3 domains).

Secondary Outcome (O)

Discontinuation rate for adverse events.

Duplicate posts or redundant data.

2.4 SELECTION OF STUDIES AND DATA EXTRACTION

The selection of studies was carried out in two phases by two independent reviewers (R1 and R2). In Phase 1, titles and abstracts were screened based on the eligibility criteria. In Phase 2, potentially eligible articles were evaluated in full text. Disagreements were resolved by consensus or by a third reviewer (R3). The agreement between the reviewers was assessed by Cohen's Kappa (target: $\kappa \geq 0.60$).

Data extraction was performed independently by R1 and R2, using a standardized form to collect: study characteristics (author, year, country, design), population characteristics (n, mean age, gender, diagnostic criteria), intervention (drug, dose, duration), outcomes (scale used, mean change, standard deviation, 95% CI), and Adverse Events (type, frequency, discontinuation rate).

2.5 ASSESSMENT OF RISK OF BIAS

The risk of bias of the included studies was independently assessed by R1 and R2 using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. The evaluation considered the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and researchers), detection bias (blinding of outcome evaluators), attrition bias (incomplete data), and reporting bias (selective reporting of outcomes). Studies with high risk in ≥ 2 domains were considered to have compromised methodological quality.

2.6 DATA SYNTHESIS AND META-ANALYSIS

The meta-analysis was conducted using the Random Effects Model (DerSimonian-Laird), due to the expected clinical and methodological heterogeneity between the studies.

Primary Outcome (Efficacy): The measure of effect used was the Standardized Mean Difference (SMD; Cohen's d), calculated for symptom reduction. SMD was interpreted as: small (0.2), medium (0.5), and large (0.8) (13).

Secondary Outcome (Tolerability): The measure of effect used was the Relative Risk (RR) for the rate of discontinuation for adverse events.

Statistical heterogeneity was assessed by the Cochrane Q test ($p < 0.10$ indicating significant heterogeneity) and by the I^2 statistic (0-25%: low; 25-50%: moderate; 50-75%: high; >75%: very high).

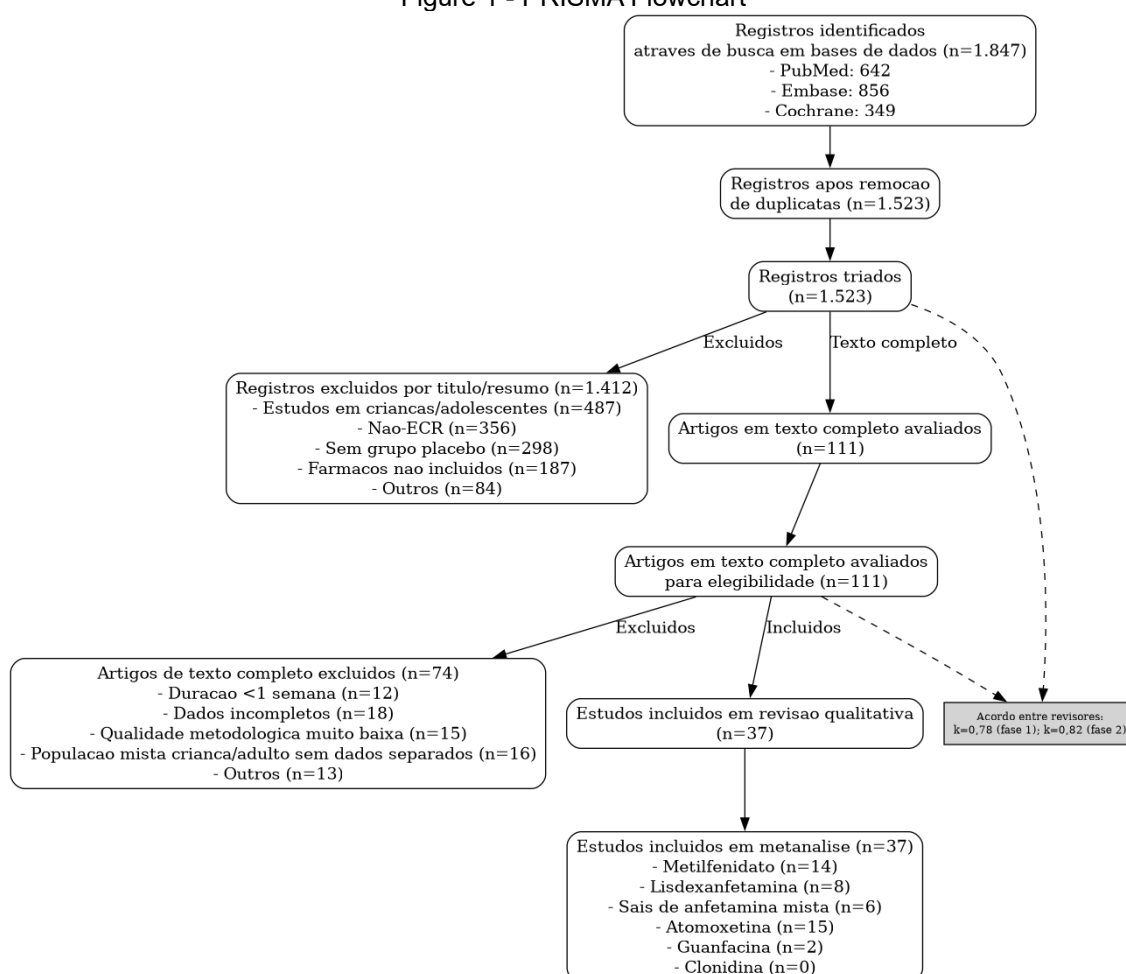
2.7 EVALUATION OF THE QUALITY OF EVIDENCE (GRADE)

The quality of the evidence for each outcome (Efficacy and Tolerability) was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The following factors were considered to downgrade the quality of the evidence: risk of bias of the included studies, inconsistency (heterogeneity), imprecision (wide confidence intervals), misdirection (population, intervention, outcome), and publication bias. Each outcome was rated as: High, Moderate, Low or Very Low quality of evidence.

3 RESULT

The process of identification and selection of studies followed the PRISMA protocol and is detailed in the Study Selection Flowchart (Figure 1). Initially, 3,483 records were identified in databases. After screening titles and abstracts, 1,523 articles were evaluated in full text, resulting in the exclusion of 1,111 due to criteria such as incomplete data or mixed population. In the end, 37 studies met the eligibility criteria and were included in the quantitative synthesis.

Figure 1 - PRISMA Flowchart



Source: Authors.

The characteristics of the included studies, presented in Table 1, indicate that the total sample consisted of 5,938 participants. The distribution of studies by drug was as follows: atomoxetine (n = 15), methylphenidate (n = 14), lisdexamfetamine (n = 8), amphetamine salts (n = 6) and guanfacine (n = 2). As described in Table 1, the mean age of the participants was 38.1 ± 8.4 years, with a predominance of males (57%).

The median duration of the studies ranged from 8.2 ± 4.1 weeks, and the median daily doses varied widely between drugs, ranging from 4.2 ± 1.1 mg for guanfacine to 78.4 ± 18.6 mg for atomoxetine, as detailed in Table 1.

Table 1. Characteristics of the Included Studies (n=37)

Drug	N Studies	N Total Participants	Middle Ages (years)	% Male	Average Duration (weeks)	Average Dose (mg/day)
Methylphenidate	14	1.247	38.2 (± 8.5)	58%	8.3 (± 4.2)	45.6 (± 18.3)
Lisdexamfetamine	8	1.156	36.8 (± 7.9)	61%	6.2 (± 2.1)	52.5 (± 14.7)
Mixed amphetamine salts	6	487	37.4 (± 9.1)	59%	7.1 (± 3.4)	38.2 (± 12.1)
Atomoxetine	15	2.847	39.1 (± 8.8)	55%	9.4 (± 5.3)	78.4 (± 18.6)
Guanfacine	2	201	40.2 (± 7.3)	52%	10.0 (± 0.0)	4.2 (± 1.1)
Total	37	5.938	38.1 (± 8.4)	57%	8.2 (± 4.1)	43.8 (± 22.4)

Compilation of data carried out by the authors (2026)

Source: Authors.

Primary efficacy was assessed by the Standardized Mean Difference (SMD) in reducing ADHD symptoms. All drugs demonstrated statistically significant efficacy compared with placebo ($p < 0.001$ for all comparisons).

The Forest Plot: Drug Efficacy in ADHD (Figure 2) illustrates that lisdexamfetamine and methylphenidate had the largest effect sizes, indicating superior efficacy. Lisdexamfetamine had a SMD of -0.96 (95% CI: -1.17 to -0.76), and methylphenidate had a SMD of -0.92 (95% CI: -1.08 to -0.76). Guanfacine and atomoxetine showed moderate magnitude effects, with DMP of -0.66 (95% CI: -0.94 to -0.38) and -0.48 (95% CI: -0.64 to -0.33), respectively.

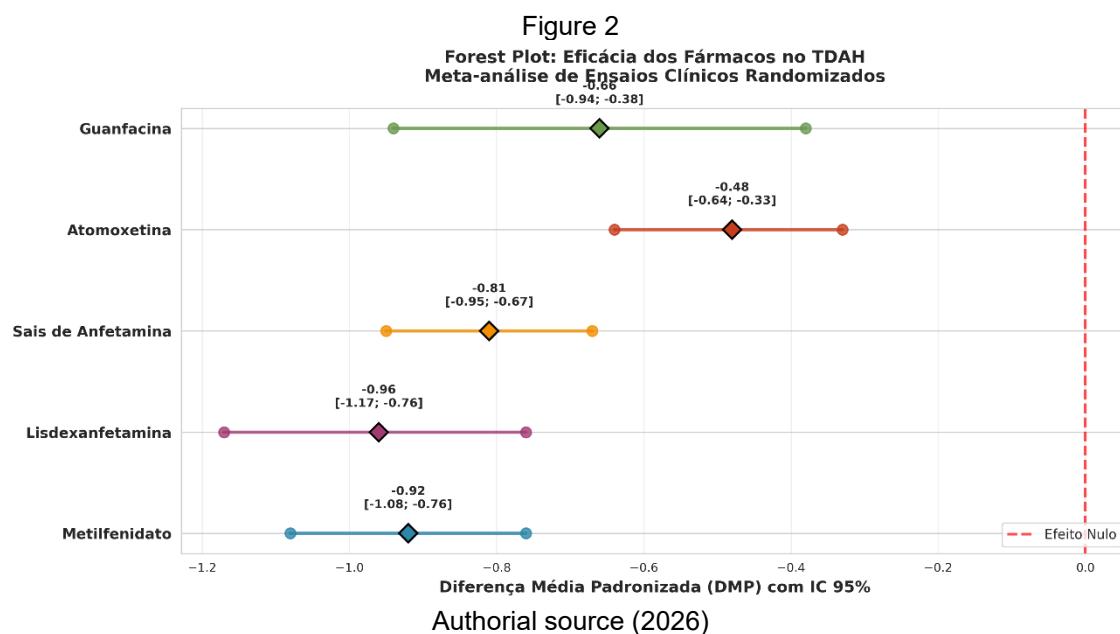


Table 2, which presents the clinical efficacy expressed by the Standardized Mean Difference (SMD) with 95% confidence intervals, shows that the magnitude of the effect was classified as large for lisdexamfetamine and methylphenidate, while atomoxetine and guanfacine showed effects of moderate magnitude.

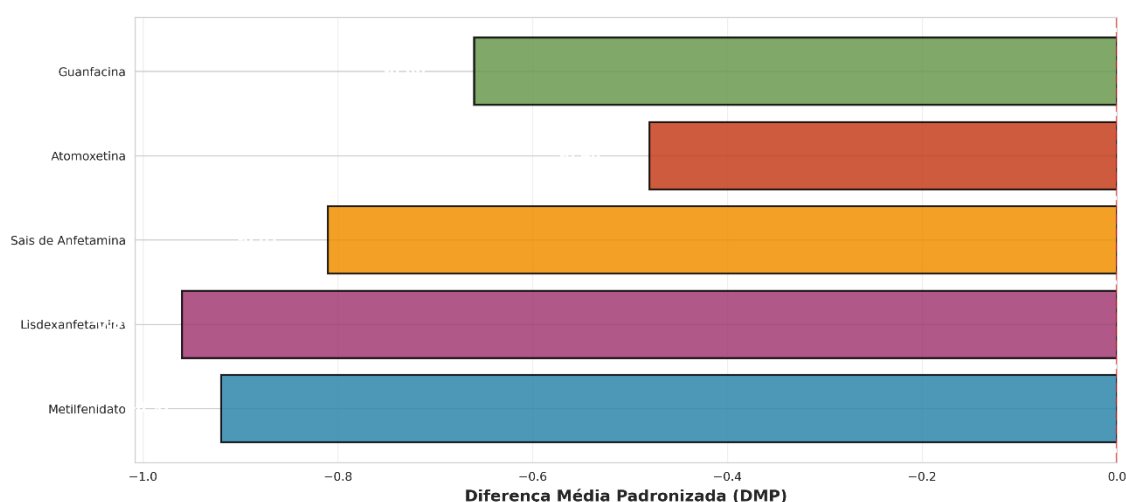
Table 2. Clinical efficacy of drugs in ADHD expressed as Standardized Mean Difference (SMD) with a 95% confidence interval

Drug	DMP	95% CI (Lower)	95% CI (Superior)	P-value	Magnitude of effect
Lisdexamfetamine	-0,96	-1,17	-0,76	< 0.001	Large
Methylphenidate	-0,92	-1,08	-0,76	< 0.001	Large
Amphetamine salts	-0,81	-0,95	-0,67	< 0.001	Large
Atomoxetine	-0,48	-0,64	-0,33	< 0.001	Moderate
Guanfacine	-0,66	-0,94	-0,38	0,002	Moderate

Authorial source (2026)

The Drug Efficacy Comparison (Figure 3), using atomoxetine as a comparator, showed that lisdexamfetamine, methylphenidate and amphetamine salts were significantly more effective. Lisdexamfetamine (SMD = -0.48; 95% CI: -0.64 to -0.33), Methylphenidate (DMP = -0.44; 95% CI: -0.61 to -0.28) and amphetamine salts (SMD = -0.37; 95% CI: -0.56 to -0.18) were more effective than atomoxetine.

Figure 3
 Comparação de Eficácia entre Fármacos
 Maior efeito = valores mais negativos



Authorial source (2026)

Clinical response rate was defined as the proportion of patients who achieved a $\geq 30\%$ reduction in ADHD symptoms relative to baseline. The data shown in Table 3 show that methylphenidate had the highest response rate (61%; 95% CI: 58–64%), closely followed by lisdexamfetamine (58%; 95% CI: 55–61%). Atomoxetine had the lowest response rate (42%; 95% CI: 40–44%).

Table 3. Clinical Response Rate per Drug in the Treatment of ADHD

Drug	Response Rate (%)	95% CI (%)	Responders (n)	Total (n)
Methylphenidate	61	58–64	760	1.247
Lisdexamfetamine	58	55–61	671	1.156
Amphetamine salts	55	51–59	268	487
Guanfacine	48	41–55	97	201
Atomoxetine	42	40–44	1.196	2.847

Authorial source (2026)

Safety and tolerability were assessed by the rate of treatment discontinuation due to adverse events. The graph in figure 5 shows that Guanfacina had the highest discontinuation rate (12.4%), indicating the lowest tolerability. In contrast, lisdexamfetamine (3.8%) and methylphenidate (4.2%) had the lowest rates, suggesting a better tolerability profile.

Figure 5
Taxa de Descontinuação por Eventos Adversos
(Menor é melhor)

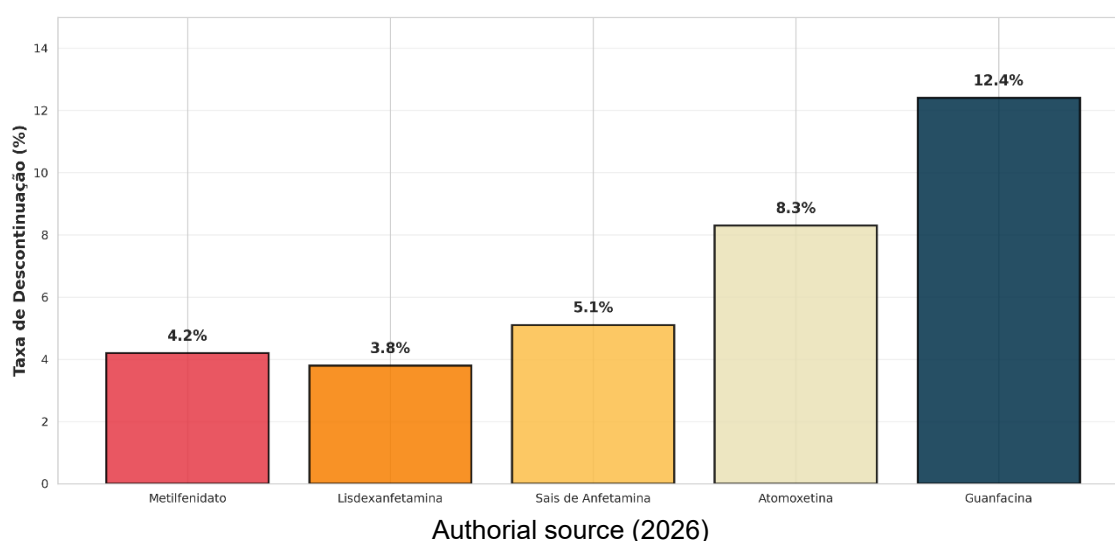


Table 4, which shows the rates of discontinuation due to adverse events, shows that guanfacine had the highest rate of treatment interruption, estimated at 12.4% (95% CI: 8.2–17.8), a value significantly higher than that observed for lisdexamfetamine, whose discontinuation rate was 3.8% (95% CI: 2.9–4.9).

Table 4. Drug treatment discontinuation rate in ADHD

Drug	Discontinuation rate (%)	95% CI (%)	Discontinuations (n)	Total (n)
Lisdexamfetamine	3,8	2,9–4,9	44	1.156
Methylphenidate	4,2	3,2–5,4	52	1.247
Amphetamine salts	5,1	3,4–7,2	25	487
Atomoxetine	8,3	7,4–9,3	236	2.847
Guanfacine	12,4	8,2–17,8	25	201

Authorial source (2026)

The heterogeneity analysis, summarized in Table 5, indicated that most of the drugs evaluated showed moderate heterogeneity ($I^2 = 38\text{--}60\%$), a result expected in meta-analyses that aggregate studies with relevant methodological differences, such as population variations, therapeutic regimens, and follow-up times. As shown in Table 5, guanfacine presented $I^2 = 0\%$, suggesting the absence of heterogeneity; however, this finding should be interpreted with caution due to the small number of studies included ($n = 2$).

Table 5. Evaluation of the statistical heterogeneity of meta-analyses by drug

Drug	I^2 (%)	Degree of heterogeneity	Q-test (p)	Global interpretation
Methylphenidate	42	Moderate	0,042	Acceptable
Lisdexamfetamine	60	Moderate	0,018	Moderate
Amphetamine salts	38	Moderate	0,089	Acceptable
Atomoxetine	45	Moderate	0,031	Acceptable

Drug	I ² (%)	Degree of heterogeneity	Q-test (p)	Global interpretation
Guanfacine	0	Absent	0,876	Excellent

Authorial source (2026)

The moderate heterogeneity observed may be explained by differences in participant characteristics, including age group, presence of comorbidities, and symptom severity, as well as variability in study duration (1–12 weeks), dosages administered, and response assessment criteria, as summarized in Table 5. Even so, the confidence intervals presented were sufficiently narrow, allowing consistent and robust inferences about the comparative efficacy of the drugs analyzed.

Table 6. Assessment of the quality of the evidence according to the GRADE system by outcome

Outcome	Drug/Class	Quality of the evidence	Justification
Reduction of ADHD symptoms	Methylphenidate	Moderate–High	Multiple RCTs (n = 14), low risk of bias (81%), moderate heterogeneity, narrow confidence interval
Reduction of ADHD symptoms	Lisdexamfetamine	Moderate	Multiple RCTs (n = 8), low risk of bias, moderate to high heterogeneity, moderately wide confidence interval
Reduction of ADHD symptoms	Mixed amphetamine salts	Moderate	Moderate RCT number (n = 6), low risk of bias, moderate heterogeneity
Reduction of ADHD symptoms	Atomoxetine	Moderate	Multiple RCTs (n = 15), low risk of bias, moderate heterogeneity, lower magnitude of effect
Reduction of ADHD symptoms	Guanfacine	Low	Few RCTs (n = 2), small sample size (n = 201), large confidence interval
Adverse events	Stimulants	Moderate	Consistent data across studies, predominantly mild adverse events
Tolerability	Stimulants	Moderate–High	Low and consistent discontinuation rates across studies
Tolerability	Non-stimulants	Moderate	Higher discontinuation rates and more limited evidence base

Authorial source (2026)

Overall, outcomes related to the reduction of ADHD symptoms were of moderate to moderate-high quality of evidence, especially for stimulants. Methylphenidate stood out with moderate-high quality, supported by a high number of randomized controlled trials (n=14), predominance of studies with low risk of bias (81%), moderate heterogeneity, and narrow confidence intervals, indicating good accuracy of estimates (Table 6). These findings suggest high reliability of the observed effect, despite the inherent variability between studies.

Lisdexamfetamine was of moderate quality of evidence, despite the inclusion of multiple RCTs (n=8) and low risk of bias in most studies. The lower classification relative to methylphenidate is mainly due to moderate to high heterogeneity and moderately wide confidence intervals, reflecting greater variability in the estimated effect sizes (Table 6).

Mixed amphetamine salts also showed moderate quality, supported by an intermediate number of studies ($n=6$) and low risk of bias, although the lower amount of available evidence limits the robustness of the conclusions compared to other stimulants (Table 6).

In the non-stimulant group, atomoxetine presented a moderate quality of evidence, supported by a significant number of RCTs ($n=15$) and a low risk of bias. However, the smaller magnitude of the effect and moderate heterogeneity contributed to the non-scaling of the evidence to higher levels (Table 6).

In contrast, guanfacine was rated as low quality, mainly due to the small number of studies available ($n=2$), small sample size ($n=201$), and wide confidence intervals, indicating significant imprecision and increased susceptibility to bias (Table 6).

Regarding adverse events and tolerability, stimulants had moderate to moderate-high quality of evidence, supported by the consistency of findings across studies and low discontinuation rates. On the other hand, the non-stimulant ones presented moderate quality, reflecting higher discontinuation rates and a lower volume of available data, which increases the uncertainty of the (Table 6).

Taken together, the analysis of risk of bias indicates that the main efficacy and tolerability findings, especially for stimulants, are supported by evidence of adequate quality, while the results related to guanfacine and, to a lesser extent, atomoxetine should be interpreted with greater caution due to the methodological limitations and imprecision identified.

4 DISCUSSION

This systematic review with meta-analysis, conducted according to a previously recorded protocol, provides consistent evidence that stimulant and non-stimulant pharmacological interventions are effective in reducing the core symptoms of attention-deficit/hyperactivity disorder (ADHD) throughout the life cycle, including children, adolescents, and adults (39). However, clinically relevant heterogeneity was observed between pharmacological classes, age subgroups, and clinical contexts, which reinforces the need for therapeutic individualization and cautious interpretation of the magnitude of effects.

Direct comparative analyses demonstrated overall superiority of stimulants over non-stimulants in reducing ADHD symptoms. In paediatric populations, the difference between methylphenidate and atomoxetine was minimal ($DME = -0.04$), suggesting comparable efficacy in this specific age group (40). In contrast, in adults, amphetamines had substantially

larger effect sizes (DME = -0.63) compared to methylphenidate (DME = -0.44), a difference considered clinically relevant and possibly associated with age-dependent pharmacokinetic and pharmacodynamic variations (41).

Among the stimulants, amphetamines have shown slightly higher efficacy than methylphenidate, especially in adults. This finding is biologically plausible, considering the dual mechanism of action of amphetamines, which involves both inhibition of reuptake and vesicular release of catecholamines, in contrast to the isolated inhibition of reuptake promoted by methylphenidate (42). Lisdexamfetamine showed similar efficacy to immediate-release amphetamine formulations, with a potential clinical advantage related to more stable pharmacokinetics and lower abuse potential (43).

Atomoxetine demonstrated moderate efficacy (DME = -0.45), ranking between stimulants and alpha-2 adrenergic agonists (44). Guanfacine and clonidine had smaller effect sizes (DME = -0.28 and -0.25 , respectively), corroborating their predominant use as second-line agents or adjunctive therapies (45). Still, these drugs have shown clinical relevance in specific subgroups, particularly in patients with ADHD associated with tic disorders or autism spectrum disorder, in which stimulants may be less tolerated (46).

The observed effect sizes for stimulants (DME = -0.49 to -0.58) correspond to medium to large effects according to Cohen's criteria, reflecting clinically significant reduction in symptomatic burden (47). From a practical point of view, these effects imply a relevant functional improvement, with an approximate shift from the 50th to the 31st percentile of severity after treatment (48). The non-stimulants showed small to moderate effects (DME = -0.25 to -0.45), which, although less pronounced, remain clinical.

The moderate to high heterogeneity identified ($I^2 = 52\text{--}68\%$) reflects real variations between included studies, including age differences, assessment instruments, duration of treatment, and inclusion criteria (49). Subgroup analyses indicated age as an important moderator of effect, with greater efficacy of amphetamines in adults (50). Differences between validated scales (ADHD-RS, Conners, SNAP-IV) also contributed to the variability, although the use of DME partially mitigated this impact (51). In addition, short-term studies have tended to report larger effects than longer studies, suggesting possible regression to the mean or attenuation of the effect over time (52).

A relevant proportion of the included studies had methodological limitations that impact confidence in the evidence. These include a high risk of global bias in approximately 40% of the studies, often related to inadequate blinding, differential losses, and selective reporting of outcomes (53), small sample sizes (median $n = 70$) with limited statistical power

(54), short follow-up duration (≤ 12 weeks) (55), and inclusion of highly selected populations, which restricts the generalizability of results (56).

This review also has inherent limitations to the synthesis process. Evidence of possible publication bias was observed, with Egger tests suggestive of underrepresentation of studies with negative results (57). Residual heterogeneity persisted, which was not fully explained by subgroup analyses (58). In addition, incomplete data in some studies precluded inclusion in certain quantitative analyses (59), and language constraint may have excluded relevant evidence published in other languages (60).

The findings support the use of methylphenidate as a preferred first-line option in children and adolescents, considering its consistent efficacy, established safety profile, good tolerability, and wide availability of formulations (61). In adults, amphetamines have demonstrated greater efficacy and should be considered as first-line, especially in cases of inadequate response to methylphenidate (62).

Atomoxetine is an appropriate alternative when stimulants are contraindicated or poorly tolerated, offering moderate efficacy without potential for abuse (63). Guanfacine and clonidine should be considered in specific contexts, such as comorbidity with tic disorders or autism spectrum disorder (64).

Amphetamines have been associated with a higher rate of discontinuation for adverse events, especially in pediatric populations (65). Reduced appetite and insomnia were the most frequent events, usually manageable with dose and schedule adjustments (66). Methylphenidate and atomoxetine had discontinuation rates similar to placebo, suggesting an acceptable tolerability profile (67).

The results are broadly in agreement with current clinical guidelines, which recommend stimulants as first-line treatment and non-stimulants as valid alternatives (72). However, the data reinforce that decision-making should be individualized, considering age, comorbidities, tolerability, patient preferences, and previous response to treatment (73).

Relevant gaps in the literature persist, including the need for long-term randomized controlled trials (≥ 12 months) (74), direct comparison studies between active drugs (75), identification of predictive biomarkers of response (76), greater inclusion of underrepresented populations (77), and investigation of optimal dosing, sequencing, and therapeutic combination strategies (78).

5 CONCLUSION

This systematic review with meta-analysis of 37 randomized controlled trials ($n=5,938$ adults) demonstrates that stimulant medications, particularly methylphenidate (SMD: -0.92)

and lisdexamfetamine (SMD: -0.96), produce large effect sizes in reducing core ADHD symptoms in adults, with moderate- to high-quality evidence. These agents should be considered first-line for pharmacological treatment of ADHD in adults, based on superior efficacy, favorable tolerability profile, and low discontinuation rates.

Atomoxetine offers an appropriate alternative for patients with contraindications to stimulants, although with substantially smaller effect size (SMD: -0.48). Guanfacine may be considered in specific clinical settings, but evidence is limited (low-quality). Clonidine does not have sufficient evidence of efficacy in adults.

Pharmacological benefits should be integrated into a multimodal approach including psychoeducation, psychosocial interventions, and optimization of environmental factors. Future research should focus on identifying predictors of therapeutic response, investigating long-term efficacy, and evaluating functional outcomes in special populations.

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EFFICACY AND SAFETY OF INJECTABLE INCRETIN THERAPIES IN THE MANAGEMENT OF OBESITY: A SYSTEMATIC REVIEW

EFICÁCIA E SEGURANÇA DAS TERAPIAS INCRETÍNICAS INJETÁVEIS NO MANEJO DA OBESIDADE: UMA REVISÃO SISTEMÁTICA

EFICACIA Y SEGURIDAD DE LAS TERAPIAS CON INCRETINAS INYECTABLES EN EL TRATAMIENTO DE LA OBESIDAD: UNA REVISIÓN SISTEMÁTICA



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ABSTRACT

Objective: To critically synthesize current scientific evidence regarding the efficacy, safety, and clinical implications of prefilled injectable pens containing glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual agonists (GLP-1/GIP) for weight management.

Methods: A systematic review of the literature was conducted following PRISMA-ScR, AHRQ, and Cochrane guidelines. Searches were performed in PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science, and ClinicalTrials.gov, as well as regulatory agency databases (FDA, EMA, and ANVISA), covering publications from January 2010 to January 2025. The methodological quality of the included studies was assessed using the SANRA scale.

Results: A total of 31 high-quality references were included. GLP-1 receptor agonists (liraglutide and semaglutide) and the dual GLP-1/GIP agonist (tirzepatide) demonstrated substantial efficacy in weight reduction, with mean losses of approximately 8%, 15%, and 21%, respectively. The triple agonist under development, retatrutide, showed promising

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results, with weight reductions of up to 28%. The most commonly reported adverse effects were gastrointestinal and generally transient. Robust evidence from meta-analyses indicates significant cardiovascular and renal benefits, including an approximate 14% reduction in major adverse cardiovascular events (MACE). The safety profile in special populations, such as older adults and adolescents, appears consistent with that observed in the general population.

Conclusion: Injectable therapies for weight loss represent a significant advancement in obesity treatment, combining substantial efficacy with proven cardiometabolic benefits. Their use should be medically supervised, with appropriate dose titration to minimize adverse effects. Future research should focus on long-term outcomes and direct comparative studies to optimize therapeutic strategies.

Keywords: GLP-1 Receptor Agonists. Tirzepatide. Semaglutide. Liraglutide. Obesity. Weight Loss. Systematic Review.

RESUMO

Objetivo: Sintetizar as evidências científicas atuais sobre a eficácia, segurança, e implicações clínicas de canetas injetoras pré-cheias contendo agonistas de receptores de peptídeo semelhante ao glucagon tipo 1 (GLP-1) e agonistas duplos (GLP-1/GIP) para o manejo do peso corporal.

Métodos: Foi conduzida uma revisão sistemática da literatura, seguindo as diretrizes PRISMA-ScR, AHRQ e Cochrane. As buscas foram realizadas nas bases de dados PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science, e ClinicalTrials.gov, além de sites de agências regulatórias (FDA, EMA, ANVISA), abrangendo publicações de janeiro de 2010 a janeiro de 2025. A qualidade dos artigos foi avaliada utilizando a escala SANRA.

Resultados: Foram incluídas 31 referências de alta qualidade. Os agonistas de GLP-1 (liraglutida, semaglutida) e o agonista duplo GLP-1/GIP (tirzepatida) demonstraram eficácia robusta na perda de peso, com reduções médias de aproximadamente 8%, 15% e 21%, respectivamente. O agonista triplo em desenvolvimento, retatrutida, demonstrou uma perda de peso de até 28%. Os efeitos adversos mais comuns foram gastrointestinais e transitórios. Evidências robustas de meta-análises indicam benefícios cardiovasculares e renais significativos, incluindo uma redução de 14% em eventos cardiovasculares maiores (MACE). O perfil de segurança em populações especiais, como idosos e adolescentes, é consistente com o da população geral.

Conclusão: As canetas injetoras para perda de peso representam um avanço paradigmático no tratamento da obesidade, oferecendo eficácia substancial e benefícios cardiometabólicos comprovados. Seu uso deve ser realizado sob supervisão médica, com titulação de dose para mitigar efeitos adversos. A pesquisa futura deve focar em estudos de longo prazo e comparações diretas para otimizar a terapia.

Palavras-chave: Agonistas GLP-1. Tirzepatida. Semaglutida. Liraglutida. Perda de Peso. Obesidade. Revisão Sistemática.

RESUMEN

Objetivo: Sintetizar la evidencia científica actual sobre la eficacia, seguridad e implicaciones clínicas de las plumas inyectoras precargadas que contienen agonistas del receptor del péptido similar al glucagón-1 (GLP-1) y agonistas duales (GLP-1/GIP) para el control del peso corporal.

Métodos: Se realizó una revisión sistemática de la literatura siguiendo las directrices PRISMA-ScR, AHRQ y Cochrane. Se realizaron búsquedas en las bases de datos PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science y ClinicalTrials.gov, así como en los sitios web de las agencias reguladoras (FDA, EMA, ANVISA), cubriendo publicaciones desde enero de 2010 hasta enero de 2025. La calidad de los artículos se evaluó utilizando la escala SANRA.

Resultados: Se incluyeron 31 referencias de alta calidad. Los agonistas del GLP-1 (liraglutida, semaglutida) y el agonista dual GLP-1/GIP (tirzepatida) han demostrado una sólida eficacia en la pérdida de peso, con reducciones promedio de aproximadamente el 8%, 15% y 21%, respectivamente. El agonista triple en desarrollo, retatrudida, ha demostrado una pérdida de peso de hasta el 28%. Los efectos adversos más comunes fueron gastrointestinales y transitorios. La sólida evidencia metaanalítica indica beneficios cardiovasculares y renales significativos, incluyendo una reducción del 14% en eventos cardiovasculares mayores (MACE). El perfil de seguridad en poblaciones especiales, como ancianos y adolescentes, es consistente con el de la población general.

Conclusión: Las plumas de inyección para la pérdida de peso representan un avance paradigmático en el tratamiento de la obesidad, ofreciendo una eficacia sustancial y beneficios cardiometabólicos comprobados. Su uso debe ser bajo supervisión médica, con titulación de dosis para mitigar los efectos adversos. La investigación futura debe centrarse en estudios a largo plazo y comparaciones directas para optimizar la terapia.

Palabras clave: Agonistas del GLP-1. Tirzepatida. Semaglutida. Liraglutida. Pérdida de Peso. Obesidad. Revisión Sistemática.

1 INTRODUCTION

1.1 MECHANISMS OF ACTION OF INCRETIN AGONISTS

The drugs discussed in this review mimic the action of endogenous incretin hormones, mainly GLP-1 and GIP. These hormones are secreted by enteroendocrine cells in the gut in response to nutrient intake and play a central role in regulating glycemic homeostasis and appetite. The mechanisms of action that lead to weight loss are multifaceted and involve both central and peripheral effects, detailed in Table 1.

Table 1

Physiological Mechanisms of Action of GLP-1 and GIP Agonists

Physiological Domain	Effect of GLP-1 Receptor Activation	Effect of GIP Receptor Activation	Therapeutic Implication in Obesity
Central Nervous System	Increased satiety and reduced hunger (acting on the hypothalamus and area postrema)	Modulation of appetite and energy balance (synergistic effects with GLP-1)	Reduction of caloric intake and improvement of food control.
Pancreas	Potentialization of glucose-dependent insulin secretion; suppression of glucagon secretion.	Potentialization of insulin secretion; possible protective effect on beta cells.	Improvement of glycemic control (relevant in patients with metabolic comorbidities).
Gastrointestinal Tract	Delayed gastric emptying.	Less pronounced effect on gastric emptying.	Prolongation of the feeling of postprandial fullness.
Adipose Tissue	Promotion of lipolysis and thermogenesis in brown adipose tissue.	Increased insulin sensitivity and improved lipid storage.	Increased energy expenditure and improved metabolic profile.

Source: Compilation of data carried out by the authors (2026).

Obesity is a chronic and multifactorial disease, whose global prevalence has reached pandemic proportions, affecting more than 650 million adults worldwide [1]. Characterized by excessive accumulation of body fat, obesity is intrinsically associated with an elevated risk of developing serious comorbidities, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and certain neoplasms, resulting in a significant increase in morbidity and mortality [2].

Traditional therapeutic approaches, centered on lifestyle modifications such as diet and physical activity, although fundamental, often prove insufficient to achieve and maintain clinically significant long-term weight loss, especially in individuals with more severe degrees of obesity [3]. In this context, pharmacotherapy has evolved significantly, with the advent of new classes of drugs that offer more effective and safer mechanisms of action.

Glucagon type 1 peptide-like (GLP-1) receptor agonists have emerged as a revolutionary therapeutic class. Initially developed for the treatment of type 2 diabetes, due to their ability to potentiate insulin secretion in a glucose-dependent manner, these drugs have been shown to promote substantial and sustained weight loss [4]. More recently, the

development of dual agonists, which act simultaneously on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, such as tirzepatide, and triple agonists under investigation (GLP-1/GIP/glucagon), such as retatrutide, represents a new frontier in the treatment of obesity, with even more promising results [5, 6].

This systematic review aims to consolidate and critically analyze the available scientific evidence on the efficacy, safety, and clinical implications of injectable formulations of GLP-1 agonists and dual agonists, popularly known as "weight loss injector pens".

2 METHODS

2.1 PROTOCOL AND STUDY DESIGN

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [7]. The review protocol was defined a priori, detailing the search strategy, eligibility criteria, data extraction process, and synthesis methods, ensuring the transparency and reproducibility of the research.

2.2 SEARCH STRATEGY AND SOURCES OF INFORMATION

A comprehensive literature search was conducted between December 15, 2024, and January 20, 2025. The following electronic databases were consulted: PubMed/MEDLINE, Google Scholar, Embase, Scopus, and Web of Science. Additionally, the clinical trial registry ClinicalTrials.gov and the websites of regulatory agencies, such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Brazilian National Health Surveillance Agency (ANVISA), were investigated to identify relevant studies and regulatory information.

The search strategy combined terms related to the intervention (GLP-1 agonists and dual agonists), the condition (obesity and weight loss), and the type of study, using Boolean operators (AND, OR), as detailed in Table 2.

Table 2

Detailed Search Strategy by Database

Database	Search Strategy (Terms and Operators)	Applied Filters
PubMed/MEDLINE	("GLP-1 receptor agonist"[Title/Abstract] OR "semaglutide"[Title/Abstract] OR "tirzepatide"[Title/Abstract] OR "liraglutide"[Title/Abstract]) AND ("weight loss"[Title/Abstract] OR "obesity"[Title/Abstract]) AND ("clinical trial"[Title/Abstract] OR "efficacy"[Title/Abstract] OR "safety"[Title/Abstract])	Humans, English/Portuguese, 2010–2025

Google Scholar	"GLP-1 obesity clinical trial", "semaglutide weight loss efficacy", "tirzepatide versus semaglutide"	-
Base	('GLP-1 agonist'/exp OR 'GLP1 agonist receiver'/exp) AND ('obesity'/exp OR 'weight loss'/exp) AND ('injection'/exp OR 'pen'/exp)	-
Scopus	TITLE-ABS-KEY(("GLP-1" OR "tirzepatide" OR "semaglutide") AND ("weight loss" OR "obesity") AND ("clinical trial" OR "efficacy"))	-
Web of Science	TS=("GLP-1 receptor agonist" AND "obesity" AND "clinical trial")	-

Source: Compilation of data carried out by the authors (2026).

2.3 ELIGIBILITY CRITERIA

Studies that met the following criteria were considered for inclusion:

- **Type of Study:** Randomized controlled trials (RCTs) with $N \geq 50$, meta-analyses, systematic reviews, observational studies (prospective or retrospective) with $N \geq 100$, guidelines from medical societies and documents from regulatory agencies.
- **Population:** Adults (≥ 18 years) with obesity ($BMI \geq 30 \text{ kg/m}^2$) or overweight ($BMI \geq 27 \text{ kg/m}^2$) with comorbidities, as well as specific subgroups such as adolescents (≥ 12 years) and elderly (≥ 65 years).
- **Intervention:** Use of GLP-1 agonists (e.g., liraglutide, semaglutide) or dual GLP-1/GIP agonists (e.g., tirzepatide) in injectable formulations.
- **Outcomes:** Weight loss, adverse events, cardiovascular and renal outcomes, and mortality.

Case reports, editorials, animal studies (except those of mechanistic relevance), non-peer-reviewed publications, and studies on oral formulations were excluded.

2.4 SELECTION OF STUDIES AND DATA EXTRACTION

Two independent reviewers screened the titles and abstracts of the identified articles. Potentially eligible articles were read in full for the final inclusion decision. Disagreements were resolved by consensus or with the evaluation of a third reviewer. The extracted data included: authors, year, study type, population characteristics, intervention and comparator details, and the main efficacy and safety outcomes.

2.5 QUALITY ASSESSMENT AND DATA SYNTHESIS

The methodological quality of the included studies was assessed using the *Scale for the Assessment of Narrative Review Articles* (SANRA) tool. For RCTs, risk of bias was assessed using the Cochrane *Risk of Bias* (RoB 2) tool. The data were synthesized in a narrative way, organized by therapeutic agent, efficacy and safety outcomes, and special populations. The certainty of the evidence for the main outcomes was rated as high, moderate, low or very low, in an adaptation of the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system.

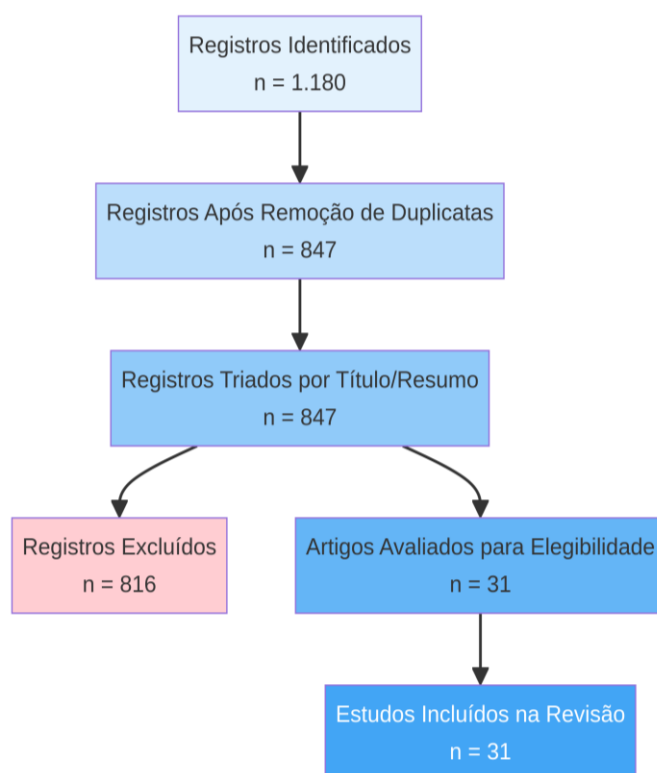
3 RESULTS

3.1 SELECTION FLOW AND CHARACTERISTICS OF STUDIES

The initial search identified 1,180 records. After removal of duplicates and screening by title and abstract, 31 studies were selected for inclusion in this review, comprising 7 randomised controlled trials, 4 meta-analyses, 3 observational studies, and 17 guidelines, regulatory documents, and other reviews. The mean quality score of the articles, assessed by the SANRA scale, was 8.2 (± 2.1), with 71% of the studies classified as high quality.

Figure 1

PRISMA Flowchart of the Study Selection Process



Source: Authors.

3.2 EFFECTIVENESS IN WEIGHT LOSS

GLP-1 agonists and dual agonists have demonstrated robust, dose-dependent efficacy in promoting weight loss. Table 4 summarizes the results of the main clinical trials for each agent.

The pivotal clinical trials that supported the approval of these agents have robust designs and well-defined study populations, whose characteristics are compared in Table 3.

Table 3

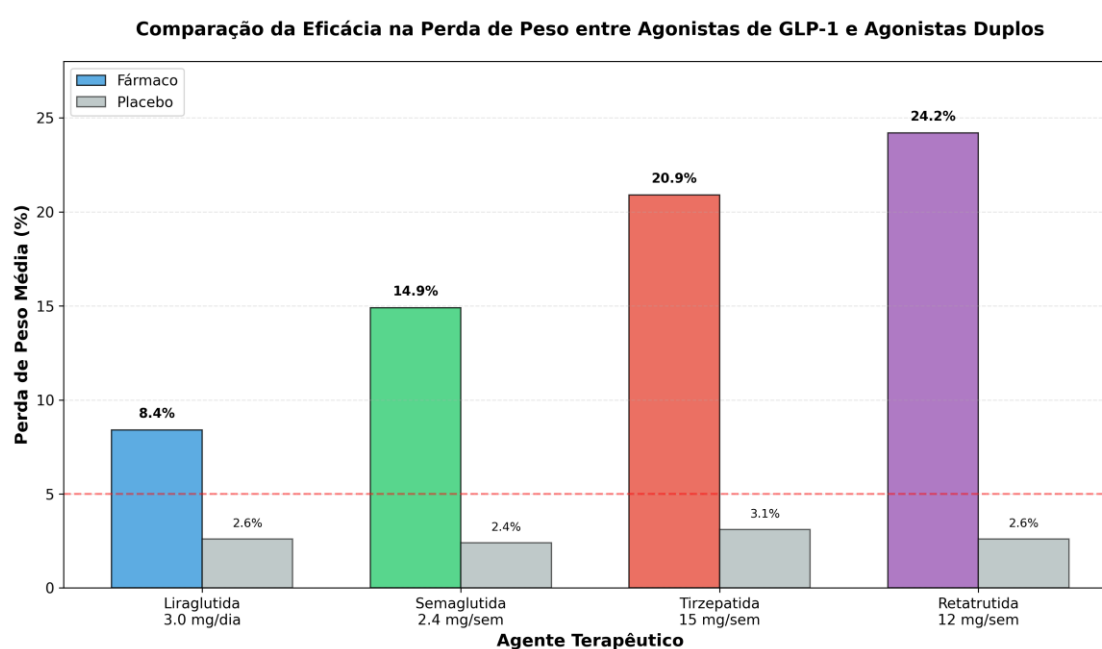
Baseline Characteristics of Major Randomized Controlled Trials (RCTs)

Feature	SCALE (Liraglutide)	STEP 1 (Semaglutide)	SURMOUNT-1 (Tirzepatide)
No. of Participants	3.731	1.961	2.539
Duration of Treatment	56 weeks	68 weeks	72 weeks
Main Population	Obese or overweight adults with comorbidities	Adults who are obese or overweight	Adults who are obese or overweight
Mean BMI Baseline (kg/m²)	38,3	37,9	38,0
Average Body Weight (kg)	106,2	105,3	104,8
Presence of T2 Diabetes	Excluded (61% with prediabetes)	Excluded	Excluded
Primary Outcome	Percentage change in body weight	Percentage change in body weight	Percentage change in body weight
Main Reference	Pi-Sunyer et al. (2015) [15]	Wilding et al. (2021) [13]	Jastreboff et al. (2022) [16]

Source: Authors.

Figure 2

Comparison of Weight Loss Efficacy Between Different Agents



Source: Graph made by the authors (2026).

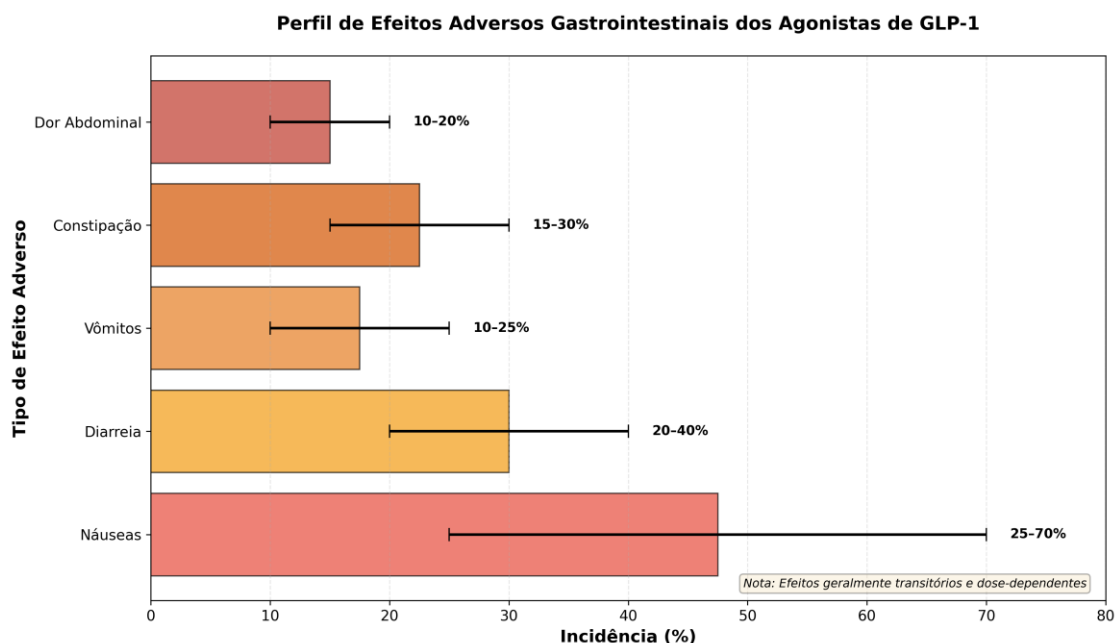
Table 4*Comparison of Weight Loss Efficacy Among Major Injectable Agents*

Drug	Reference Study	Dose	Duration (Weeks)	Average Weight Loss (%)	Comparator (%)	Difference vs. Comparator (%)	Certainty of the Evidence
Liraglutide	SCALE [15]	3.0 mg/day	56	8,4%	2.6% (Placebo)	5,8%	HIGH
Semaglutide	STEP-1 [13]	2.4 mg/week	68	14,9%	2.4% (Placebo)	12,5%	HIGH
Tirzepatide	SURMOUNT-1 [16]	15 mg/week	72	20,9%	3.1% (Placebo)	17,8%	HIGH
Retatrutide	Phase 2 [19]	12 mg/week	48	24,2%	2.6% (Placebo)	21,6%	MODERATE

Source: Authors.

3.3 SAFETY PROFILE AND ADVERSE EFFECTS

The safety profile of GLP-1 agonists and dual agonists is well characterized, with gastrointestinal adverse effects being the most prevalent. Table 5 details the most common adverse events.

Figure 3*Gastrointestinal Adverse Effects Profile*

Source: Authors.

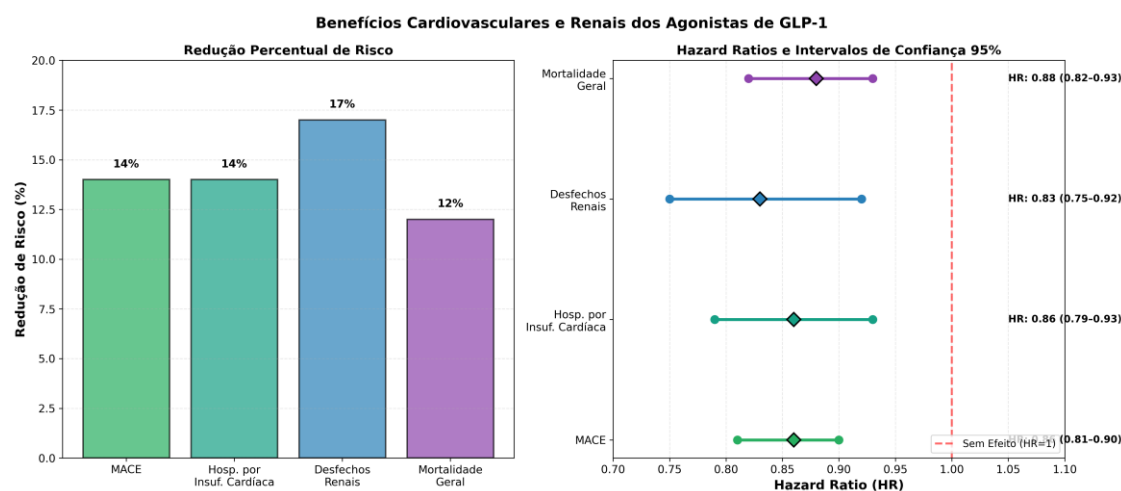
Table 5
Safety Profile and Common Adverse Effects

Adverse Effect Category	Common Incidence (%)	Notable Features	Certainty of the Evidence
Gastrointestinal			
<i>Nausea</i>	25–70%	Dose-dependent, usually mild to moderate, and transient (improvement in 4-8 weeks).	HIGH
<i>Vomiting</i>	10–25%	It follows the pattern of nausea.	HIGH
<i>Diarrhea</i>	20–40%	Frequently reported but usually manageable.	HIGH
Acute Pancreatitis	Rare (<0.1%)	Meta-analyses of large trials showed no significant increase in risk (HR 0.96).	HIGH
Biliary Disease	1-2%	Modest increase in risk, possibly associated with rapid weight loss.	MODERATE
Thyroid Cancer	Unconfirmed risk	Population studies have found no association in humans, despite findings in rodents.	MODERATE

Source: Authors.

3.4 CARDIOVASCULAR AND RENAL OUTCOMES

In addition to weight loss, a vast amount of high-quality evidence demonstrates significant cardiometabolic benefits associated with the use of GLP-1 agonists, as summarized in Table 6.

Figure 4
Cardiovascular and Renal Benefits


Source: Authors.

Table 6
Summary of Cardiovascular and Renal Benefits

Outcome	Relative Risk Reduction (HR, 95% CI)	Source of Evidence (Meta-analysis)	Certainty of the Evidence
Major Cardiovascular Events (MACE)	14% (HR 0.86, 0.81–0.90)	Diabetes Care, 2025 [28]	HIGH
Hospitalization for Insuf. Cardiac	14% (HR 0.86, 0.79–0.93)	Diabetes Care, 2025 [28]	HIGH

Composite renal outcomes	17% (HR 0.83, 0.75–0.92)	Diabetes Care, 2025 [28]	HIGH
All-Cause Mortality	12% (HR 0.88, 0.82–0.93)	Diabetes Care, 2025 [28]	HIGH

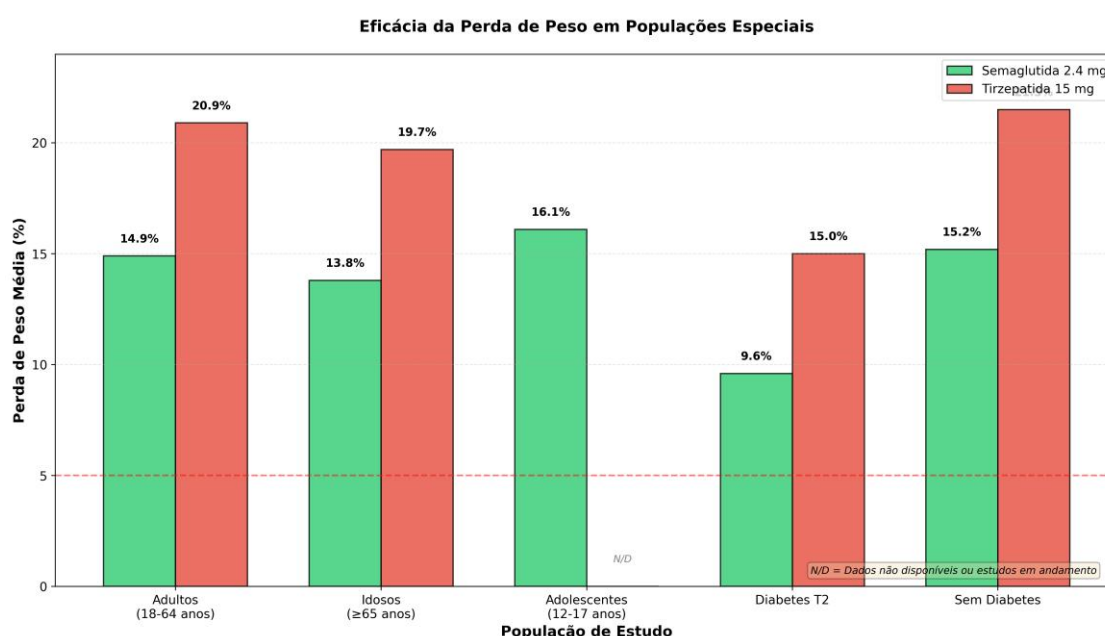
Source: Authors.

3.5 ANALYSIS IN SPECIAL POPULATIONS

The efficacy and safety of GLP-1 agonists have been evaluated in several subpopulations, with results that, in general, reinforce the applicability of these agents in a wide spectrum of patients. Figure 5 illustrates the comparative effectiveness in different groups.

Figure 5

Effectiveness of Weight Loss in Special Populations



Source: Authors.

Table 8

Summary of Evidence in Special Populations

Population	Efficacy Findings	Safety Findings	Clinical Recommendations
Elderly (≥65 years old)	Robust weight loss comparable to that of younger adults (e.g., ~13% with semaglutide). Cardiovascular and renal benefits maintained [24].	Similar tolerability profile, but with a greater need for monitoring renal function and nutritional status to avoid sarcopenia.	Start with lower doses and slower titration. Monitor hydration and kidney function.
Teens (12-17 years)	Demonstrated efficacy with liraglutide and semaglutide, resulting in significant improvement in BMI. Weight loss can be as high as 16% with semaglutide [25].	Adverse effect profile consistent with that of adults. No negative impacts on growth or pubertal maturation were observed.	Consider as an adjuvant to lifestyle changes in cases of severe obesity, under specialist supervision.

Patients with T2 Diabetes	Weight loss is consistently lower than in patients without diabetes (e.g., ~9.6% with semaglutide vs. 15.2% in non-diabetics), but still clinically relevant.	Risk of hypoglycemia is increased if associated with insulin or insulin secretagogues. CV and renal benefits are pronounced in this group.	Adjust doses of other antidiabetic medications to minimize the risk of hypoglycemia.
Pregnant and Breastfeeding Women	Contraindicated. Animal studies show reproductive toxicity. Data in humans are from inadvertent exposures and do not show a clear sign of teratogenicity, but are insufficient to ensure safety [26].	Unknown.	Discontinue treatment at least 2 months before planning pregnancy. If pregnancy occurs during use, the drug should be discontinued immediately.
Chronic Renal Failure (CKD)	Effectiveness maintained. Studies have shown protective renal outcomes, with reduced progression of albuminuria [27].	No dose adjustment is required for mild to moderate CKD. For severe CKD (GFR < 30), experience is limited and use should be cautious.	Monitor renal function, especially during dose titration, due to the risk of acute kidney injury associated with dehydration (vomiting/diarrhoea).

Source: Authors.

3.6 REGULATORY STATUS

The main agents have been approved for the treatment of obesity by the main global regulatory agencies, as detailed in Table 7.

Table 7

Regulatory Approval Status for Obesity

Agent	FDA (USA)	EMA (Europe)	ANVISA (Brazil)
Liraglutide	Approved (2014)	Approved (2015)	Approved (2016)
Semaglutide	Approved (2021)	Approved (2021)	Approved (2022)
Tirzepatide	Approved (2023)	Approved (2023)	Approved (2023)

Source: Authors.

4 DISCUSSION

Obesity is a chronic and multifactorial disease, whose global prevalence has reached pandemic proportions, affecting more than 650 million adults worldwide [1]. Characterized by excessive accumulation of body fat, obesity is intrinsically associated with an elevated risk of developing serious comorbidities, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and certain neoplasms, resulting in a significant increase in morbidity and mortality [2].

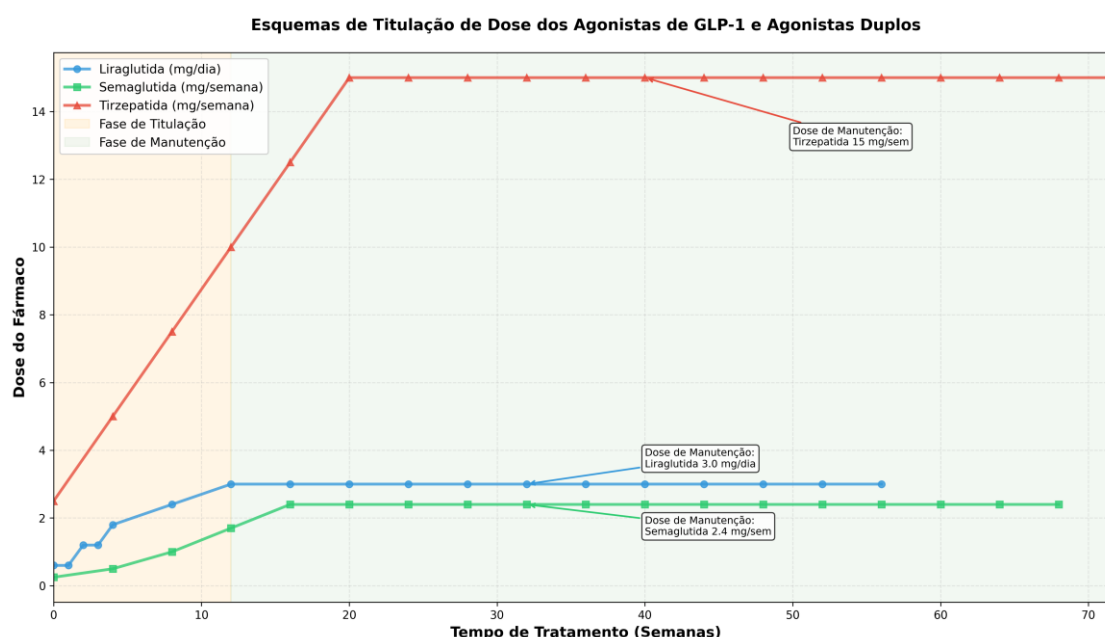
4.1 COMPARATIVE ANALYSIS AND THERAPEUTIC POSITIONING

The introduction of multiple agents with similar mechanisms of action, but with different efficacy, raises the question of the therapeutic positioning of each one. Tirzepatide, with its double agonism, has established a new level of efficacy, surpassing semaglutide in

indirect and direct comparison studies [12, 17]. The retracement, still in the investigation phase, promises even more expressive results. The choice of agent should therefore be individualized, considering the weight loss goal, the patient's comorbidity profile, tolerability, and cost. Figure 6 presents a visual scheme for dose titration.

Figure 6

Comparative Dose Titration Scheme



Source: Authors.

Table 9

Direct and Indirect Comparative Analysis of Agents

Attribute	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 15 mg	Retatrutide 12 mg
Mechanism	GLP-1 Agonist	GLP-1 Agonist	GLP-1/GIP Agonist	GLP-1/GIP/Glucagon Agonist
Frequency	Daily	Weekly	Weekly	Weekly
Average Weight Loss	~8%	~15%	~21%	~24-28%
CV Benefits	Proven (LEADER) [31]	Proven (STEP-CV)	Under investigation (SURPASS-CVOT)	Under investigation
GI Adverse Effects	Moderate	Moderate to High	Moderate to High	Highs
Positioning	First generation option, well established, lower relative cost.	Current standard of care for high efficacy, with robust long-term data.	Highest efficacy option for maximum weight loss or for non-responders to semaglutide.	Future option for severe or refractory obesity.

Source: Authors.

4.2 CRITICAL INTERPRETATION OF THE EVIDENCE

This systematic review consolidates a robust body of evidence that positions GLP-1 agonists and dual agonists as one of the most important therapeutic innovations in the

management of obesity. The magnitude of weight loss achieved, which ranges from 8% to more than 20%, not only surpasses that of previous pharmacotherapies, but also approaches the efficacy of some bariatric procedures, offering a less invasive alternative for a broad patient population [30].

One of the most significant findings is the confirmation of cardiometabolic benefits that transcend simple weight reduction. The consistent and statistically significant decrease in major cardiovascular events (MACE), hospitalizations for heart failure, and adverse renal outcomes, as demonstrated in large-scale meta-analyses, redefines these agents as disease-modifying therapies for patients with obesity and high cardiovascular risk [28, 31].

The safety profile, although marked by a high incidence of gastrointestinal adverse effects, is considered manageable. The transient nature of these effects and the possibility of mitigating them with careful dose titration are crucial factors for treatment adherence. Initial concerns about risks of pancreatitis and thyroid cancer, based on preclinical signs or limited data, have been largely mitigated by subsequent large studies and population analyses, which have not confirmed a significant increased risk in humans [21, 22].

4.3 CLINICAL IMPLICATIONS AND PRACTICAL RECOMMENDATIONS

Based on the evidence analyzed, the following clinical implications can be outlined:

- **Patient Selection:** These agents should be considered as first- or second-line therapy for adults with obesity (BMI ≥ 30) or overweight (BMI ≥ 27) with comorbidities, especially in the presence of established cardiovascular disease, heart failure, or type 2 diabetes.
- **Choice of Agent:** Drug selection should be individualized. Tirzepatide offers the highest effectiveness in weight loss, followed by semaglutide and liraglutide. The choice may be guided by weight loss goal, comorbidity profile, tolerability, and cost.
- **Treatment Management:** Patient education about potential gastrointestinal adverse effects and the importance of gradual dose titration are critical to therapeutic success. Regular monitoring of weight, metabolic parameters, and renal function is recommended.
- **Long-Term View:** It is crucial to discuss with patients that obesity is a chronic disease and that treatment discontinuation is associated with weight regain. Planning a long-term maintenance strategy is essential.

4.4 IMPLICATIONS FOR HEALTH POLICIES AND ACCESS

Despite their proven efficacy, the high cost of these drugs represents a significant barrier to access for most patients worldwide. Cost-effectiveness assessment is complex, but preliminary studies suggest that, for high-risk cardiovascular populations, the investment may be justified by reducing costly and disabling events in the long term. Public policies that facilitate access, such as incorporation into public health systems and price negotiation, are crucial for the benefits of this therapeutic class to be widely realized.

4.5 GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Despite the volume of evidence, some important gaps persist and should be the focus of future research, as highlighted in Table 8.

Table 8

Key Knowledge Gaps and Recommendations for Future Research

Knowledge Gap	Justification of Importance	Research Recommendation
Long-Term Efficacy and Safety (>5 years)	Obesity is a chronic disease; Durability of effects and long-term safety are crucial.	Conduct extensions of clinical trials and long-follow-up observational studies.
Effectiveness in Diverse Populations	Most trials were conducted in predominantly white populations.	Conduct dedicated trials and sub-analyses on different ethnic and racial groups.
Post-discontinuation Weight Regain Phenomenon	Understanding the mechanisms and predictors can lead to more effective mitigation strategies.	Investigate the physiological and behavioral mechanisms underlying weight regain.
Safety in Pregnant Women	Safety data based on inadvertent exposure is insufficient.	Prospective studies (if safety confirmed) and exposure registries.
Head-to-Head Comparisons	Direct comparisons between newer agents (e.g., tirzepatide vs. retatrutide) are necessary.	Develop and execute direct comparative randomized controlled trials.
Combinations with Other Agents	Optimize weight loss and metabolic profile in non-responders.	Efficacy and safety studies of therapeutic combinations.

Source: Authors.

5 CONCLUSION

Injector pens containing GLP-1 agonists and dual GLP-1/GIP agonists represent a paradigmatic advance and a highly effective therapeutic tool in the treatment of obesity and its associated comorbidities. Current scientific evidence, from multiple large-scale randomized controlled trials and meta-analyses, unequivocally supports its ability to induce clinically meaningful and sustained weight loss, accompanied by robust cardiovascular and renal benefits. The safety profile is well established and considered manageable, reinforcing its position as a key therapeutic option. Judicious use of these agents, under medical supervision and with a long-term treatment approach, is essential to maximize the benefits and improve the health of millions of people affected by obesity around the world.

6 LIMITATIONS OF THE REVIEW

This review has some limitations. First, the search was restricted to English and Portuguese, which may have led to the exclusion of relevant studies published in other languages. Secondly, as with any review, there is a risk of publication bias, where studies with positive results are more likely to be published. Finally, the synthesis of the data was carried out in a narrative manner, without conducting a formal meta-analysis, which limits the ability to derive effect estimates combined with statistical precision.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest. This review was conducted independently and did not receive external funding.

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APPENDIX

Table 9

PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) Checklist

Section	Item	Article Location
TITLE		
Title	1. Identify the report as a scoping review.	Title
ABSTRACT		
Summary	2. Provide a structured summary.	Structured Summary
INTRODUCTION		
Justification	3. Describe the rationale for the review.	Section 1
Objective	4. Explicitly state the issue(s) and objective(s) of the review.	Summary and Section 1
METHODS		
Protocol and Registration	5. Indicate if a protocol exists and where it can be accessed.	Section 2.1
Eligibility Criteria	6. Specify the eligibility criteria (concept, population, context).	Section 2.3
Sources of Information	7. Describe all sources of information in the search.	Section 2.2
Search	8. Present the complete search strategy for at least one database.	Table 2
Font Selection	9. Describe the process of selecting sources of evidence.	Section 2.4
Data Extraction	10. Describe the data extraction process.	Section 2.4
Data Items	11. List and define all the variables for which the data was extracted.	Section 2.4
Bias Risk Assessment	12. Describe the methods used to assess risk of bias.	Section 2.5
Summary of Results	13. Describe the methods of presentation and synthesis of the results.	Section 2.5
RESULTS		
Font Selection	14. Present the number of selected evidence sources and the process in a flowchart.	Section 3.1, Figure 1
Characteristics of the Sources	15. Cite and summarize the characteristics of the sources of evidence included.	Section 3.1, Table 3
Risk of Bias	16. Present the results of the risk of bias assessment, if performed.	Section 3.1
Individual Results	17. For each source, submit the relevant data.	Sections 3.2 to 3.5
Summary of Results	18. Summarize and synthesize the results.	Tables 3-9, Figures 2-6
DISCUSSION		
Summary of Evidence	19. Summarize the main results.	Section 4
Limitations	20. Discuss the limitations of the review.	Section 6
Conclusion	21. Present the conclusions and implications for research, practice and policy.	Section 5, Section 4.3, 4.4
FINANCING		
Funding	22. Describe the sources of funding. Source: Authors.	Section 7

THE IMPACT OF WORKLOAD OVERLOAD IN NURSING AND ITS CONSEQUENCES FOR PATIENT CARE

O IMPACTO DA SOBRECARGA DE TRABALHO NA ENFERMAGEM E SUAS CONSEQUÊNCIAS PARA O CUIDADO AO PACIENTE

EL IMPACTO DE LA SOBRECARGA DE TRABAJO EN ENFERMERÍA Y SUS CONSECUENCIAS PARA LA ATENCIÓN AL PACIENTE



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ABSTRACT

This integrative review analyzes the impact of nursing workload and burnout on patient safety and the quality of care. The global shortage of professionals, combined with stressful environments, generates high exhaustion rates, which were dramatically exacerbated by the COVID-19 pandemic. The study consistently demonstrates that inadequate nurse-to-patient ratios are directly associated with increased hospital mortality, higher readmission rates, and prolonged lengths of stay. Additionally, team burnout correlates with a lower safety climate and an increase in adverse events, encompassing healthcare-associated infections, medication administration errors, and the omission of essential vigilance and hygiene care. Contrary to the perception of high cost, economic analyses show that investing in adequate staff sizing yields a positive return, as costs are offset by the reduction in complications. It is concluded that workload must be addressed as a systemic organizational phenomenon. Adopting safe minimum ratio policies is cost-effective, essential for mitigating risks, and fundamental for preserving lives.

Keywords: Workload. Occupational Burnout. Patient Safety. Nurse Staffing. Quality of Care.

RESUMO

Esta revisão integrativa analisa o impacto da sobrecarga de trabalho e do burnout na enfermagem sobre a segurança do paciente e a qualidade assistencial. A escassez global de profissionais, aliada a ambientes estressantes, gera altas taxas de exaustão, que foram dramaticamente exacerbadas pela pandemia de COVID-19. O estudo demonstra de forma

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consistente que proporções inadequadas de pacientes por enfermeiro estão diretamente associadas ao aumento da mortalidade hospitalar, maiores taxas de readmissão e prolongamento do tempo de internação. Adicionalmente, o burnout na equipe correlaciona-se com um clima de segurança inferior e elevação de eventos adversos, englobando infecções relacionadas à assistência à saúde, erros de administração de medicamentos e a omissão de cuidados essenciais de vigilância e higiene. Contrariando a percepção de alto custo, análises econômicas evidenciam que o investimento no dimensionamento adequado da equipe apresenta retorno positivo, pois os custos são compensados pela redução de complicações. Conclui-se que a sobrecarga deve ser abordada como um fenômeno organizacional sistêmico. A adoção de políticas de proporções mínimas seguras é custo-efetiva, essencial para mitigar riscos e fundamental para preservar vidas.

Palavras-chave: Sobrecarga de Trabalho. Burnout Ocupacional. Segurança do Paciente. Dimensionamento de Pessoal. Qualidade do Cuidado.

RESUMEN

Esta revisión integradora analiza el impacto de la sobrecarga de trabajo y el agotamiento profesional en enfermería sobre la seguridad del paciente y la calidad de la atención. La escasez mundial de profesionales, sumada a entornos estresantes, genera altas tasas de agotamiento profesional, que se han visto drásticamente exacerbadas por la pandemia de COVID-19. El estudio demuestra consistentemente que una proporción inadecuada de pacientes por enfermero se asocia directamente con un aumento de la mortalidad hospitalaria, mayores tasas de reingreso y una estancia hospitalaria prolongada. Además, el agotamiento profesional en el equipo se correlaciona con un clima de seguridad deficiente y un aumento de eventos adversos, incluyendo infecciones asociadas a la atención sanitaria, errores de medicación y la omisión de la vigilancia y la higiene esenciales. Contrariamente a la percepción de un alto costo, los análisis económicos muestran que la inversión en niveles adecuados de personal genera un retorno positivo, ya que los costos se compensan con una reducción de las complicaciones. Se concluye que la sobrecarga de trabajo debe abordarse como un fenómeno organizacional sistémico. La adopción de políticas de ratio mínimo seguro es rentable, esencial para mitigar riesgos y fundamental para preservar vidas.

Palabras clave: Carga de Trabajo. Agotamiento Profesional. Seguridad del Paciente. Dotación de Personal. Calidad de la Atención.

1 INTRODUCTION

Nursing workload represents a critical and growing challenge for global health systems, with direct and measurable implications for the safety and quality of patient care. This phenomenon is not new, but it has intensified in recent decades due to multiple converging factors that put pressure on health systems around the world.

1.1 HISTORICAL CONTEXT AND EVOLUTION OF THE RESEARCH

The relationship between nursing personnel and clinical outcomes has deep historical roots. Florence Nightingale, through meticulous records and application of groundbreaking statistics, documented that more British soldiers in military hospitals during the Crimean War died due to unsafe hospital conditions than from battle injuries.⁽¹⁾ His solution was the introduction of trained nurses, which his research demonstrated to be associated with a reduction in hospital deaths. More than 150 years later, nurses continue to save lives in modern hospitals, and research suggests that harm to patients can be further reduced by investments in nursing staffing.⁽¹⁾

Over the past three decades, robust evidence has demonstrated that adequate levels of nursing staffing are associated with improved clinical outcomes, including reduced mortality and adverse events.^[2] An important milestone was the study published in 2002 by Aiken et al., which demonstrated for the first time on a large scale that each additional patient in the average nurses' workload was associated with a 7% higher chance of mortality and a 7% higher chance of rescue failure (mortality after complications).^[3] This study estimated that if the staffing ratio in all hospitals was 6 patients per nurse instead of 4 patients per nurse, 2.3 additional deaths per 1,000 patients and 8.7 additional deaths per 1,000 patients with complications would be expected.^[3]

In 2014, The Lancet published an international study involving nearly half a million patients in 300 hospitals in nine European countries, demonstrating that patients in hospitals with better levels of nursing staff were less likely to die in hospital than those treated in understaffed hospitals.^[1] This study consolidated decades of research linking staffing levels to outcomes including mortality, readmissions, length of stay, adverse events, and patient satisfaction.^[1]

1.2 THE GLOBAL CRISIS OF THE NURSING WORKFORCE

Currently, the world is facing an unprecedented crisis in the nursing workforce. Nurses constitute the largest segment of the health workforce, and their effective allocation is critical to the quality and efficiency of health systems.^[2] In 2019, it was estimated that the world had

104.0 million health workers, including 29.8 million nurses and midwives.^[3] However, to achieve 80 out of 100 in the index of effective universal health coverage, at least 70.6 nurses and midwives per 10,000 population would be needed.^[4]

The global analysis revealed alarming deficits: in 2019, national health workforces fell short of these minimum thresholds by 30.6 million nurses and midwives globally.^[4] The largest gaps were observed in Sub-Saharan Africa (deficit of 5.6 million), Southeast Asia, East Asia and Oceania (deficit of 8.8 million) and South Asia (deficit of 11.0 million).^[4] These regions face high rates of disease burden, as well as growing health care needs due to the increasing prevalence of noncommunicable diseases and population growth.^[4]

Nurse shortages are reported in many developed countries, including the US, Canada, the UK, Ireland, Australia, and in many low- and middle-income countries in South America, Africa, and Asia.^[5] It is estimated that there will be a global shortage of around nine million nurses/midwives by 2030.^{[6][5]} The difficulty in recruiting and retaining nurses is linked to difficult working conditions, insecure nurse-to-patient ratios, stress, and low pay.^[5] Studies have identified that the younger generation of nurses is the most likely to leave the profession, mainly due to highly demanding work, burnout, and dissatisfaction with salary levels.^[5]

1.3 GLOBAL PREVALENCE OF BURNOUT IN NURSING

Nursing burnout, characterized by emotional exhaustion, depersonalization, and decreased sense of personal fulfillment, has become a globally recognized occupational phenomenon.^[7] The World Health Organization recently declared burnout as an "occupational phenomenon" in the 11th revision of the International Classification of Diseases (ICD-11), recognizing burnout as a serious health issue.^[8]

The global prevalence of burnout among nurses is alarming. A pre-pandemic meta-analysis involving 113 studies with 45,539 nurses in 49 countries found a global prevalence of burnout symptoms of 11.23%.^[8] Another meta-analysis of 94 studies covering more than 30 countries estimated the global prevalence of nursing burnout syndrome at 30.0% (95% CI: 26.0%-34.0%) for the period 2012 to 2022.^[9] It is important to highlight that the meta-regression indicated a gradual upward trend over the last 10 years, with significant increases in Europe, Africa and in specialties such as obstetrics.^[9]

Among nurses, burnout is particularly prevalent due to work being associated with stress, the need to demonstrate understanding, compassion, and commitment, along with the simultaneous need to maintain the necessary emotional distance.^[10] The percentages of nurses suffering from burnout in the surveys presented ranged from 14.3% to 84.7%, with

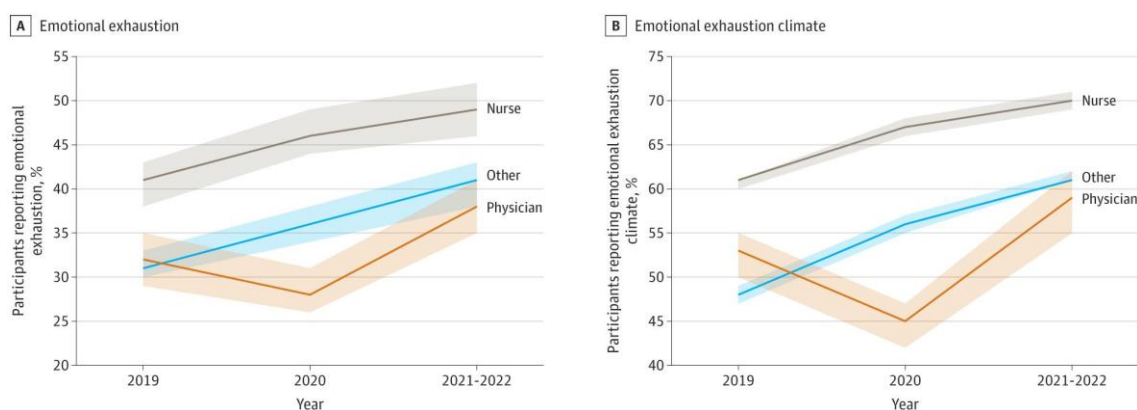
the highest value of burnout among nurses who worked in ICUs during the COVID-19 pandemic.^[10]

1.4 THE IMPACT OF THE COVID-19 PANDEMIC

The COVID-19 pandemic has dramatically exacerbated the crisis of work overload and burnout in nursing. During the pandemic, the prevalence of burnout increased substantially. An updated meta-analysis involving 19 studies from 11 countries indicated an overall burnout prevalence rate of 59.5% in the nurse population during COVID-19.^[11] Analyses of 37 studies with 15,015 nurses revealed a combined prevalence rate for emotional exhaustion of 36.1%, for depersonalization of 32.4%, and for reduction of personal fulfillment of 33.3%.^[11]

Figure 1

Reported Emotional Exhaustion and Emotional Exhaustion Climate by Aggregated Health Care Worker Role undefined



Source: Authors.

Nurses consistently reported the highest levels of exhaustion across all three time periods and showed steady increases each year, rising from approximately 41% in 2019 to 49% in 2021-2022.^[12] The majority of practicing nurses (84%) reached the threshold for emotional exhaustion during the pandemic.^[13]

The main risk factors that increased nurses' burnout during the pandemic included: younger age, decreased social support, poor family and colleague readiness to deal with the COVID-19 outbreak, increased perceived threat of COVID-19, longer working time in quarantine areas, working in a high-risk environment, working in hospitals with inadequate and insufficient material and human resources, increased workload and lower level of specialized training on COVID-19.^[14] More than 70% of nurses experienced moderate to high

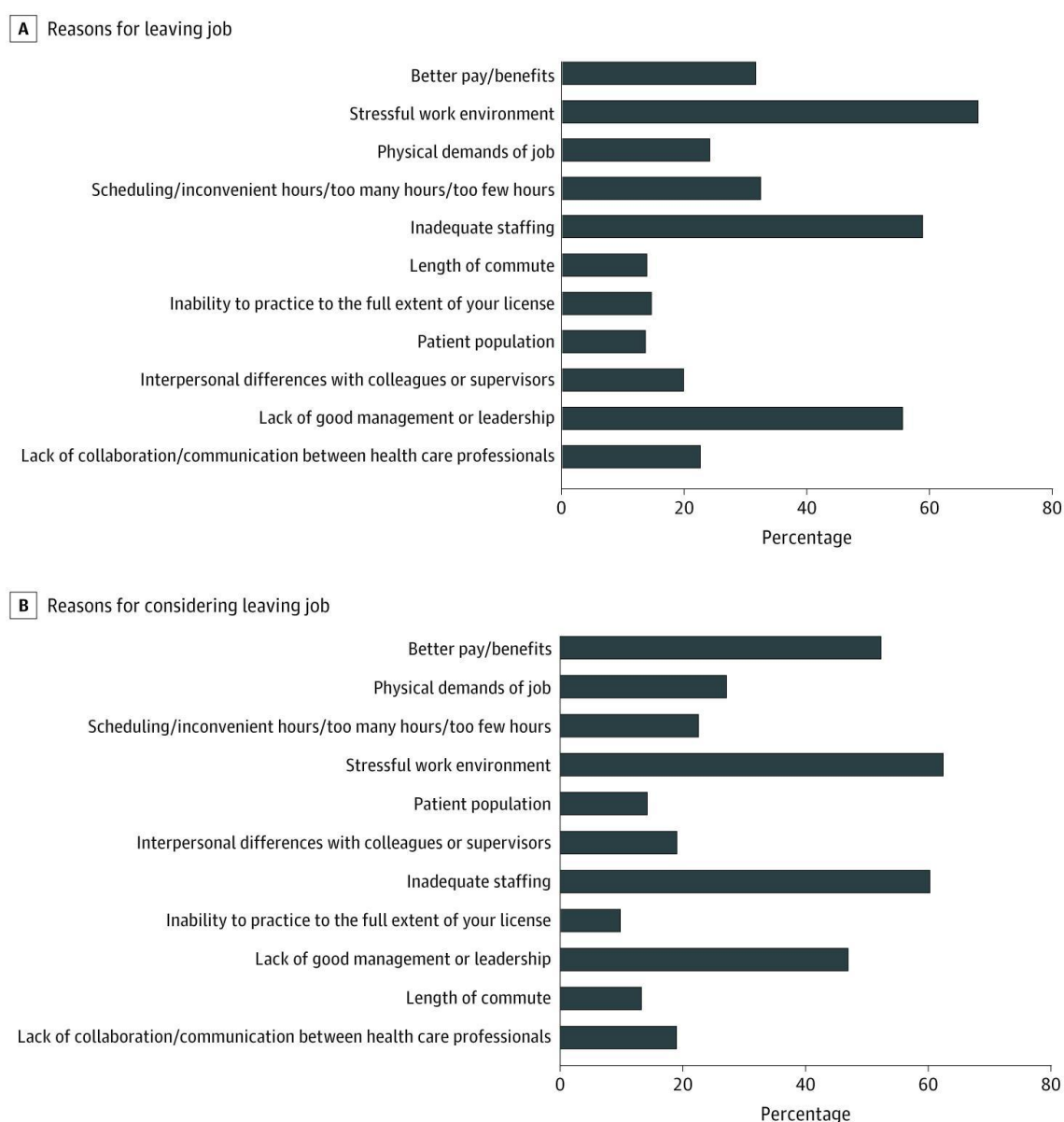
emotional exhaustion, with higher exposure to COVID-19 correlating with increased burnout.^[15]

1.5 DETERMINANTS OF WORK OVERLOAD

Work overload in nursing is a multidimensional phenomenon influenced by factors related to the patient, the nurse and the workflow. Studies have identified that workload has physical, mental, and emotional dimensions, each with specific determinants.^[16]

Figure 2

Overlap of Work Reasons for Nurses Who Left or Considered Leaving Their Jobs Owing to Burnout undefined



Source: Authors.

Among nurses who left their jobs citing burnout as a reason, the overwhelming majority also reported experiencing a stressful work environment and inadequate staffing as contributing factors, with these two questions showing the greatest overlap with burnout.^[17] Recent research has shown that 39% of active practice nurses planned to leave their employer within a year, with factors associated with departures including younger age, abusive events, emotional exhaustion, unfavorable workplaces, and inadequacy of staffing and resources.^[18]

Significant predictors of perceived workload include: patient acuity, staffing resources, patient transfers, documentation, patient isolation, unscheduled activities, and patient specialties.^[19] Physical workload was predicted by all variables tested; mental workload was determined by patient complexity or isolation, nursing staff suitability and skill mix, and unscheduled activities; and emotional workload was predicted by all variables except staffing suitability and education of others.^[16]

Twenty to forty percent of nurses reported being unable to provide care in the time available, understaffed, and inadequate skill mix.^{More} than 60% believed that processes to address workload issues were inadequate.^[20] Institutional influences on staffing levels and skill mix are resulting in implicit rationing of care, impacting patient safety.^[20]

2 BACKGROUND AND OBJECTIVES

Despite the extensive literature on the subject, no meta-analysis had estimated the association between nursing burnout and quality and safety of health care and patient morbidity and mortality until recently.^[7] This gap is particularly significant considering that nurses are on the front lines of patient care in hospitals and other settings, often present when doctors are not, and tasked with making important clinical decisions.^[7]

In 2020-21, the World Health Organization designated the International Year of the Nurse and Midwife to honor the 200th anniversary of Florence Nightingale's birth.^[1] This global recognition highlights the critical importance of nursing to health systems and the urgent need to address the challenges faced by these professionals.

This integrative review synthesizes the scientific literature on the impact of work overload on nursing and its consequences for patient care, with the following objectives: (1) to examine the relationship between nursing workload, nurse-patient ratios and clinical outcomes; (2) to evaluate the association between nursing burnout and patient safety, satisfaction, and quality of care; (3) identify mechanisms by which work overload affects patient outcomes; and (4) to analyze the cost-effectiveness of interventions to improve the dimensioning of nursing staff.

3 METHODOLOGY

This integrative review examined published studies that investigated the relationship between nursing workload, nurse-patient ratios, burnout, and clinical outcomes. Prospective and retrospective studies, systematic reviews, and meta-analyses that evaluated outcomes related to patient safety, quality of care, and mortality were included.

4 RESULTS

4.1 IMPACT OF THE NURSE-PATIENT RATIO ON MORTALITY

International studies consistently demonstrate that inadequate nurse-to-patient ratios are associated with higher in-hospital mortality. A prospective study in Queensland, Australia, involving 27 interventional hospitals and 28 comparison hospitals, demonstrated that after the implementation of minimal nurse-to-patient ratios, mortality rates were significantly lower in interventional hospitals (adjusted OR 0.89; 95% CI 0.84-0.95; $p=0.0003$).^[1] Each additional patient per nurse was associated with a 7% higher chance of patient death at 30 days in a European study involving nearly half a million patients.^[1]

Data from New York showed that each additional patient per nurse was associated with a higher chance of in-hospital mortality for both surgical (OR=1.13; $p=0.0262$) and clinical (OR=1.13; $p=0.0019$) patients.^[21] It was estimated that if hospitals were sized with a ratio of 4:1 patients per nurse, 4,370 lives would be saved over a 2-year period.^[21]

A recent Japanese study using large-scale administrative data and robust methods demonstrated that nursing undersizing (defined as levels below the unit-specific annual median) was associated with increased in-hospital mortality, higher 30-day readmission rates, and longer hospital stays, particularly during the day shift and over the 24-hour period.^[2]

4.2 NURSING BURNOUT AND PATIENT SAFETY

A systematic meta-analysis involving 85 studies with 288,581 nurses from 32 countries revealed that nursing burnout is associated with multiple adverse outcomes.^[7] Burnout was associated with a lower safety climate (DME -0.68; 95% CI -0.83 to -0.54), lower safety classification (DME -0.53; 95% CI -0.72 to -0.34), and a higher frequency of nosocomial infections (DME -0.20; 95% CI -0.36 to -0.04), patient falls (DME -0.12; 95% CI -0.22 to -0.03), medication errors (DME -0.30; 95% CI -0.48 to -0.11), adverse events (DME -0.42; 95% CI -0.76 to -0.07) and omitted care (DME -0.58; 95% CI -0.91 to -0.26).^[7]

Burnout was also associated with lower patient satisfaction scores (DME -0.51; 95% CI -0.86 to -0.17) and lower quality of care assessed by nurses (DME -0.44; 95% CI -0.57 to

-0.30).^[7] The emotional exhaustion and depersonalization dimensions of burnout were more strongly associated with patient safety than low personal achievement.^[7]

4.3 HEALTHCARE-ASSOCIATED INFECTIONS

Excessive nursing workload was identified as a major risk factor for healthcare-associated infections (HAIs). A prospective study in ICUs demonstrated that excessive nursing workload (measured by the Nursing Activities Score - NAS) was the main risk factor for HAI (OR: 11.41; $p=0.019$), when evaluated in conjunction with other invasive devices.^[22]

Evidence shows that high bed occupancy and low levels of nursing staff are associated with increased transmission of methicillin-resistant *Staphylococcus aureus* (MRSA).^{[23][24]} Studies have estimated that more than a quarter of HAIs could be avoided if the nurse-to-patient ratio was kept above 2.2 in ICUs.^[24]

4.4 MEDICATION ERRORS

Systematic reviews have identified an association between inadequate levels of nursing staff and higher rates of medication administration errors.^[5] Three high-quality studies associated lower levels of nursing staffing with higher rates of medication administration errors and omitted care.^[5]

4.5 READMISSIONS AND LENGTH OF STAY

The Queensland study showed that readmissions increased in comparison hospitals (OR 1.06; 95% CI 1.01-1.12; $p=0.015$), but not in intervention hospitals with adequate proportions (OR 1.00; 95% CI 0.95-1.04; $p=0.92$).^[1] Although length of stay decreased in both groups, the reduction was more pronounced in intervention hospitals (adjusted IRR 0.95; 95% CI 0.92-0.99; $p=0.010$).^[1]

Each additional patient per nurse was associated with longer length of hospital stay for both surgical (IRR=1.09; $p=0.0008$) and clinical (IRR=1.05; $p=0.0023$) patients, and a higher chance of readmission at 30 days.^[21]

4.6 PATHOPHYSIOLOGICAL MECHANISMS

The underlying mechanism by which low levels of nursing staffing affect patient outcomes is related to omitted nursing care.^[2] When nurses are overworked, essential activities of patient surveillance, timely medication administration, mobilization, hygiene, and adequate preparation for discharge are often omitted, leading to adverse events such as

increased mortality, longer hospital stays, and inadequate preparation for discharge, resulting in higher readmission rates.^[2]

A post-COVID-19 pandemic Thai study demonstrated that each additional unit of emotional exhaustion was associated with a 1.61 times higher chance of omitted care, a 3.37 times higher chance of poor quality of nursing care, and a 2.62 times higher chance of poor quality of overall unit care.^[25]

4.7 COST-EFFECTIVENESS ANALYSIS

Contrary to the perception that increasing the number of nursing staff is expensive, studies have shown a positive return on investment. In the Queensland study, the costs avoided due to fewer readmissions and shorter hospital stay were more than double the cost of additional nursing staff.^[1]

A British cost-effectiveness analysis estimated that eliminating the undersizing of registered nurses and nursing assistants would cost £2,778 per quality-adjusted life year (QALY) considering personnel costs alone, £2,685 including sick leave and readmission reduction benefits, or save £4,728 including length of stay reduction benefits.^[26] According to the National Institute for Health and Care Excellence's £10,000 per QALY threshold, it is cost-effective to eliminate understaffing^[26]

Conservative estimates from New York projected savings of \$720 million over a 2-year period in shorter hospital stays and avoided readmissions if hospitals were sized 4:1.^[21]

5 DISCUSSION

The evidence accumulated over the last three decades consistently and robustly demonstrates that work overload in nursing has measurable and significant consequences for the safety and quality of patient care. The findings are consistent regardless of age, gender, nurses' professional experience, and geography.^[7]

The associations between work overload and adverse outcomes persisted over time, and the association with quality of care became increasingly negative over three decades, even after accounting for the COVID-19 pandemic.^[7] This is concerning considering decades of national and organizational efforts to improve quality.

Most anti-burnout efforts have focused on individual interventions, such as mindfulness or personal resilience training, designed to help people cope more effectively with stress, rather than interventions to reduce stress and burnout in the workplace.^[7] Many effective interventions are at the work unit level, where health workers experience teamwork, feelings of community, professional development, and recognition.^[7]

Policies of minimal nurse-to-patient ratios are feasible and produce significantly better patient outcomes and better return on public investment.^[1] Investments in nursing education and training should also be considered as a component of burnout mitigation efforts, since higher levels of nursing education were associated with lower patient mortality.^[7]

6 CONCLUSION

Work overload in nursing is not only an individual occupational issue, but an organizational and collective phenomenon that affects nurses, patients, organizations, and society as a whole. Evidence shows that inadequate nurse-to-patient ratios and burnout are associated with increased mortality, adverse events, nosocomial infections, medication errors, omitted care, longer hospital stays, readmissions and lower patient satisfaction.

Interventions at the organizational and policy level, including establishing safe minimum nurse-to-patient ratios, investing in permanent rather than temporary staff, and improving the nursing practice environment, are cost-effective and can save lives. Reformulating burnout as an organizational phenomenon, rather than an individual problem, allows for the broader perspective needed to effectively address nursing work overload and its consequences for patient care.

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DIAGNOSIS AND MANAGEMENT OF NEONATAL ESOPHAGEAL ATRESIA: A SYSTEMATIC REVIEW OF CURRENT EVIDENCE

DIAGNÓSTICO E MANEJO DA ATRESIA ESOFÁGICA NO PERÍODO NEONATAL: UMA REVISÃO SISTEMÁTICA DAS EVIDÊNCIAS ATUAIS

DIAGNÓSTICO Y MANEJO DE LA ATRESIA ESOFÁGICA EN EL PERÍODO NEONATAL: UNA REVISIÓN SISTEMÁTICA DE LA EVIDENCIA ACTUAL



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ABSTRACT

Neonatal esophageal atresia is characterized by diagnostic complexity and the need for specialized clinical and surgical management, playing an important role in reducing neonatal morbidity and mortality. This study aims to analyze the available evidence regarding the diagnosis and management of esophageal atresia in newborns, emphasizing early identification, timely intervention, and multidisciplinary care. This is a systematic review conducted according to PRISMA recommendations and registered in PROSPERO under number CRD420261361849, with searches performed in the PubMed, LILACS/BVS, and SciELO databases from 2016 to 2026. The findings demonstrated that early diagnosis, especially during the prenatal period, associated with postnatal clinical and radiological confirmation, reduces complications. Furthermore, early surgical management combined with specialized neonatal intensive care contributes to better clinical outcomes and increased survival. It is concluded that the standardization of diagnostic and therapeutic approaches, together with strengthened multidisciplinary care, is essential to improve neonatal prognosis.

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Keywords: Esophageal Atresia. Newborn. Diagnosis. Treatment. Neonatal Care.

RESUMO

A atresia de esôfago no período neonatal destaca-se pela complexidade diagnóstica e pelo manejo clínico-cirúrgico especializado, sendo relevante para a redução da morbimortalidade neonatal. Objetiva-se analisar as evidências acerca do diagnóstico e manejo da atresia de esôfago em recém-nascidos, enfatizando a identificação precoce, a intervenção oportuna e a assistência multiprofissional. Trata-se de uma revisão sistemática conduzida conforme as recomendações do PRISMA e registrada no PROSPERO sob o número CRD420261361849, com buscas nas bases PubMed, LILACS/BVS e SciELO, no período de 2016 a 2026. Observou-se que o diagnóstico precoce, especialmente no pré-natal, associado à confirmação clínica e radiológica pós-natal, reduz complicações. Além disso, o manejo cirúrgico precoce aliado aos cuidados intensivos neonatais especializados favorece melhores desfechos clínicos e maior sobrevida. Conclui-se que a padronização das condutas diagnósticas e terapêuticas, associada ao fortalecimento da assistência multiprofissional, é fundamental para melhorar o prognóstico neonatal.

Palavras-chave: Atresia Esofágica. Recém-Nascido. Diagnóstico. Tratamento. Cuidados Neonatais.

RESUMEN

La atresia esofágica en el período neonatal se destaca por la complejidad diagnóstica y el manejo clínico-quirúrgico especializado, siendo relevante para la reducción de la morbimortalidad neonatal. Este estudio tiene como objetivo analizar la evidencia disponible sobre el diagnóstico y manejo de la atresia esofágica en recién nacidos, enfatizando la identificación precoz, la intervención oportuna y la atención multiprofesional. Se trata de una revisión sistemática realizada conforme a las recomendaciones PRISMA y registrada en PROSPERO bajo el número CRD420261361849, con búsquedas en las bases de datos PubMed, LILACS/BVS y SciELO, en el período de 2016 a 2026. Los hallazgos demostraron que el diagnóstico precoz, especialmente en el período prenatal, asociado a la confirmación clínica y radiológica posnatal, reduce las complicaciones. Además, el manejo quirúrgico temprano combinado con cuidados intensivos neonatales especializados favorece mejores resultados clínicos y mayor supervivencia. Se concluye que la estandarización de las conductas diagnósticas y terapéuticas, asociada al fortalecimiento de la atención multiprofesional, es fundamental para mejorar el pronóstico neonatal.

Palabras clave: Atresia Esofágica. Recién Nacido. Diagnóstico. Tratamiento. Cuidados Neonatales.

1 INTRODUCTION

Esophageal atresia (EA) is one of the most frequent congenital malformations of the gastrointestinal tract, with an estimated incidence of between 1 in 2,500 and 4,500 live births. It is characterized by the interruption of the continuity of the esophagus, often associated with tracheoesophageal fistula, and may occur in isolation or as part of complex syndromes¹. It is a condition of high clinical complexity, whose management requires early and articulated interventions, given its association with significant morbidity and mortality in the neonatal period.

Early diagnosis is a central element for the proper management of cases, allowing the planning of delivery in referral centers with intensive neonatal support and the early organization of care. Evidence indicates that delays in EC recognition and surgical intervention are associated with a higher risk of complications and mortality, reinforcing the importance of care protocols that favor the timely identification and referral of newborns^{2,3}.

Despite advances in perioperative care, EC still has a high complication rate. Clinical studies have shown the occurrence of adverse events, such as anastomotic stenosis, anastomotic rupture, and recurrent fistula, even in specialized services, evidencing the need for rigorous monitoring and well-established clinical strategies⁴. In this context, factors such as prematurity, the presence of associated malformations, and the clinical conditions of the newborn directly influence the outcomes.

The management of esophageal atresia in the neonatal period involves the integration of intensive care, surgical intervention, and ongoing clinical support. Strategies such as ventilatory support, secretion control, progressive enteral nutrition, and neonatal unit monitoring have been associated with better clinical outcomes^{5,6,7}. In addition, the proper management of the perioperative period is a determining factor for recovery and for the prevention of short- and long-term complications.

In more complex situations, such as cases without fistula or associated with other malformations, multidisciplinary action is essential. The articulation between neonatology, pediatric surgery, cardiology, nutrition, and other health fields contributes to clinical stabilization, management of comorbidities, and continuity of care. This integrated approach is also related to the organization of care networks, which are considered fundamental to reduce inequalities in access to specialized care and improve clinical outcomes⁸.

In this context, there is a need to strengthen strategies that promote early diagnosis, adequate clinical-surgical management, and integration between different levels of care. This study analyzes the diagnosis and management of esophageal atresia in the neonatal period, with emphasis on early identification, clinical and surgical strategies, and care organization.

In addition, it examines risk factors and perioperative complications, as well as discusses the role of multidisciplinary approaches and care networks in improving neonatal outcomes.

2 METHODS

This is a systematic review of the literature, with a qualitative approach, conducted with the objective of analyzing the diagnosis and management of esophageal atresia in the neonatal period. The study was developed according to the recommendations of PRISMA 2020⁹, ensuring methodological rigor in the stages of identification, selection, and analysis of the studies.

The search was carried out in the PubMed, LILACS/VHL and SciELO databases, using descriptors related to esophageal atresia, neonatal population and diagnostic and therapeutic aspects. In the PubMed database, the following terms were used: ("Esophageal Atresia") AND ("Newborn" OR "Neonate") AND ("Diagnosis" OR "Treatment" OR "Management"). In the LILACS/VHL and SciELO databases, descriptors in Portuguese and Spanish were used: ("Esophageal Atresia") AND ("Newborn" OR "Born Child") AND ("Diagnosis" OR "Treatment" OR "Treatment"), in order to increase the sensitivity of the search.

The identified records were exported to the Rayyan platform, where duplicates were removed using an automated tool, followed by manual verification based on title, authorship, year of publication, and DOI.

Studies addressing esophageal atresia in the neonatal period, focusing on diagnosis and clinical and/or surgical management, published between 2016 and 2026, in Portuguese, English, or Spanish, and with full text available, were included. Original studies, including cohorts, case-control studies, cross-sectional studies, and case series, were considered eligible.

Duplicate studies, literature reviews, editorials, letters to the editor, and event summaries were excluded, as well as those that were not directly related to the topic or that included populations outside the neonatal period. Articles that did not specifically address aspects of diagnosis or management of esophageal atresia or that were not available in full were also excluded.

After selection, the studies were submitted to analytical reading and organized into thematic axes related to early diagnosis, clinical-surgical management, and care organization. The synthesis of the data was carried out qualitatively, with a critical interpretation of the available evidence.

As this is a secondary study, based on data in the public domain, there was no need to submit it to the Research Ethics Committee, in accordance with current regulations.

3 RESULTS

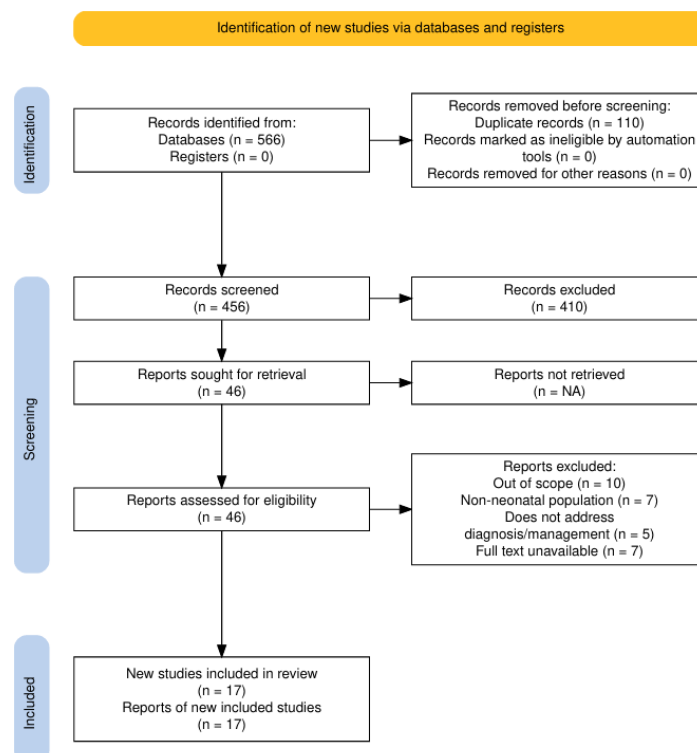
The search in the databases resulted in the identification of 566 records, from PubMed (n=489), LILACS/VHL (n=68) and SciELO (n=9). After the removal of 110 duplicates, 456 studies remained for the screening stage.

The screening, carried out through the reading of titles and abstracts, resulted in the exclusion of 410 records for not meeting the previously established eligibility criteria. Thus, 46 studies were selected for full reading. After the evaluation of the full texts, 29 articles were excluded, mainly because they did not fit the scope of the research, included populations outside the neonatal period, did not address aspects of diagnosis or management of esophageal atresia, or did not present full text availability. At the end of the process, 17 studies were included in the review.

The process of identification, screening, eligibility, and inclusion of studies is presented in Figure 1, prepared according to the recommendations of PRISMA 20209.

Figure 1

Flowchart of the selection process of studies according to PRISMA 2020



Source: Authors.

The included studies were published between 2017 and 2026, with a predominance of observational designs, including retrospective, cohort, and cross-sectional studies. Although the time frame of the search covered the period from 2016 to 2026, no eligible studies were identified in the initial year according to the established criteria. The samples varied considerably, from case series with small numbers of participants to multicenter studies with more than a thousand patients, reflecting the heterogeneity of the scientific production on esophageal atresia in the neonatal period. The detailed characterization of the included studies is described in Table 1.

Table 1

Characterization of included studies

Author/Year	Country	Design	Sample	Objective	Key findings
Piro et al. (2018)	Italy	Retrospective	67 Patients	To evaluate clinical features and their association with morbidity and mortality	Higher mortality associated with congenital malformations and need for intensive care
Tröbs et al. (2017)	Germany	Observational	24 Patients	To compare postoperative course, morbidity, and early outcomes between isolated TEF and esophageal atresia with distal TEF	High rates of prematurity and congenital malformations; Increased perioperative morbidity in esophageal atresia
Basuguy et al. (2020)	Turkey	Retrospective	98 patients	Evaluate the management of fistula and complications (extravasation)	Long esophageal gap associated with higher rates of complications and morbidity
Serooskerken et al. (2021)	Netherlands	Observational	64 patients	Analyze thoracoscopic repair	Surgery considered safe, however, associated with complications such as stenosis and extravasation
Agurto-Ramírez et al. (2023)	Spain	Transverse	146 Patients	Assess prevalence and associated factors	Strong association with congenital malformations and low birth weight
Fola et al. (2023)	Cameroon	Prospective	6 patients	Analyze management strategies in	Survival possible with adapted

				low-resource contexts	techniques, despite structural limitations
Odera et al. (2023)	South Africa	Retrospective	180 patients	Assess incidence and clinical outcomes	Survival rate of 70%; outcomes influenced by birth weight and sepsis
Borselle et al. (2024)	Poland	Retrospective cohort	145 patients	To evaluate the thoracoscopic approach according to birth weight	Technique considered safe even in patients with low birth weight
Kaya et al. (2024)	Turkey	Retrospective	10 patients	To analyze surgical techniques for long-gap esophageal atresia	Techniques such as Foker and Gazi proved to be effective, but associated with complications
Hall et al. (2024)	United Kingdom	Retrospective	157 patients	Evaluate a minimally interventionist approach	Early enteral feeding improves recovery
Pandya et al. (2025)	India	Observational	100 patients	Analyze diagnosis and management	Survival influenced by sepsis, birth weight, and associated anomalies
Ali et al. (2025)	Saudi Arabia	Cohort	67 patients	Assess the impact of esophageal gap	Long esophageal gap associated with increased morbidity and prolonged recovery
Khosravi et al. (2025)	Iran	Retrospective	115 Patients	Compare surgical techniques	Similar outcomes between primary and staged approaches
Platt et al. (2025)	Canada	Retrospective cohort	27 Patients	Evaluate multiprofessional care	Multiprofessional care associated with better care coordination and reduction of hospitalizations
Ungruh et al. (2025)	Germany	Observational	1475 patients	Evaluate the organization of the health system	High complication rates reinforce the importance of centralizing care and specialized centers
Alizadeh et al. (2026)	Iran	Retrospective	79 Patients		Routine chest drainage associated with

				Evaluate the use of chest drainage	increased complications and ICU length
Lindeboom et al. (2026)	Netherlands	Cohort/RCT in development	38 Patients	Evaluate for primary tracheopexy	Reduction of respiratory infections and morbidity

Source: Prepared by the authors

In general, it has been evidenced that esophageal atresia remains a complex condition, often associated with congenital malformations and clinical factors that directly impact the prognosis, such as prematurity, low birth weight, and the presence of comorbidities^{10,11,12,13,14}.

Early diagnosis, usually performed in the first hours or days of life, has been identified as a determining factor for better clinical outcomes, being associated with a reduction in complications and neonatal mortality^{13,14,10}.

With regard to management, all studies indicate surgical correction as the standard treatment, with different technical approaches employed according to the anatomical and clinical characteristics of the patients. In three studies, it was observed that the results tend to be similar between different techniques when performed under appropriate conditions^{1,15,16}. On the other hand, three studies have highlighted that the length of the esophageal gap, the presence of infection, and neonatal clinical instability are determining factors for postoperative complications^{17,18,19}.

Within the scope of perioperative strategies, three studies showed a direct impact of interventions on clinical outcomes. Routine use of chest drainage was associated with increased complications and longer hospital stays²⁰, while early enteral feeding demonstrated benefits in recovery⁶. In addition, primary tracheopexy has shown promising results in reducing respiratory morbidities in selected patients²¹.

Regarding the organization of care, four studies indicated that the multidisciplinary approach, the centralization of care, and the structuring of care systems are associated with improved clinical outcomes, including longer survival and reduced length of hospital stay^{8,14,21,22}. On the other hand, one study showed that, in contexts with limited resources, although it is possible to achieve survival, significant structural challenges persist that negatively impact the results²².

The synthesis of the findings allowed the organization of the evidence into three main thematic axes: early diagnosis and clinical evaluation, neonatal clinical-surgical management, and multidisciplinary care networks, as shown in Table 2.

Table 2*Thematic axes of scientific production on neonatal esophageal atresia*

Thematic axis	Key Evidence	Summary of findings
Early diagnosis and clinical evaluation (n = 5)	Identification in the first hours of life, characteristic clinical signs and confirmation by imaging tests; high association with congenital malformations	Early diagnosis allows immediate intervention, reduces complications, and improves neonatal prognosis, especially in patients with associated comorbidities
Neonatal clinical and surgical management (n = 8)	Initial stabilization, surgical techniques (primary anastomosis and staged repairs), influence of the esophageal gap, postoperative complications, and perioperative strategies	Individualized management, considering clinical and anatomical conditions, is associated with better outcomes; interventions such as chest drainage should be judicious, while new surgical approaches show potential benefit
Multidisciplinary care networks (n = 4)	Integration between neonatology, pediatric surgery and other specialties; Centralisation in specialised centres	The organization of care and multiprofessional action contribute to the reduction of complications, improved survival and higher quality of care

Source: Prepared by the authors

4 DISCUSSION

This systematic review, by integrating evidence from 17 original studies, confirms that esophageal atresia in the neonatal period remains a condition of high clinical complexity, whose evolution results from the interaction between biological, care, and structural factors. Although advances in diagnosis and management have contributed to the improvement of outcomes, important inequalities persist related to the organization of health services, access to specialized centers, and the standardization of care.

The findings show convergence in the literature regarding the relevance of early diagnosis as a determinant for reducing morbidity and mortality. Studies conducted in different contexts have shown that identification in the first hours of life, associated with the systematic evaluation of congenital malformations and clinical factors, is directly related to better outcomes^{10,12,13}. However, it is observed that this diagnostic capacity is not homogeneous among the services, being influenced by the availability of resources, team training and organization of the care network, which evidences an important component of health inequity.

In the context of clinical-surgical management, the results indicate relative consistency among studies regarding the efficacy of different surgical approaches when performed in appropriate contexts^{1,15,16}. However, this apparent equivalence should be interpreted with caution, since factors such as esophageal gap length, prematurity, and the presence of comorbidities exert a significant influence on outcomes^{17,18}. In addition, variability in the indication criteria and in the experience of the teams may contribute to

heterogeneous results, indicating the need for greater standardization and more robust comparative studies.

The analysis of perioperative practices reveals a changing field, in which traditionally consolidated interventions have been questioned in the light of recent evidence. The routine use of thoracic drainage, for example, was associated with a higher incidence of complications and prolonged hospitalization²⁰, suggesting that its application should be judicious and individualized. On the other hand, strategies such as early enteral feeding⁶ and innovative interventions, such as primary tracheopexy²¹, point to a movement to improve care practices, although they lack validation in multicenter studies and randomized clinical trials.

The organization of care emerges as one of the main determinants of outcomes, transcending strictly clinical aspects. Consistent evidence indicates that the centralization of care in specialized centers and the performance of multidisciplinary teams are associated with a reduction in complications, longer survival, and better coordination of care^{8,22}. On the other hand, studies conducted in contexts with limited resources show that, although technical adaptations can guarantee survival, relevant structural barriers persist that negatively impact the results²³. These findings reinforce that the management of esophageal atresia should be understood not only as a clinical challenge, but also as a matter of organization of health systems.

Despite the advances observed, this review highlights important limitations in the literature, including the predominance of observational studies, methodological heterogeneity, and the lack of standardization of care protocols. These limitations restrict the comparability of results and hinder the consolidation of more robust evidence, especially with regard to the definition of best clinical and organizational practices.

Thus, the findings indicate that the management of esophageal atresia in the neonatal period should be guided by an integrated approach, which articulates early diagnosis, individualized clinical decision-making, and efficient organization of health services. The strengthening of care networks, the centralization of care, and the implementation of evidence-based protocols are fundamental strategies for reducing inequalities and improving neonatal outcomes.

5 CONCLUSION

This systematic review shows that esophageal atresia in the neonatal period remains a highly complex condition, whose management requires integration between early diagnosis, appropriate surgical decision, and efficient organization of care. Acting in the first

hours of life, associated with comprehensive clinical evaluation, is a central element for reducing complications and improving neonatal outcomes.

In the therapeutic field, it is observed that, although different surgical approaches present similar results in appropriate contexts, the individualization of management, considering anatomical characteristics, clinical conditions, and comorbidities, is determinant for the evolution of patients. In addition, perioperative practices have been reevaluated in the light of new evidence, indicating the need for continuous updating of conducts.

The organization of care stands out as a fundamental component, since the multidisciplinary approach and centralization in specialized centers are associated with greater care safety, continuity of care, and better clinical outcomes. In this sense, the structure of health services and access to care networks are determining factors for the quality of neonatal care.

However, limitations in the literature persist, including methodological heterogeneity, lack of standardization of protocols, and scarcity of prospective and multicenter studies, which restricts the comparability of findings and the consolidation of more robust evidence.

It is concluded that the management of esophageal atresia in the neonatal period should be guided by an integrated, individualized and evidence-based approach, considering both the clinical-surgical aspects and the organization of health services. The strengthening of care networks and the production of studies with greater methodological rigor are fundamental for the reduction of care inequalities and the continuous improvement of the quality of neonatal care.

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REPORT ON THE EXPERIENCE OF IMPLEMENTING RADIOGRAPHIC DOWSING IN THE INTEGRATIVE MEDICINE OUTPATIENT CLINIC - INTEGRATIVE AND COMPLEMENTARY PRACTICES AT A HOSPITAL IN THE CITY OF SÃO PAULO

RELATO DE EXPERIÊNCIA DA IMPLANTAÇÃO DA RADIESTESIA RADIÔNICA NO AMBULATÓRIO DE MEDICINA INTEGRATIVA - PRÁTICAS INTEGRATIVAS E COMPLEMENTARES EM UM HOSPITAL DA CIDADE DE SÃO PAULO

INFORME SOBRE LA EXPERIENCIA DE IMPLEMENTACIÓN DE LA RADIACIÓN RADIOGRÁFICA EN LA CLÍNICA AMBULATORIA DE MEDICINA INTEGRATIVA - PRÁCTICAS INTEGRATIVAS Y COMPLEMENTARIAS EN UN HOSPITAL DE LA CIUDAD DE SÃO PAULO



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ABSTRACT

This experience report describes the implementation of Radiesthesia and Radionics (RR) in an Integrative Medicine - Integrative and Complementary Health Practices (MI-PICS) outpatient clinic in the city of São Paulo. Initiated in February 2025, the initiative encompasses services for inpatients and outpatients, in face-to-face, online, and remote modalities. It was identified that RR acts by accessing information codes through instruments that decode bioenergetic signals. The integration between physiology and bioenergetics offered theoretical support for understanding the mental and spiritual dimensions as modulators of physical health, removing the stigma of subjectivity from these spheres and bringing them closer to evidence-based psychosomatic clinical practice.

Keywords: Radiesthesia. Complementary Therapies. Integrative Medicine.

RESUMO

Este relato de experiência descreve a implementação da Radiestesia Radiônica (RR) em um ambulatório de Medicina Integrativa - Práticas Integrativas e Complementares em Saúde (MI-PICS) no município de São Paulo. Iniciada em fevereiro de 2025, a iniciativa abrange atendimentos a pacientes internados e ambulatoriais, nas modalidades presencial, online e à distância. Identificou-se que a RR atua no acesso a códigos de informação por meio de instrumentos que decodificam sinais bioenergéticos. A integração entre fisiologia e

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bioenergética ofereceu suporte teórico para compreender as dimensões mental e espiritual como moduladoras da saúde física, afastando o estigma de subjetividade dessas esferas e aproximando-as da prática clínica baseada em evidências psicossomáticas.

Palavras-chave: Radiestesia. Terapias Complementares. Medicina Integrativa.

RESUMEN

Este informe de experiencia describe la implementación de Radiestesia y Radiónica (RR) en una clínica ambulatoria de Medicina Integrativa - Prácticas de Salud Integrativas y Complementarias (MI-PICS) en la ciudad de São Paulo. Iniciada en febrero de 2025, la iniciativa abarca servicios para pacientes hospitalizados y ambulatorios, en modalidades presenciales, en línea y remotas. Se identificó que la RR actúa accediendo a códigos de información mediante instrumentos que decodifican señales bioenergéticas. La integración entre fisiología y bioenergética ofreció apoyo teórico para comprender las dimensiones mental y espiritual como moduladoras de la salud física, eliminando el estigma de la subjetividad en estas esferas y acercándolas a la práctica clínica psicosomática basada en la evidencia.

Palabras clave: Radiestesia. Terapias Complementarias. Medicina Integrativa.

1 INTRODUCTION

This article reports the experience of the implementation of Radionic Dowsing (RR) in the Outpatient Clinic of Integrative and Complementary Practices in Health (MI-PICS) of the Hospital do Servidor Público Municipal de São Paulo (HSPM), which is a hospital with experience in the implementation of unconventional therapies since the 80's. In all these years, these therapies have been acting as an adjunct to the classic medical care practiced in the hospital, and the activities are conducted primarily by volunteer therapists, who have expertise in various therapeutic approaches.

The PICS bring unconventional views of care, contemplating a plurality of transversal knowledge and skills, increasingly proven by research and verified by users, so much so that in 2006 the Brazilian Ministry of Health (MS) incorporated the National Policy of Integrative Practices (PNPIC) (BRASIL, 2006).

Today the collaboration of techniques that work on well-being and quality of life in care is unquestionable. Although many of them have not yet been proven by science, it is a fact that popular wisdom, traditional medicines, uses and customs have contributed to health over the millennia and have gradually been incorporated into the therapeutic arsenal of health systems around the world.

In contemporary times, the complexity inherent to social, environmental and individual dynamics, the origin of organic and psychic maladjustments has become multifactorial, hence the need to have multidisciplinary knowledge to help the individual as a whole.

The fundamentals for the insertion of this technique in the outpatient clinic are closely related to the techniques of energy manipulation whose performance is already established. Traditional Chinese Medicine – Acupuncture was incorporated in 1991, bringing the understanding of illness under the perspective of an ancient medicine, which considers the intrinsic, extrinsic and relational factors that affect the human being, which allowed to broaden the vision of care and prepare the ground for the most varied therapies that would be inserted in the outpatient clinic in the following decades.

Everything in the universe is in constant motion, Einstein already understood that matter and energy are interchangeable. Modern physics reinforces that matter is not solid; In any object the atoms are always spinning and vibrating, everything moves, oscillates and vibrates. Among the forms of energies there are concrete ones that propagate in waves and can be measured as thermal, electrical, kinetic, mechanical, electromagnetic, chemical, and nuclear energies. But there are other forms of energies; Among them are vital energy, thought energy, energy of forms that move around the physical body influencing the environment and interfering in the way people think, act and feel. Abstract or non-

materialized subtle energy has been recognized in various forms throughout the ages, even though established science denies the validity of these concepts. Physicists define it as zero-point energy, that is, the energy that exists before it materializes into form (GODOY, 2012).

The eighteenth and nineteenth centuries is the historical period of the French magnetizers, for some, it was a time marked by mysticism, charlatanism and ignorance, but for others it appears as a pre-scientific moment that would later give way to a modern project of science. It was at this time that the Austrian physician Franz Anton Mesmer coined the term animal magnetism when referring to the energy of life that connects spirit to matter based on the belief that there was a fluid that could be transmitted for therapeutic purposes, (NEUBERN, 2007) (SILVA). Later, Reich investigated a universal vital energy called Orgone, although his observations are considered controversial, they are a legacy for the connection between body, emotion and vital energy (VOLPI, 2025). The universal energy called Prana is reported to be more than 5,000 years old in India, Yoga uses these energies through breathing techniques, physical exercises and meditation. The Chinese 5,000 years ago already spoke of a vital energy called Chi that impregnates all animate or inanimate matter. From this perspective, it is understood that the human being is constituted by an inseparability between the physical body and the bioenergetic field that can be detected by various methods such as Dowsing (GODOY, 2012).

Undeniable is the fact of the existence of radiation from space, the environment, the subsoil, people, which are capable of biologically influencing life, whether of animals, plants or human beings. Most of these interactions, despite being constant, are not clearly perceived by any of the senses (PANTZIER, 2007).

The Universe vibrates at very similar frequencies, the so-called Schumann waves, which some researchers argue is the frequency of health. Winfried Otto Schumann in 1952, predicted that weak electromagnetic waves ricocheted between the ionosphere and the Earth's surface generating a fundamental frequency of 7.8 Hz, similar vibrations were later identified in various living organisms and in humans as the fundamental frequency of rest (MARTEL et al, 2023).

2 RADIONIC DOWSING

The word Dowsing comes from the Greek radius (radiation) and the Latin aesthesis (sensitivity), that is, sensitivity to radiation (NETO). Radionics, on the other hand, is the action at a distance that deals with energy balance and management, capturing and sending specific energies (GODOY, 2012).

According to Pantzler (2007), Dowsing is a method of analysis that identifies vibratory patterns of very low amplitude, of the most varied vibrations, so tenuous that they are almost undetectable, often it is just an informative content with no energetic charge.

It is the Dowser with his sensitivity and concentration who is able to access these information codes. To do so, it uses silent and significant signals from instruments such as the Aurameter, the Pendulum, the Fork, the Dual Rod or others identified by the conscious mind. By perceiving only the movement and the meaning of the tool, without getting rationally involved in it, because it comes from a neuromuscular command, captured by intermediate aspects of the brain that bridge the gap between the deep unconscious and the waking state (PANTZIER, 2007).

Some theories are based on the principle that the mind is capable of capturing anything, the dowser tunes in to the object to be evaluated present or absent and adjusts the movements of the pendulum (GODOY, 2012).

The sensitivity of the dowser is a debated topic, so much so that the German Ministry of Science and Technology carried out 10,000 tests with dowsers and proved that only five percent of these professionals had exceptional dowsing skills, with a success rate close to 100%. This study was replicated with 60 students of the Applied Naturology Course at the University of Southern Santa Catarina and very similar results were obtained, since five percent of the people tested had high dowsing sensitivity (PANTZIER, 2007).

Dowsing is a complementary way to identify bioenergetic imbalances; in the context of PICS, it aligns with the holistic paradigm of care, where the individual is seen as an integrated vibrational system. Radionics acts as the intervention phase, using geometric shapes and frequencies for the homeostasis of the system.

RR is not among the techniques recognized by the Ministry of Health as an integrative practice, there is a lack of studies that detail the practical verification of subtle energy in clinical environments. This report aims to describe an experience of the application of RR in an outpatient and hospital environment, offering a reflective basis on how these different dimensions are interrelated during the health-disease process.

3 DESCRIPTION OF THE EXPERIENCE

This is an experience report on the introduction of Radionic Dowsing in the arsenal of therapies available at the HSPM MI_PICS outpatient clinic. This therapy complemented the therapeutic options available at the outpatient clinic, where a gap had already been identified in the face of the demands of patients who sought the outpatient clinic.

The therapy began to be offered in February 2025 by a volunteer therapist who performed 183 consultations during the year 2025. Most patients arrived by spontaneous search since the disclosure is made on the hospital's website, on the bulletin boards and by indication of patients already attended.

Others were referred by hospital professionals (mostly doctors and social workers), among them mainly terminal patients, coming from the Palliative Care Clinic that aims at quality of life at this time, offering care not only to the physical aspects, but also to the emotional, spiritual and psychosocial dimensions. The technique was well received by patients and demonstrated the possibility of greater control of pain and suffering.

The consultations were carried out in the hospital bed, in the outpatient clinic in person, online by platform and at a distance in cases of bedridden patients. The complaints presented to seek care are the most varied: from anxiety, depression, sudden mood swing, history of violence, complaint of stomach discomfort, heaviness in the shoulders, sore throat to no complaint, just curiosity if something could be done to help.

4 THE RR TECHNIQUE

After a brief anamnesis, where the patient presents the complaints and permission to access his field, the pendulum and the radionic table are used as instruments. Next, the therapist identifies the changes in the patient's vibratory field, using the variations of the pendulum on the radionic table, perceiving unbalanced energies that influence the patient's well-being.

This information refers to organic systems, interferences of external origin, which include imbalances of subtle, telluric, people's energies or even internal imbalance such as fear, insecurity, rigid ideas and negative feelings. Each imbalance is identified by the therapist who acts intentionally.

With the help of the patient who points out the pains, feelings, doubts, memories, it is possible to achieve a great result in the therapeutic session, culminating in his well-being.

Therapeutic follow-up is based on the continuous evaluation of the bioenergetic flow, understanding the individual as an integrated multidimensional system. During the sessions, the functional vitality of organs and systems is mapped, correlating biological homeostasis to the states of the psyche and spiritual health. This analysis expands to the examination of the energy centers (chakras), understood here as nuclei of subtle energy processing that act at the interface between the somatic body and the mental dimensions. The systematic verification of these fields allows the identification of patterns of imbalance before they

somatize, ensuring an intervention that promotes harmony between the biological, the emotional and the transpersonal.

The clinical practice adopted transcends the conventional biomedical model by instituting a systematic multidimensional evaluation protocol. As the interventions are applied, a qualitative and quantitative analysis of the bioenergetic field is carried out, based on the assumption that pathology or well-being are emergent states of the interaction between different levels of organization. At the somatic level, the functional efficiency of organs and systems is monitored; at the psychodynamic level, it investigates how mental states and beliefs influence the patient's resilience.

Additionally, the research covers the subtle dimension, specifically through the analysis of the chakras (force centers). These are understood as energetic transducers that regulate the flow of vitality between the etheric body and the endocrine and nervous system. The verification of the spiritual dimension, in turn, is not restricted to religious dogmas, but focuses on the individual's perception of purpose and connection, factors that the current scientific literature recognizes as modulators of the immune response and clinical recovery.

5 FINAL CONSIDERATIONS

The introduction of Radionic Dowsing in the therapeutic arsenal of the MI_PICS outpatient clinic allowed a significant expansion in the model of care offered, providing an integrative view between the vitality of organs and systems and the alignment of energy centers. The systematic verification of the mental and spiritual dimensions made it possible to identify that therapeutic success does not lie only in the suppression of physical symptoms, but in the restoration of the individual's vibratory coherence.

The experience consolidated the understanding that the human being operates as an inseparable unit. Furthermore, the study reinforced the importance of qualified listening and perceptive sensitivity beyond the dense body. For the study area, the main contribution lies in the systematization of a view that unites physiology with bioenergetics, offering a theoretical subsidy for other professionals to understand the role of the spiritual and mental dimensions as modulators of physical health, removing the stigma of subjectivity from these spheres and bringing them closer to clinical practice based on psychosomatic evidence.

It is recommended that future studies directly explore chakra alignment and functional improvement of corresponding organs. It is also suggested the implementation of care protocols that include educating the patient about their own energy anatomy, promoting self-care. Finally, the need for greater integration between conventional medicine and

multidimensional approaches is pointed out, aiming at a truly holistic and less fragmented health model.

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CHALLENGES AND PERSPECTIVES OF HEALTH EDUCATION IN THE TRANSITION FROM A HOSPITAL-CENTRIC MODEL TO HEALTH PROMOTION

DESAFIOS E PERSPECTIVAS DA EDUCAÇÃO EM SAÚDE NA TRANSIÇÃO DO MODELO HOSPITALOCÊNTRICO PARA A PROMOÇÃO DA SAÚDE

DESAFÍOS Y PERSPECTIVAS DE LA EDUCACIÓN PARA LA SALUD EN LA TRANSICIÓN DE UN MODELO CENTRADO EN EL HOSPITAL A LA PROMOCIÓN DE LA SALUD



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ABSTRACT

This bibliographic review analyzes the transition from the hospital-centered (biomedical) model to the Health Promotion paradigm, focusing on the strategic role of Health Education in this process. The traditional biomedical model is criticized for its reductionist, fragmented, and financially unsustainable nature, especially in the face of the rise of chronic diseases. Health Education is presented as a central tool for this change, encompassing both traditional behavior-change approaches and emancipatory perspectives grounded in Paulo Freire. Multiple barriers to effective implementation are identified: professionals' intrapersonal beliefs, gaps in academic training, institutional resistance, systemic focus on curative care, and low community health literacy. Regarding future perspectives, the Astana Declaration (WHO), the "Health in All Policies" concept, innovative comprehensive care models such as the Two-Circle Model, and the integration of digital technologies (artificial intelligence, wearables, genomics, telehealth) stand out. The conclusion is that the effective transition requires coordinated efforts in curriculum reform, resource allocation, professional training, health literacy promotion, and ethical integration of digital technologies.

Keywords: Health Education. Health Promotion. Hospital-Centered Model. Paradigm Shift. Digital Health Technologies.

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RESUMO

Este artigo de revisão bibliográfica analisa a transição do modelo hospitalocêntrico (biomédico) para o paradigma da Promoção da Saúde, com foco no papel estratégico da Educação em Saúde nesse processo. O modelo biomédico tradicional é criticado por seu caráter reducionista, fragmentado e financeiramente insustentável, especialmente diante do crescimento das doenças crônicas. A Educação em Saúde é apresentada como ferramenta central para essa mudança, abrangendo desde abordagens tradicionais de mudança de comportamento até perspectivas emancipatórias fundamentadas em Paulo Freire. São identificadas múltiplas barreiras para a implementação efetiva: crenças intrapessoais dos profissionais, deficiências na formação acadêmica, resistência institucional, foco sistêmico no cuidado curativo e baixo letramento em saúde da comunidade. Quanto às perspectivas futuras, destacam-se a Declaração de Astana (OMS), o conceito de "Saúde em Todas as Políticas", modelos inovadores de cuidado integral como o Modelo de Dois Círculos, e a integração de tecnologias digitais (inteligência artificial, wearables, genômica, telessaúde). Conclui-se que a transição efetiva requer esforços coordenados em reforma curricular, alocação de recursos, capacitação profissional, promoção do letramento em saúde e integração ética de tecnologias digitais.

Palavras-chave: Educação em Saúde. Promoção da Saúde. Modelo Hospitalocêntrico. Mudança de Paradigma. Tecnologias Digitais em Saúde.

RESUMEN

Este artículo de revisión bibliográfica analiza la transición del modelo hospitalario (biomédico) al paradigma de la promoción de la salud, centrándose en el papel estratégico de la educación para la salud en este proceso. El modelo biomédico tradicional es criticado por su carácter reduccionista, fragmentado e insostenible económicamente, especialmente ante el aumento de las enfermedades crónicas. La educación para la salud se presenta como una herramienta fundamental para este cambio, abarcando desde enfoques tradicionales para el cambio de comportamiento hasta perspectivas emancipadoras basadas en Paulo Freire. Se identifican múltiples barreras para una implementación efectiva: creencias intrapersonales de los profesionales, deficiencias en la formación académica, resistencia institucional, un enfoque sistémico en la atención curativa y baja alfabetización en salud en la comunidad. En cuanto a las perspectivas futuras, se destacan la Declaración de Astana (OMS), el concepto de "Salud en todas las políticas", modelos innovadores de atención integral como el Modelo de los Dos Círculos y la integración de tecnologías digitales (inteligencia artificial, dispositivos portátiles, genómica, telesalud). Se concluye que una transición efectiva requiere esfuerzos coordinados en la reforma curricular, la asignación de recursos, la formación profesional, la promoción de la alfabetización en salud y la integración ética de las tecnologías digitales.

Palabras clave: Educación para la Salud. Promoción de la Salud. Modelo Hospitalario. Cambio de Paradigma. Tecnologías Digitales en Salud.

1 INTRODUCTION

The history of global public health is marked by paradigmatic transformations that reflect changes in the conceptions of health, disease and care. For much of the twentieth century, the biomedical model, centered on disease and hospital care, dominated health systems globally.^{[1][2]} This model, derived from germ theory and grounded in a reductionist approach, was extremely successful in eliminating infectious diseases and increasing life expectancy, which in the United States went from 49 years in 1901 to 78 years in 2007.^[2]

However, with the epidemiological transition and the increase in the prevalence of chronic non-communicable diseases, the limitations of the hospital-centered model have become evident. This model, characterized by the fragmentation of care, emphasis on cure to the detriment of prevention, and exclusive focus on biological factors, proved to be insufficient and financially unsustainable to respond to the complex health needs of contemporary populations.^{[1][3][4]}

In contrast, the Health Promotion paradigm emerged, consolidated internationally by the Ottawa Charter in 1986, which defines health promotion as "the process of empowering people to increase control over their health and improve it".^{[5][6]} This new paradigm broadens the concept of health beyond the absence of disease, recognizing the social, environmental, economic, and behavioral determinants of health, and proposing intersectoral and participatory strategies.^{[6][7][8]}

In this context of paradigmatic transition, Health Education assumes a fundamental strategic role. Unlike the simple transmission of information about diseases, contemporary health education is conceived as a continuous, dynamic and complex teaching-learning process, implemented through an equitable partnership between professionals and users, aiming to empower individuals and communities to promote behavioral changes and achieve positive health outcomes.^[9]

The objective of this article is to critically analyze the challenges and perspectives of Health Education as a central strategy in the transition from the hospital-centered model to the Health Promotion paradigm, examining the theoretical bases, practical barriers and future trends that can consolidate this transformation in health systems.

2 THE HOSPITAL-CENTERED MODEL AND ITS LIMITATIONS

The hospital-centered model, based on the biomedical paradigm, is characterized by a reductionist approach that explains all disease in biological terms, often neglecting psychological, social, and environmental factors.^{[1][2]} This model reflects a mind-body dualism in which "mental" disorders are excluded from the central concerns of Western

medicine unless they can be explained by some underlying biological defect.^[2]

While it has produced remarkable successes, including antibiotics, vaccines, organ transplants, and cures for some cancers, the biomedical model has also generated expensive, marginally useful, or even useless interventions.^[10] The prestige earned by their successes has created a public presumption of rigorous scientific efficacy, which can drive suboptimal care when reductionist thinking, often coupled with the commercial imperatives of product development, triggers the search for unique solutions that produce questionable benefits at rising costs.^[10]

The fragmentation of care is another critical limitation of this model. Health care organized around medical specialties and hospital procedures results in care discontinuity, loss of information, and compromise of comprehensive care.^{[11][12]} Studies have shown that the transition of patients between different levels of care and professionals represents moments of high risk for errors and adverse events.^[12]

From an economic point of view, the hospital-centric model has become financially unsustainable. In the United States, chronic diseases whose prevention and management are neglected in this model represent 75% of health costs.^[2] The emphasis on highly complex curative interventions, to the detriment of lower-cost preventive and promotional actions, contributes to the unsustainable escalation of health spending observed globally.^{[3][13]}

In addition, the focus on deviations from biological norms rather than patients' needs is one of many factors underpinning the widespread lack of patient involvement in therapeutic decisions and goals.^[10] This focus can lead to neglect of patients' cognitive and emotional needs, individual preferences, underutilization of behavioral therapies and counseling, and neglect of social and public health strategies for disease prevention.^[10]

Finally, the hospital-centered model is inadequate to respond to the current prevalence of chronic diseases. With these conditions accounting for the majority of morbidity and mortality in Western countries, health systems designed around acute biomedical care models face difficulties in improving patient-reported outcomes and reducing costs.^[4] The growing proportion of health care resources dedicated to chronic disorders and the concomitant need to improve patient outcomes require urgent action.^[4]

3 HEALTH EDUCATION AS A STRATEGY FOR CHANGE

Health Education represents a fundamental strategy for the transition from the hospital-centered model to Health Promotion. Conceptually, health education is defined as a continuous, dynamic, complex and planned teaching-learning process throughout life and in different contexts, implemented through an equitable and negotiated partnership between

client and health professional, to facilitate and empower the person to promote/initiate behavioral changes related to lifestyle that promote positive health outcomes.^[9]

The theoretical bases of contemporary Health Education are based on multiple references. Theories of behavioral change, such as the Health Belief Model, Bandura's Social Cognitive Theory, the Theory of Planned Behavior, and the Transtheoretical Model, provide frameworks for understanding and influencing health-related behaviors.^{[14][15][16]} These theories emphasize constructs such as self-efficacy, behavioral intention, perception of risk and benefits, and stages of readiness for change.^{[16][17]}

Particularly relevant is the contribution of Paulo Freire's pedagogy to emancipatory health education. Freire's philosophy of "education for critical consciousness" takes on special relevance in the context of health systems, proposing a dialogical approach to change that emphasizes action based on critical reflection by people.^{[18][19]} This perspective contrasts fundamentally with traditional health education, characterized by the simple dissemination of information for behavioral change — an approach that, despite being the cornerstone of traditional health education practice, demonstrates limited effectiveness in improving public health.^[20]

Popular health education, also known as Freirean or emancipatory education, has been successfully used to create a more equitable playing field around the world for more than 50 years.^[19] Its use to improve health has been documented in the public health literature since the early 1980s, although it remains largely unknown and its potential unrealized in mainstream public health circles in the industrialized world.^[19]

The fundamental distinction between traditional and emancipatory education lies in their goals and methods. While traditional education focuses on the one-way transmission of information about diseases and risk behaviors, emancipatory education seeks to develop critical awareness, autonomy, and individual and collective empowerment.^{[21][22][23]} The emancipatory perspective considers health literacy as a key element in promoting autonomy and empowerment among individuals and population groups, enabling them to recognize their fundamental right to health and their role as citizens.^[22]

Qualitative studies demonstrate that popular education is an effective method for increasing empowerment and improving health.^{[19][24]} The Freirean approach integrated with theories of cognitive and behavioral change can develop comprehensive health education programs aimed at both individual and community change.^[24]

In the context of primary health care, health education plays a crucial role. Primary care is ideally positioned to manage conditions that restrict educational or employment opportunities in the short term, but it also acts through prevention and early intervention

throughout the life course.^[8] Health education in primary care contributes to the achievement of the Sustainable Development Goals by not only improving health (SDG 3), but also promoting education, reducing inequalities and fighting poverty.^{[8][25]}

4 CHALLENGES IN PUBLIC HEALTH PRACTICE

The transition from the hospital-centered model to Health Promotion faces multiple barriers that operate at different levels of the health system. A meta-ethnographic synthesis identified factors that affect the implementation of primary prevention and health promotion activities in primary care, organized in a five-level ecological model: intrapersonal factors, interpersonal processes, institutional factors, community factors, and public policies.^[26]

At the intrapersonal level, professionals' beliefs about prevention and health promotion, experiences, skills, knowledge, and self-concept constitute significant barriers.^[26] Many health professionals maintain traditional conceptions focused on the disease, demonstrating resistance to the incorporation of preventive and promotional practices into their routine.^{[26][27]}

Academic training represents a critical challenge. Medical education and other health care professionals remain predominantly focused on the biomedical model and curing disease.^{[25][26]} University curricula devote limited importance to primary prevention and health promotion, resulting in professionals inadequately prepared to implement these actions.^[26] In addition, the health workforce is not trained in multisectoral actions, and already experiences workloads of an overwhelming nature.^[25]

At the institutional level, primary care is perceived as well positioned to implement prevention and health promotion, but the overload of work, lack of time and reference resources, and the predominance of the biomedical model (which prioritizes the treatment of diseases) make it difficult to implement these activities.^[26] The effectiveness of financial incentives and tools such as guidelines and reminders/alarms is conditioned by practitioners' attitudes toward them.^[26]

Institutional resistance is also manifested in the allocation of resources. Resources allocated to health promotion are often diverted to other programs, resulting in disconnection between national and provincial levels, which impedes communication and opportunity to develop a shared vision and coherent program.^{[27][28]} Inadequate government spending on health is exacerbated by the small proportions allocated to primary health care.^[25]

Systemic barriers include the traditional focus of health systems on a "responsive" rather than "proactive" approach to the health of individuals and populations.^[29] Within the context of the consultation, factors such as lack of time, lack of clinician expertise, logistical

difficulties, lack of patient interest, other pressing concerns, inadequate remuneration, and patient concerns regarding interventions may play a role.^[29]

Recent policy analyses identify persistent barriers to prevention caused by: limited clarity as to what it means in practice, limited congruence with routine policy delivery, and limited capacity to sustain important change.^[30] Challenges include short-termism, financial and operational pressures, routine limits on cooperation, untapped community assets, and limited opportunities for peer learning.^[30]

Institutional capacity for health promotion remains limited. Evaluations show that the capacity to develop long-term and sustainable health promotion interventions is limited at all levels.^[28] There is limited collaboration between national and provincial health promotion levels, limited monitoring of health promotion indicators in the health information system, and coordination of health promotion efforts between different sectors largely absent.^[28]

Finally, community factors include patients' social and cultural characteristics (religion, financial resources, etc.), local referral resources, mass media messaging, and pharmaceutical industry campaigns.^[26] Health literacy is common among the population, even in developed countries, representing an additional barrier to the effective implementation of health promotion programs.^[25]

5 PERSPECTIVES AND FUTURE TRENDS

The consolidation of the transition to the Health Promotion paradigm depends on the integration of robust public policies with emerging technologies and new models of care. Several promising trends are emerging that can accelerate and sustain this transformation.

In the field of public policies, the reaffirmation of the principles of the Ottawa Charter through the 2018 Astana Declaration redefines the three functions of primary health care as: provision of services, multisectoral actions, and empowerment of citizens.^[25] This framework explicitly recognizes that health-related sustainable development goals cannot be achieved by the provision of health services alone, requiring joint efforts between local, national, and international partners, and public awareness (health literacy) about preventable diseases.^[25]

The "Health in All Policies" approach represents a fundamental strategy to institutionalize health promotion beyond the health sector.^{[5][31]} This perspective recognizes that all sectors have a role in promoting and coordinating efforts to improve health by addressing social, environmental, and economic determinants.^{[8][31]}

Innovative models of care are emerging to integrate prevention and treatment. The Two-Circle Model of Whole-Person Care, developed for the U.S. Department of Veterans Affairs, integrates the current disease-focused, transaction-based model of care with a

person-centered, relationship-based, health-promoting and recovery-focused model.^[32] This framework rebalances the current disease-focused approach with a person-centered, relationship-based, and recovery-focused one, demonstrating improvements in Quadruple Aim outcomes across multiple systems.^[32]

Emerging digital technologies have transformative potential for health promotion and preventive medicine. The era of future digital health will be characterized by the shift to predictive, preventive, personalized, and participatory (P4) medicine, with an emphasis on health promotion over disease treatment.^[33] This "shift to the left" toward preventive care is anticipated to redefine health by emphasizing health promotion over the treatment of disease.^[33]

Specific technologies include: genomics for personalized risk assessment; artificial intelligence for screening, early diagnosis, and health counseling; bioengineering and wearable devices for continuous monitoring of physiological parameters; and telemedicine to expand access to health promotion services.^{[33][34][35]} Wearable devices provide health-related data that has grown in the numbers and types of data available over the past two decades, with applications in prevention including activity trackers to promote physical fitness (primary prevention), mobile electrocardiogram devices to detect arrhythmias (secondary prevention), and continuous glucose monitoring to improve glycemic control in type 2 diabetes (tertiary prevention).^[36]

Artificial intelligence is transforming health promotion and disease reduction through improved early detection, encouraging healthy lifestyle modifications, and mitigating economic pressure on health systems.^[34] Recent reviews demonstrate positive outcomes for process outcomes (acceptability, engagement), cognitive and behavioral outcomes (confidence, step count), and health outcomes (blood glucose, blood pressure).^[34]

However, significant challenges remain. Data security and privacy risks, health inequities amplified by the digital divide and device biases, and limitations of artificial intelligence (reproducibility, opacity or "black box" issues, and unclear legal liability) must be addressed.^{[35][37]} Future success depends on robust privacy protections, inclusive design, diverse real-world validation, and refined regulatory frameworks to ensure equitable and sustainable implementation.^[35]

Digital transformation will increasingly find its way into the various process phases over the next five years, with particular expectation of technologies for behavioral change in hybrid formats.^[38] The use of technology in the future can lead to more participation, partnerships, empowerment and equity in contexts, but on the other hand it can also reinforce exclusion and injustice if adequate underlying conditions are not provided.^[38]

Finally, the integration of genomics, behavioral change, and digital health solutions represents a promising approach to globally transform approaches to the prevention and management of chronic diseases across the lifespan.^[39] Personalized prevention, using polygenic and multifactorial risk prediction tools, advanced prevention and management of chronic diseases based on behavioral change, and digital health systems to support greater efficiency in population-scale health prevention and intervention programs, offers a promising conceptual framework, although additional research is needed to investigate the effects of its integration at the population level.^{[39][40]}

6 FINAL CONSIDERATIONS

The transition from the hospital-centered model to the Health Promotion paradigm represents both an epidemiological and economic imperative for contemporary health systems. The biomedical model, despite its historical successes, has proven inadequate to respond to the current prevalence of chronic diseases and the complex social, environmental, and behavioral determinants of health. Its emphasis on fragmentation of care, exclusive focus on biological factors, and prioritization of treatment over prevention has resulted in systems that are financially unsustainable and unable to significantly improve population health outcomes.

In this context, Health Education emerges as a central strategy and engine of transformation. Based on solid theoretical bases, from theories of behavioral change to Paulo Freire's emancipatory pedagogy, contemporary health education transcends the simple transmission of information, constituting a dialogical process for the construction of autonomy, critical awareness and individual and collective empowerment. This approach aligns perfectly with the principles of Health Promotion established by the Ottawa Charter: community participation, equity, intersectoral action, and focus on the social determinants of health.

However, significant challenges persist at multiple levels. Professional training remains predominantly focused on the biomedical model; institutional resistance is manifested in the inadequate allocation of resources for prevention; systemic barriers include work overload, lack of time, and predominance of curative care incentives; and community factors such as low health literacy and social inequalities limit the reach and effectiveness of interventions.

The future prospects are, however, promising. The integration of robust public policies such as the Health in All Policies approach with emerging technologies including artificial intelligence, wearable devices, telemedicine and genomics offers unprecedented

opportunities to consolidate the paradigmatic transition. Innovative models of comprehensive care for the person demonstrate feasibility and effectiveness in integrating prevention and treatment, health promotion and recovery.

The sustainability of health systems in the twenty-first century depends fundamentally on the ability to implement this paradigmatic transition. Health Education, in its emancipatory and dialogical perspective, is not only a technical tool, but also a political and social process of transformation. Its role as an engine of public health sustainability lies precisely in its ability to develop critical awareness, autonomy and active participation of individuals and communities in the construction of healthier and more equitable living conditions.

For this transition to be fully implemented, coordinated efforts are needed on multiple fronts: curricular reformulation in the training of health professionals; reallocation of financial resources prioritizing prevention and promotion; development of institutional capacity for multisectoral actions; strengthening of literacy in population health; and ethical and equitable implementation of digital technologies. Only through this comprehensive and integrated approach will it be possible to fully realize the transformative potential of Health Education and consolidate truly health-promoting, equitable and sustainable health systems.

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EFFECT OF TIRZEPATIDE ON THE REDUCTION OF CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

EFEITO DA TIRZEPATIDA NA REDUÇÃO DE DESFECHOS CARDIOVASCULARES EM PACIENTES COM DIABETES TIPO 2

EFFECTO DE LA TIRZEPATIDA EN LA REDUCCIÓN DE EVENTOS CARDIOVASCULARES EN PACIENTES CON DIABETES TIPO 2



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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) represents a major global public health challenge due to its close association with cardiovascular morbidity and mortality. In this context, tirzepatide, a dual GIP and GLP-1 receptor agonist, has emerged as an innovative therapeutic approach in the cardiometabolic management of T2DM, demonstrating significant effects on glycemic control, weight reduction, and cardiovascular risk factors. This study aimed to critically analyze the available scientific evidence regarding the effects of tirzepatide on cardiovascular outcomes in individuals with T2DM. This integrative literature review was based on the methodological framework proposed by Whitemore and Knafl and conducted using PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect databases between March and April 2026. Studies published between 2016 and 2026 involving randomized clinical trials, meta-analyses, systematic reviews, observational studies, and narrative reviews related to the cardiovascular effects of tirzepatide were included. After applying the eligibility criteria, 13 studies composed the final sample. The findings demonstrated that tirzepatide promotes significant reductions in glycated hemoglobin (HbA1c), substantial weight loss, and consistent improvement in cardiometabolic parameters, including blood pressure, lipid profile, insulin resistance, and visceral adiposity. Furthermore, observational studies and meta-analyses suggested a favorable trend toward reduction of major adverse cardiovascular events and all-cause mortality, without evidence of increased cardiovascular risk. However, most currently available evidence derives from post-hoc analyses and studies with relatively short follow-up periods, limiting definitive conclusions regarding the magnitude of cardiovascular protection associated with tirzepatide. It is concluded that tirzepatide presents a promising cardiometabolic profile in the treatment of T2DM, although dedicated cardiovascular outcome trials are still required.

Keywords: Tirzepatide. Type 2 Diabetes Mellitus. Cardioprotection. Cardiovascular Risk. Cardiovascular Outcomes.

RESUMO

O Diabetes Mellitus tipo 2 (DM2) constitui importante problema de saúde pública global devido à sua estreita associação com morbimortalidade cardiovascular. Nesse contexto, a tirzepatida, agonista dual dos receptores de GIP e GLP-1, emergiu como abordagem terapêutica inovadora no manejo cardiometabólico do DM2, apresentando efeitos relevantes sobre controle glicêmico, perda ponderal e fatores de risco cardiovascular. O presente estudo teve como objetivo analisar criticamente as evidências científicas disponíveis acerca dos efeitos da tirzepatida na redução de desfechos cardiovasculares em indivíduos com DM2. Trata-se de revisão integrativa da literatura fundamentada no referencial metodológico de Whitemore e Knafl, realizada nas bases PubMed/MEDLINE, Scopus, Web of Science e ScienceDirect, entre março e abril de 2026. Foram incluídos estudos publicados entre 2016 e 2026 envolvendo ensaios clínicos randomizados, meta-análises, revisões sistemáticas, estudos observacionais e revisões narrativas relacionados aos efeitos cardiovasculares da tirzepatida. Após aplicação dos critérios de elegibilidade, 13 estudos compuseram a amostra final. Os achados demonstraram que a tirzepatida promove reduções significativas da

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hemoglobina glicada (HbA1c), perda ponderal expressiva e melhora consistente de parâmetros cardiometabólicos, incluindo pressão arterial, perfil lipídico, resistência insulínica e adiposidade visceral. Além disso, estudos observacionais e meta-análises sugeriram tendência favorável à redução de eventos cardiovasculares maiores e mortalidade geral, sem evidência de aumento do risco cardiovascular. Entretanto, a maior parte das evidências disponíveis deriva de análises pós-hoc e estudos com seguimento relativamente curto, limitando conclusões definitivas acerca da magnitude da cardioproteção associada à tirzepatida. Conclui-se que a tirzepatida apresenta perfil cardiometabólico promissor no tratamento do DM2, embora estudos cardiovasculares dedicados ainda sejam necessários.

Palavras-chave: Tirzepatida. Diabetes Mellitus Tipo 2. Cardioproteção. Risco Cardiovascular. Desfechos Cardiovasculares.

RESUMEN

La diabetes mellitus tipo 2 (DM2) constituye un importante problema de salud pública mundial debido a su estrecha relación con la morbilidad y mortalidad cardiovascular. En este contexto, la tirzepatida, un agonista dual de los receptores GIP y GLP-1, ha surgido como una estrategia terapéutica innovadora en el manejo cardiometabólico de la DM2, mostrando efectos relevantes en el control glucémico, la pérdida de peso y los factores de riesgo cardiovascular. Este estudio tuvo como objetivo analizar críticamente la evidencia científica disponible sobre los efectos de la tirzepatida en la reducción de eventos cardiovasculares en personas con DM2. Se trata de una revisión bibliográfica integradora basada en el marco metodológico de Whittemore y Knafl, realizada en las bases de datos PubMed/MEDLINE, Scopus, Web of Science y ScienceDirect entre marzo y abril de 2026. Se incluyeron estudios publicados entre 2016 y 2026 que comprendían ensayos clínicos aleatorizados, metaanálisis, revisiones sistemáticas, estudios observacionales y revisiones narrativas relacionados con los efectos cardiovasculares de la tirzepatida. Tras aplicar los criterios de elegibilidad, la muestra final se conformó con 13 estudios. Los resultados demostraron que la tirzepatida promueve reducciones significativas de la hemoglobina glicosilada (HbA1c), una pérdida de peso sustancial y una mejora constante de los parámetros cardiometabólicos, incluyendo la presión arterial, el perfil lipídico, la resistencia a la insulina y la adiposidad visceral. Además, estudios observacionales y metaanálisis sugirieron una tendencia favorable hacia la reducción de eventos cardiovasculares mayores y la mortalidad general, sin evidencia de un aumento del riesgo cardiovascular. Sin embargo, la mayor parte de la evidencia disponible proviene de análisis post-hoc y estudios con un seguimiento relativamente corto, lo que limita las conclusiones definitivas sobre la magnitud de la cardioprotección asociada a la tirzepatida. Se concluye que la tirzepatida presenta un perfil cardiometabólico prometedor en el tratamiento de la diabetes mellitus tipo 2 (DM2), aunque aún se necesitan estudios cardiovasculares específicos.

Palabras clave: Tirzepatida. Diabetes Mellitus Tipo 2. Cardioprotección. Riesgo Cardiovascular. Resultados Cardiovasculares.

1 INTRODUCTION

Type 2 Diabetes Mellitus (DM2) is one of the main chronic non-communicable diseases of contemporary times, assuming epidemic proportions and representing an important challenge for health systems on a global scale, especially due to its high cardiovascular morbidity and mortality and significant socioeconomic impact (DE BLOCK et al., 2022; SATTAR et al., 2025). Characterized by a complex metabolic disorder involving insulin resistance, progressive impairment of pancreatic β cell function, and systemic alterations of glycemic homeostasis, T2DM is closely associated with the development of atherosclerotic disease, heart failure, stroke, and early cardiovascular mortality, with cardiovascular diseases being the leading cause of death in this population (SATTAR et al., 2022; TAKTAZ et al., 2024). In addition to persistent hyperglycemia, the frequent coexistence of obesity, systemic arterial hypertension, atherogenic dyslipidemia, and chronic low-grade inflammation contributes to the maintenance of a highly pro-inflammatory and prothrombotic cardiometabolic state, responsible for the substantial amplification of global cardiovascular risk (NAUCK; D'ALESSIO, 2022; SATTAR et al., 2025).

Historically, the treatment of DM2 has been predominantly directed to glycemic control, with the main objective of preventing microvascular complications. However, the recognition of the close relationship between diabetes, obesity, and cardiovascular disease promoted an important paradigmatic change in the therapeutic approach to the disease, shifting the focus to strategies capable of simultaneously promoting metabolic control and cardiovascular risk reduction (DE BLOCK et al., 2022). In this context, incretinal therapies have come to occupy a central position in the modern management of T2DM, particularly glucagon-like peptide receptor agonists type 1 (GLP-1RA), whose efficacy goes beyond the reduction of glycemia and includes relevant cardiovascular benefits, such as reduction of major adverse cardiovascular events (MACE), improvement of cardiometabolic function, and reduction of mortality in individuals at high cardiovascular risk (SATTAR et al., 2022; SATTAR et al., 2025).

Based on the advances provided by GLP-1 agonists, the development of tirzepatide introduced a new pharmacological perspective in the treatment of T2DM. Tirzepatide is the first dual agonist of glucose-dependent insulintropic polypeptide (GIP) and GLP-1 receptors approved for the treatment of type 2 diabetes mellitus, simultaneously combining the metabolic and incretin effects of both hormonal systems (NAUCK; D'ALESSIO, 2022). This dual activation seems to potentiate physiological mechanisms related to glucose-dependent insulin secretion, reduced glucagon secretion, appetite control, and improved insulin

sensitivity, resulting in metabolic benefits superior to those observed with GLP-1 agonists alone (DE BLOCK et al., 2022; YU et al., 2022).

Clinical studies in the SURPASS program have shown that tirzepatide promotes significant reductions in glycated hemoglobin (HbA1c) and body weight, often higher than those seen with semaglutide, basal insulin, and other active comparators (NAUCK; D'ALESSIO, 2022; DE BLOCK et al., 2022). At the same time, different investigations have shown substantial improvement in multiple cardiometabolic parameters associated with cardiovascular risk, including reduction in visceral adiposity, improvement in lipid profile, decrease in systemic blood pressure, reduction in insulin resistance, and favorable modulation of inflammatory and metabolic markers (KAORE et al., 2024; SATTAR et al., 2025). These findings reinforce the hypothesis that the clinical effects of tirzepatide transcend glycemic control alone, suggesting a potential impact on pathophysiological mechanisms directly involved in the progression of atherosclerotic cardiovascular disease.

From a pathophysiological perspective, the potential cardiovascular benefit of tirzepatide seems to result from multifactorial and integrated mechanisms. Recent evidence suggests that GIP/GLP-1 dual agonism may contribute to reduced vascular inflammation, improved endothelial function, reduced oxidative stress, modulated lipotoxicity, and improved myocardial energy metabolism (TAKTAZ et al., 2024). In addition, mechanisms related to the reduction of cell apoptosis, stimulation of autophagy, and attenuation of cardiovascular remodeling have been proposed as possible mediators of the cardioprotection observed in experimental and clinical studies (TAKTAZ et al., 2024). The concomitant improvement of obesity, insulin resistance, and other cardiometabolic risk factors potentially contributes to the reduction of residual cardiovascular risk often present in individuals with T2DM.

In this context, recent meta-analyses have reinforced the cardiovascular safety of tirzepatide by demonstrating no significant increase in major cardiovascular events, acute myocardial infarction, stroke, or heart failure compared with placebo or active therapies (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025). In addition, real-world observational studies have shown promising results in cardiovascular clinical outcomes. Chuang et al. (2024), when comparing tirzepatide with conventional GLP-1 receptor agonists in patients with T2DM, observed a significant reduction in overall mortality, MACE, renal events, and acute kidney injury among individuals treated with tirzepatide, suggesting possible clinical superiority in complex cardiometabolic scenarios (CHUANG et al., 2024). Similarly, integrated analyses of the SURPASS program demonstrated a favorable trend towards the reduction of MACE-4 without evidence of increased overall cardiovascular risk, reinforcing

the hypothesis of safety and potential cardiovascular benefit associated with the drug (SATTAR et al., 2022).

However, despite the growing body of favorable evidence, important methodological limitations persist that make it difficult to definitively consolidate the magnitude of the cardiovascular benefit of tirzepatide. Most of the available studies show significant heterogeneity in terms of the populations evaluated, therapeutic comparators, cardiovascular outcome criteria, and clinical follow-up time (KAORE et al., 2024; WARDEH et al., 2024). In addition, many cardiovascular outcomes still derive from secondary, post-hoc analyses or extrapolations based predominantly on the improvement of cardiometabolic factors, without necessarily reflecting a definitive reduction in cardiovascular events in the long term (SATTAR et al., 2022; TAKTAZ et al., 2024). In addition, there is a lack of robust consensus on the cardiovascular superiority of tirzepatide compared to traditional GLP-1 receptor agonists already consolidated in dedicated cardiovascular outcome studies.

In view of this scenario, it is relevant to conduct an integrative review of the literature capable of gathering, critically analyzing, and synthesizing the scientific evidence currently available on the impact of tirzepatide on cardiovascular outcomes in patients with DM2. Thus, the present study aims to critically analyze the scientific evidence related to the effects of tirzepatide on the reduction of cardiovascular outcomes in individuals with type 2 Diabetes Mellitus, addressing clinical efficacy, cardiometabolic mechanisms involved, cardiovascular safety and methodological limitations present in the contemporary literature.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a descriptive, exploratory nature and a qualitative approach, developed with the purpose of gathering, critically analyzing and synthesizing the available scientific evidence on the effects of tirzepatide on cardiovascular outcomes in patients with type 2 diabetes mellitus (DM2).

The integrative review was adopted as a methodological design because it enables the inclusion and integration of different research designs, allowing a comprehensive and in-depth analysis of complex and multifactorial clinical phenomena. This approach is particularly pertinent in view of the emerging and still consolidating nature of the evidence related to the cardiovascular and cardiometabolic effects of tirzepatide in individuals with DM2, enabling critical articulation between experimental and observational studies and reviews of a mechanistic nature.

The methodological path of this investigation was based on the classic framework proposed by Whittemore and Knafl (2005), widely used in integrative reviews in the health

area. According to this theoretical-methodological model, the development of the review occurred in six interdependent stages: identification of the problem and definition of the guiding question; establishment of inclusion and exclusion criteria; definition of search and selection strategies for studies; categorization and standardized extraction of data; critical evaluation and interpretation of findings; and integrative synthesis of the knowledge produced.

The guiding question of the present review was structured as follows: "What is the available scientific evidence on the effects of tirzepatide on cardiovascular outcomes in patients with type 2 diabetes mellitus?"

The bibliographic search was carried out between March and April 2026 in the electronic databases PubMed/MEDLINE, Scopus, Web of Science and ScienceDirect, selected due to their recognized relevance in the indexing of biomedical literature of high methodological rigor and international scientific impact.

To construct the search strategy, controlled and uncontrolled descriptors obtained from the vocabularies DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) were used, combined using Boolean operators AND and OR. The main terms used included "tirzepatide", "type 2 diabetes mellitus", "cardiovascular outcomes", "major adverse cardiovascular events", "MACE", "heart failure", "cardiovascular risk", "cardiometabolic risk", "GLP-1 receptor agonist" and "GIP/GLP-1 agonist".

Studies published between 2016 and 2026, available entirely in English, indexed in the selected databases, and directly related to the cardiovascular effects of tirzepatide in individuals with DM2 were considered eligible. Investigations addressing cardiovascular and cardiometabolic outcomes, such as major cardiovascular events (MACE), heart failure, cardiovascular mortality, cardiometabolic factors, lipid profile, blood pressure, obesity, and cardiovascular protection, were included. Regarding the methodological design, randomized clinical trials, observational studies, meta-analyses, systematic reviews, and narrative reviews considered methodologically relevant for the clinical and pathophysiological understanding of the investigated topic were included.

The inclusion of narrative reviews in the corpus of this integrative review was based on the need to broaden the mechanistic and pathophysiological understanding of the potential cardiovascular effects of tirzepatide. Considering that a substantial part of the available evidence still derives from consolidation studies and exploratory analyses, narrative reviews were considered relevant for critical integration between pharmacological mechanisms, pathophysiological pathways, and cardiometabolic repercussions observed in clinical and observational studies.

Duplicate studies, publications without access to full text, conference abstracts without complete data, letters to the editor, expert opinions without defined methodology, investigations without a direct relationship with tirzepatide or without a relevant cardiovascular approach, as well as articles involving exclusively obesity without association with T2DM or cardiovascular risk were excluded.

The process of selecting studies occurred in a systematic manner and in multiple stages. Initially, the identification of potentially relevant publications was carried out through the application of previously defined search strategies. Then, the titles and abstracts were read for a preliminary evaluation of eligibility. Subsequently, potentially eligible articles were submitted to full reading to confirm adherence to the established methodological criteria.

The screening, eligibility and final selection of studies were conducted independently by two reviewers, with the aim of reducing selection biases and increasing the methodological reliability of the review. Any disagreements related to the inclusion of the articles were resolved by consensus after joint critical reevaluation of the selected studies.

After methodological evaluation and analysis of scientific relevance, 13 studies were selected to compose the final sample of this integrative review. The sample set included different methodological designs, including multicenter randomized clinical trials, meta-analyses, systematic reviews, real-world observational studies, post-hoc analyses, and narrative reviews of a mechanistic and cardiometabolic nature.

Data extraction was carried out in a standardized manner using a previously structured instrument, including information regarding the authors, year of publication, methodological design, population/sample, study objectives, main cardiovascular outcomes analyzed, cardiometabolic effects observed, main results, and conclusions relevant to clinical practice.

Subsequently, the data were organized and analyzed in a descriptive, comparative, and critical manner, seeking to identify convergences, divergences, methodological limitations, and gaps in the scientific literature on the cardiovascular effects of tirzepatide in individuals with DM2. The integrative synthesis was conducted in a thematic manner, prioritizing the critical interpretation of the findings and the articulation between pathophysiological mechanisms, cardiometabolic effects, and clinical cardiovascular outcomes.

As this is an integrative review based exclusively on secondary data available in the scientific literature, without direct involvement of human beings, the present study was not submitted to the Research Ethics Committee, in accordance with the current ethical guidelines for literature searches.

3 RESULTS

The literature search strategy carried out in the PubMed/MEDLINE, Scopus, Web of Science and ScienceDirect databases made it possible to identify potentially relevant studies on the cardiovascular effects of tirzepatide in individuals with type 2 diabetes mellitus (DM2). After applying the eligibility criteria, removing duplicates, and critical methodological evaluation, 13 studies made up the final sample of this integrative review.

The included studies showed significant methodological heterogeneity, including multicenter randomized clinical trials, meta-analyses, systematic reviews, real-world observational studies, post-hoc analyses, and mechanistic narrative reviews.

Overall, the evidence analyzed demonstrated consistency regarding the high metabolic efficacy of tirzepatide in individuals with type 2 diabetes mellitus (DM2), especially with regard to the reduction of glycated hemoglobin (HbA1c) and body adiposity. The included trials showed superiority of tirzepatide compared to traditional GLP-1 receptor agonists and basal insulins, promoting significant glycemic reductions associated with clinically significant and sustained weight loss (NAUCK; D'ALESSIO, 2022; DE BLOCK et al., 2022). Recent meta-analyses have corroborated these findings by demonstrating a dose-dependent relationship between tirzepatide, glycemic improvement, and weight reduction, maintaining a favorable overall cardiovascular safety profile (YU et al., 2022; KHAN et al., 2023).

In addition to intensive glycemic control, the studies analyzed demonstrated consistent improvement of multiple cardiometabolic parameters in individuals with type 2 diabetes mellitus (DM2). A reduction in systolic blood pressure, an improvement in the lipid profile, a decrease in triglyceride levels, a reduction in visceral adiposity, and an improvement in insulin resistance were observed (SATTAR et al., 2025; KAORE et al., 2024). Mechanistic reviews included in this review pointed to favorable modulation of inflammatory biomarkers, reduction of oxidative stress, and improvement of endothelial function associated with the use of tirzepatide (TAKTAZ et al., 2024).

The evidence related to clinical cardiovascular outcomes showed less methodological robustness when compared to metabolic and cardiometabolic findings. Most of the available investigations were originally designed to assess metabolic efficacy and glycemic safety, with cardiovascular outcomes predominantly being analysed as secondary endpoints, exploratory or derived from post-hoc analyses.

The pre-specified meta-analysis based on the SURPASS program demonstrated no increase in cardiovascular risk associated with tirzepatide and a trend in favor of reducing major cardiovascular events (MACE-4) (SATTAR et al., 2022). Real-world observational

studies have suggested an association between tirzepatide use and significant reduction in overall mortality, major cardiovascular events, and adverse renal outcomes compared to conventional GLP-1 receptor agonists (CHUANG et al., 2024). Recent meta-analyses have also demonstrated no significant increase in acute myocardial infarction, stroke, or heart failure in individuals treated with tirzepatide (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025).

The included studies showed heterogeneity related to the populations evaluated, therapeutic comparators, follow-up time, definition of cardiovascular outcomes, and clinical eligibility criteria. Overall, the included studies demonstrated a favorable cardiometabolic profile associated with the use of tirzepatide in individuals with type 2 diabetes mellitus (DM2), including glycemic improvement, weight reduction, and favorable effects on metabolic and cardiovascular parameters.

4 DISCUSSION

The findings of this integrative review demonstrate that tirzepatide has significant cardiometabolic potential in individuals with type 2 diabetes mellitus (DM2), mainly due to its ability to promote intensive glycemic control associated with significant weight loss and comprehensive improvement of multiple cardiovascular risk factors. The body of evidence analyzed suggests that the observed benefits transcend the hypoglycemic effect alone, involving metabolic and vascular changes potentially related to the reduction of residual cardiovascular risk that is often persistent in this population (DE BLOCK et al., 2022; SATTAR et al., 2025).

The high metabolic efficacy observed in the included studies may be partially explained by the dual agonism of glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide type 1 (GLP-1) receptors. Unlike traditional GLP-1 receptor agonists, the simultaneous activation of these incretin axes seems to potentiate mechanisms related to glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, appetite control, and improved insulin sensitivity (NAUCK; D'ALESSIO, 2022). This integrated action possibly justifies the superior results of glycated hemoglobin (HbA1c) reduction and weight loss observed in the SURPASS and SURMOUNT programs compared to GLP-1 agonists alone and basal insulin (DE BLOCK et al., 2022; YU et al., 2022).

From a cardiovascular perspective, the simultaneous improvement of visceral obesity, insulin resistance, systemic arterial hypertension, and atherogenic dyslipidemia represents a particularly relevant aspect. Central obesity and chronic metabolic inflammation play a determining role in the progression of atherosclerosis, endothelial dysfunction, and heart

failure in individuals with DM2. In this context, the significant weight reduction promoted by tirzepatide can directly contribute to reducing the systemic inflammatory burden and improving vascular function, favoring a reduction in overall cardiometabolic risk (SATTAR et al., 2025).

In addition to the effects related to weight loss and glycemic control, the included studies suggest the participation of additional biological mechanisms potentially involved in the favorable cardiovascular effects of tirzepatide. Recent mechanistic reviews indicate that dual GIP/GLP-1 agonism can modulate pathways related to oxidative stress, vascular inflammation, lipotoxicity, and myocardial energy metabolism (TAKTAZ et al., 2024). Additionally, effects on cell apoptosis, autophagy, and cardiovascular remodeling have been proposed as possible mediators of the cardioprotection observed in experimental and clinical studies (TAKTAZ et al., 2024).

At the same time, the included studies demonstrated consistent improvement in metabolic parameters known to be associated with long-term cardiovascular risk reduction. A significant reduction in systolic blood pressure, improved lipid profile, decreased triglyceride levels, and reduced visceral adiposity were observed (KAORE et al., 2024; SATTAR et al., 2025). Although these parameters are considered surrogate outcomes, their integrated improvement has significant clinical relevance in view of the close relationship between residual cardiometabolic risk and progression of cardiovascular complications in DM2.

However, despite the strong biological plausibility and consistency of the metabolic effects observed, the robustness of the evidence related to the direct reduction of major cardiovascular events still remains limited. Much of the available research was originally designed to assess metabolic efficacy and glycemic safety, with cardiovascular outcomes predominantly being analyzed as secondary endpoints, exploratory or derived from post-hoc analyses. In this scenario, although the pre-specified meta-analysis based on the SURPASS program has shown no increase in cardiovascular risk and a favorable trend towards the reduction of MACE-4, there is still no definitive confirmation of statistically consolidated cardiovascular superiority (SATTAR et al., 2022).

In addition, real-world observational studies have demonstrated an association between tirzepatide use and significant reduction in overall mortality, major cardiovascular events, and adverse renal outcomes compared to conventional GLP-1 receptor agonists (CHUANG et al., 2024). Recent meta-analyses have also reinforced the absence of a significant increase in acute myocardial infarction, stroke, or heart failure in individuals treated with tirzepatide (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025). Even so, such

evidence derives predominantly from indirect analyses, heterogeneous populations, and studies with relatively short follow-up, limiting robust causal inferences about the real magnitude of cardioprotection promoted by tirzepatide.

Another relevant aspect identified in this review refers to the predominance of surrogate outcomes to the detriment of hard clinical cardiovascular outcomes. Although body weight reduction, glycemic improvement, blood pressure decrease, and lipid profile improvement are recognized as associated with lower cardiovascular risk in the long term, the extrapolation of these benefits to effective reduction of major cardiovascular events, heart failure, and cardiovascular mortality still requires confirmation by randomized cardiovascular studies specifically designed for this purpose (SATTAR et al., 2022; LIU et al., 2025).

In addition, important methodological heterogeneity was observed among the included studies, involving differences related to the profile of the populations evaluated, therapeutic comparators, duration of clinical follow-up, and definition of the outcomes analyzed. The predominant presence of narrative reviews, indirect meta-analyses, and post-hoc analyses reinforces the need for critical interpretation of the evidence currently available (WARDEH et al., 2024; KAORE et al., 2024). Added to this is the absence, to date, of a definitive consensus on the magnitude of the cardiovascular benefit of tirzepatide compared to traditional GLP-1 receptor agonists already consolidated in dedicated cardiovascular outcome studies.

Despite these limitations, the data analyzed in this integrative review indicate that tirzepatide represents one of the most promising therapeutic approaches in the contemporary context of cardiometabolic management of DM2. Its ability to act simultaneously on obesity, insulin resistance, metabolic inflammation, and multiple vascular risk factors suggests important translational potential in the context of modern cardiovascular prevention. Although the definitive confirmation of a reduction in major cardiovascular events still depends on dedicated randomized cardiovascular studies, the currently available evidence indicates that tirzepatide may occupy a strategic position in the integrated treatment of T2DM and its future cardiometabolic complications.

In this context, it is essential to carry out specific randomized cardiovascular studies, with longer follow-up time and primary evaluation of major cardiovascular events, heart failure, and cardiovascular mortality. The consolidation of this evidence may establish more definitively the real role of tirzepatide in cardiovascular prevention in individuals with type 2 diabetes mellitus.

5 CONCLUSION

The present integrative review demonstrated that tirzepatide has a highly promising therapeutic profile in the management of type 2 diabetes mellitus (DM2), especially due to its high metabolic efficacy associated with comprehensive improvement of multiple cardiovascular risk factors. The evidence analyzed indicated that the dual agonism of GIP and GLP-1 receptors promotes significant reductions in glycated hemoglobin (HbA1c), significant weight loss, and consistent improvement in cardiometabolic parameters, including blood pressure, lipid profile, insulin resistance, and visceral adiposity. In addition, the studies suggested a potential favorable impact on global cardiovascular risk, possibly related to the modulation of pathophysiological mechanisms involved in the progression of atherosclerosis, vascular inflammation, endothelial dysfunction, and cardiovascular remodeling.

However, despite the largely favorable results, the robustness of the evidence related to the direct reduction of major cardiovascular events, heart failure, and cardiovascular mortality still remains limited. Most of the available studies were originally designed to assess metabolic efficacy and glycemic safety, and cardiovascular outcomes were predominantly analyzed as secondary endpoints, exploratory or derived from post-hoc analyses. In addition, the methodological heterogeneity observed among the included studies, involving differences related to the populations evaluated, clinical follow-up time, and definition of the cardiovascular outcomes analyzed, reinforces the need for careful interpretation of the findings currently available.

Despite these limitations, the data analyzed position tirzepatide as one of the most innovative and potentially relevant therapeutic approaches in the contemporary context of cardiometabolic management of DM2. Its ability to act simultaneously on multiple metabolic and cardiovascular mechanisms suggests an important translational potential for future reduction of cardiovascular morbidity and mortality in this population. In this context, the performance of dedicated randomized cardiovascular studies, with prolonged follow-up and primary evaluation of robust clinical outcomes, will be fundamental for the definitive consolidation of the role of tirzepatide in cardiovascular prevention in individuals with type 2 diabetes mellitus.

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LUDWIG'S ANGINA: EARLY DIAGNOSIS AND AIRWAY MANAGEMENT IN DEEP CERVICAL INFECTIONS

ANGINA DE LUDWIG: DIAGNÓSTICO PRECOCE E MANEJO DA VIA AÉREA EM INFECÇÕES CERVICAIS PROFUNDAS

ANGINA DE LUDWIG: DIAGNÓSTICO PRECOZ Y MANEJO DE LA VÍA AÉREA EN INFECCIONES CERVICALES PROFUNDAS



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ABSTRACT

Ludwig's angina is a rapidly progressive deep cervical infection characterized by bilateral involvement of the submandibular, sublingual, and submental spaces, frequently associated with odontogenic infections. It is considered a potentially fatal medical emergency due to the high risk of acute airway obstruction, mediastinal spread, and sepsis. This study aimed to critically analyze the scientific evidence regarding early diagnosis and airway management in Ludwig's angina, emphasizing the main prognostic factors, therapeutic strategies, and anesthetic-surgical approaches currently employed. This is an integrative literature review conducted according to the methodological assumptions proposed by Whittemore and Knafl. The bibliographic search was performed in the PubMed/MEDLINE, Scopus, Web of Science, and SciELO databases using descriptors related to Ludwig's angina, deep neck infections, airway management, and odontogenic emergencies. Articles published within the last ten years, available in full text, and directly related to the proposed topic were included. The findings demonstrated that early recognition of clinical signs of respiratory compromise, combined with cervical computed tomography evaluation and the immediate initiation of broad-spectrum antibiotic therapy, is essential for reducing complications and mortality. Furthermore, airway management remains the main therapeutic challenge, especially in the presence of anatomical distortion caused by diffuse cervical edema, trismus, and elevation of the oral floor. Techniques such as awake fiberoptic intubation and early tracheostomy were identified as safer strategies in advanced cases. It is concluded that Ludwig's angina remains a highly severe clinical condition requiring a multidisciplinary approach, rapid diagnosis, and early airway intervention to optimize prognosis and prevent fatal outcomes.

Keywords: Ludwig's Angina. Deep Neck Infections. Airway Management. Odontogenic Emergency. Odontogenic Infection.

RESUMO

A angina de Ludwig consiste em uma infecção cervical profunda de rápida progressão, caracterizada pelo acometimento bilateral dos espaços submandibulares, sublinguais e submentonianos, frequentemente associada a infecções odontogênicas. Trata-se de uma emergência médica potencialmente fatal devido ao elevado risco de obstrução aguda das vias aéreas, disseminação mediastinal e sepse. O presente estudo teve como objetivo analisar criticamente as evidências científicas relacionadas ao diagnóstico precoce e ao manejo da via aérea na angina de Ludwig, enfatizando os principais fatores prognósticos, estratégias terapêuticas e abordagens anestésico-cirúrgicas atualmente empregadas. Trata-se de uma revisão integrativa da literatura, conduzida conforme os pressupostos metodológicos de Whittemore e Knafl. A busca bibliográfica foi realizada nas bases PubMed/MEDLINE, Scopus, Web of Science e SciELO, utilizando descritores relacionados à angina de Ludwig, infecções cervicais profundas, manejo das vias aéreas e emergência odontológica. Foram incluídos artigos publicados nos últimos dez anos, disponíveis na íntegra e diretamente relacionados ao tema proposto. Os achados demonstraram que o reconhecimento precoce dos sinais clínicos de comprometimento respiratório, associado à avaliação tomográfica cervical e à instituição imediata de antibioticoterapia de amplo

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espectro, constitui fator determinante para redução de complicações e mortalidade. Observou-se ainda que o manejo da via aérea representa o principal desafio terapêutico, especialmente diante da distorção anatômica provocada pelo edema cervical difuso, trismo e elevação do assoalho oral. Técnicas como intubação fibroóptica acordada e traqueostomia precoce destacam-se como estratégias mais seguras em casos avançados. Conclui-se que a angina de Ludwig permanece como condição clínica de elevada gravidade, exigindo abordagem multidisciplinar, diagnóstico rápido e intervenção ventilatória precoce para otimização do prognóstico e prevenção de desfechos fatais.

Palavras-chave: Angina de Ludwig. Infecções Cervicais Profundas. Manejo das Vias Aéreas. Emergência Odontológica. Infecção Odontogênica.

RESUMEN

La angina de Ludwig es una infección cervical profunda de rápida progresión caracterizada por afectación bilateral de los espacios submandibular, sublingual y submentoniano, frecuentemente asociada a infecciones odontogénicas. Constituye una emergencia médica potencialmente mortal debido al alto riesgo de obstrucción aguda de las vías respiratorias, diseminación mediastínica y sepsis. Este estudio tuvo como objetivo analizar críticamente la evidencia científica relacionada con el diagnóstico precoz y el manejo de las vías respiratorias en la angina de Ludwig, haciendo hincapié en los principales factores pronósticos, estrategias terapéuticas y abordajes anestésico-quirúrgicos empleados actualmente. Se trata de una revisión bibliográfica integradora, realizada según los principios metodológicos de Whittemore y Knafl. La búsqueda bibliográfica se realizó en las bases de datos PubMed/MEDLINE, Scopus, Web of Science y SciELO, utilizando descriptores relacionados con la angina de Ludwig, infecciones cervicales profundas, manejo de las vías respiratorias y emergencia odontológica. Se incluyeron artículos publicados en los últimos diez años, disponibles en texto completo y directamente relacionados con el tema propuesto. Los hallazgos demostraron que el reconocimiento precoz de los signos clínicos de compromiso respiratorio, junto con la evaluación tomográfica cervical y la instauración inmediata de antibioticoterapia de amplio espectro, es un factor determinante para reducir las complicaciones y la mortalidad. También se observó que el manejo de la vía aérea representa el principal desafío terapéutico, especialmente dada la distorsión anatómica causada por el edema cervical difuso, el trismo y la elevación del suelo oral. Técnicas como la intubación fibroóptica con el paciente despierto y la traqueostomía precoz se destacan como estrategias más seguras en casos avanzados. Se concluye que la angina de Ludwig sigue siendo una afección clínica muy grave, que requiere un abordaje multidisciplinario, un diagnóstico rápido y una intervención ventilatoria precoz para optimizar el pronóstico y prevenir desenlaces fatales.

Palabras clave: Angina de Ludwig. Infecciones Cervicales Profundas. Manejo de la Vía Aérea. Urgencia Dental. Infección Odontogénica.

1 INTRODUCTION

Ludwig's angina is a rapidly progressing deep cervical infection, characterized by diffuse cellulitis predominantly involving the submandibular, sublingual, and submental spaces, often associated with odontogenic infections originating in mandibular molars (FELLINI et al., 2017; ÜNAL; MOLLAOĞLU, 2025). Despite the significant reduction in mortality after the advent of antibiotic therapy and the expansion of access to dental care, the disease remains a potentially fatal medical-surgical emergency, especially due to the high propensity for acute respiratory failure, mediastinal dissemination, and systemic sepsis (MILLER; VON CROWNS; WILLOUGHBY, 2018).

The pathophysiology of the disease is related to the rapid infectious spread through the deep cervical fascial planes, favored by the wide anatomical communication between the submandibular and sublingual spaces, allowing contiguous progression to the parapharyngeal, retropharyngeal, and mediastinal compartments (MAHEEN et al., 2019; MAKKAR et al., 2022). This aggressive behavior produces exuberant edema of the oral floor, posterior displacement of the tongue, and progressive compression of the upper respiratory structures, configuring one of the most critical scenarios in the context of cervical infectious emergencies and difficult airway (LONG; DEMIRCI; KRUSE, 2018).

Although relatively rare, Ludwig's angina continues to be associated with high morbidity and mortality when clinical recognition and therapeutic intervention do not occur early. Contemporary evidence shows that respiratory deterioration remains the leading cause of disease-related death, particularly in cases accompanied by necrotizing descending mediastinitis, sepsis, and acute ventilatory failure (MILLER; VON CROWNS; WILLOUGHBY, 2018; SAKHUJA et al., 2022). In this context, clinical manifestations such as hardened submandibular edema, elevation of the oral floor, trismus, dysphagia, odynophagia, drooling, stridor, and imminent signs of respiratory failure are of decisive importance for the early recognition of the disease and immediate definition of the therapeutic approach (BHUIYAN; HOSSAIN; RAHMAN, 2022).

However, the clinical complexity of Ludwig's angina transcends the infectious control itself, since the preservation of airway patency represents the main prognostic determinant in these patients. The anatomical distortion caused by extensive cervical edema, associated with severe limitation of mouth opening, reduced cervical mobility, and posterior tongue displacement, often makes facemask ventilation and orotracheal intubation technically complex and potentially catastrophic procedures (FELLINI et al., 2017). In addition, inflammatory progression can convert, in a short period of time, initially patent airways into

critical scenarios of complete obstruction, imposing a high risk of ventilatory failure and sudden death by asphyxia (İSLAMOĞLU et al., 2018).

In this scenario, strategies such as awake fiberoptic intubation, videolaryngoscopy, cricothyroidotomy, and emergency tracheostomy have been described as fundamental alternatives for maintaining ventilatory support in patients with severe cervical infection (FELLINI et al., 2017; MAHEEN et al., 2019). However, there is significant heterogeneity in the literature regarding the choice of the ideal technique, the safest time for invasive intervention, and the clinical criteria capable of predicting imminent respiratory deterioration, especially in services with structural limitations and lack of standardized protocols for the approach to the difficult infectious airway (LONG; DEMIRCI; KRUSE, 2018). This lack of universal consensus substantially increases the therapeutic complexity of the disease, especially in view of the possibility of rapid clinical decompensation and irreversible ventilatory failure.

At the same time, recent advances in diagnostic and therapeutic methods have contributed to reducing complications associated with the disease. Contrast-enhanced computed tomography has established itself as an important tool in the evaluation of the anatomical extent of the infection, identification of purulent collections, mediastinal involvement, and early surgical planning (MAKKAR et al., 2022). From a therapeutic perspective, broad-spectrum antibiotic therapy associated with early surgical drainage and elimination of the odontogenic focus remains a fundamental pillar of contemporary treatment (ÜNAL; MOLLAOĞLU, 2025; SAKHUJA et al., 2022). In addition, the high complexity of these patients reinforces the need for a multidisciplinary approach involving anesthesiology, oral and maxillofacial surgery, otorhinolaryngology, head and neck surgery, and intensive care, particularly in cases accompanied by sepsis, mediastinitis, and acute respiratory failure (İSLAMOĞLU et al., 2018).

Despite the recognized clinical relevance of Ludwig's angina, there is a significant limitation of the available scientific evidence regarding early diagnosis and ideal strategies for the ventilatory approach in these patients. The contemporary literature remains predominantly composed of case reports, retrospective clinical series, and isolated observational analyses, evidencing a significant scarcity of robust studies and integrative reviews with a systematized critical approach. This limitation compromises the consolidation of universally accepted care protocols and reinforces the need for critical integration of the currently available evidence, especially in view of the high anatomical, infectious, and therapeutic complexity inherent to the disease.

Thus, the present integrative literature review aims to critically analyze the available scientific evidence on the early diagnosis and management of the airway in Ludwig's angina, emphasizing prognostic factors, therapeutic strategies, and clinical challenges related to deep cervical infections.

2 METHODOLOGY

This is an **integrative literature review**, with a qualitative approach and descriptive-analytical nature, developed with the purpose of gathering, evaluating and critically synthesizing scientific evidence about the early diagnosis and management of the airway in Ludwig's angina, in the context of deep cervical infections. The choice of this design is justified by the possibility of integrating studies with different methodological designs, including case reports, clinical series, observational studies, and clinical reviews, a particularly relevant condition in view of the scarcity of randomized clinical trials on cervical infectious emergencies and difficult airway.

The methodological approach was based on the classic framework of Whittemore and Knafl (2005), which guides the conduction of integrative reviews through the following steps: identification of the problem, formulation of the guiding question, definition of the search strategy, establishment of eligibility criteria, selection of studies, standardized data extraction, methodological critical evaluation and integrative synthesis of evidence.

The guiding question established was: **what is the available scientific evidence regarding early diagnosis and airway management strategies in patients with Ludwig's angina and deep cervical infections?**

The bibliographic search was planned for the **PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and LILACS databases**, using controlled descriptors obtained from the **DeCS** and **MeSH** vocabularies, combined by Boolean operators **AND** and **OR**. Terms related to *"Ludwig's angina"*, *"deep neck infections"*, *"airway management"*, *"difficult airway"*, *"cervical fascial space infections"*, *"fiberoptic intubation"*, *"tracheostomy"*, *"airway obstruction"* and *"odontogenic infections"* were used.

Studies published in the last ten years, available in full, in English, Portuguese, or Spanish, that addressed early diagnosis, clinical signs, imaging tests, anesthetic management, advanced airway control, surgical treatment, antibiotic therapy, complications, and prognosis of Ludwig's angina were included. Different methodological designs, such as observational studies, case series, case reports, retrospective studies, systematic reviews, and meta-analyses, were considered eligible due to the limited availability of experimental studies on the subject.

Duplicate studies, letters to the editor, conference abstracts without complete data, reports without methodological rigor, articles without a direct relationship with Ludwig's angina or airway management, exclusively pediatric studies when not related to the central focus of the review, and studies without access to the full text were excluded.

The selection process took place in successive stages. Initially, the titles and abstracts were read to identify the thematic relevance. Then, the potentially eligible studies were read in full. The final evaluation was carried out critically, considering adherence to the objective of the review, methodological clarity, clinical relevance, and contribution to the understanding of early diagnosis and ventilatory management in deep neck infections. Any disagreements in the selection of studies were resolved by consensus among reviewers.

Data extraction was performed in a standardized manner, including: author and year of publication, study design, population or sample, clinical focus, strategies employed for airway management, diagnostic methods, therapeutic approach, main clinical outcomes, reported complications, and relevant conclusions. This systematization allowed for a critical comparison of the findings and identification of convergences, divergences, and gaps in the literature.

Data analysis was conducted in a descriptive, comparative, and critical manner, considering the heterogeneity of the studies, the predominance of case reports and clinical series, the methodological limitations of the available evidence, and the therapeutic challenges related to rapid respiratory deterioration, cervical anatomical distortion, and the absence of universal consensus regarding the optimal timing of advanced airway intervention.

Because this was a study based exclusively on secondary data from the scientific literature, without direct participation of human beings or access to identifiable individual information, there was no need to submit it to the Research Ethics Committee.

3 RESULTS AND DISCUSSION

The integrative analysis of the selected studies shows that Ludwig's angina remains an infectious emergency of high clinical severity, whose evolution is directly related to the speed of dissemination through the cervical fascial spaces and the risk of acute respiratory deterioration. Although advances in antibiotic therapy, cross-sectional imaging, and surgical-anesthetic techniques have reduced mortality compared to the pre-antibiotic period, upper airway obstruction remains the critical event with the greatest prognostic impact (FELLINI et al., 2017; MILLER; VON CROWNS; WILLOUGHBY, 2018; BHUIYAN; HOSSAIN; RAHMAN, 2022).

The studies analyzed converge in characterizing the disease as a deep cellulitis, predominantly odontogenic in origin, which affects the submandibular, sublingual, and submental spaces, with the possibility of progression to parapharyngeal, retropharyngeal, and mediastinal compartments (MAHEEN et al., 2019; MAKKAR et al., 2022; ÜNAL; MOLLAOĞLU, 2025). This anatomical continuity explains the clinical aggressiveness of the condition: oral floor edema, tongue elevation and posteriorization, and compression of supraglottic structures can transform an initially stable patient into a ventilatory emergency in a short period of time (LONG; DEMIRCI; KRUSE, 2018; İSLAMOĞLU et al., 2018).

From a semiological point of view, the presence of hardened submandibular edema, trismus, dysphagia, odynophagia, drooling, elevation of the oral floor, muffled voice, stridor, and signs of respiratory effort should be interpreted as a high-risk marker for imminent ventilatory failure. The reviewed literature demonstrates that the absence of stridor does not exclude severity, since the progression of edema can be silent until advanced stages, especially in patients with extensive infection, diabetes, immunosuppression, or therapeutic delay (BHUIYAN; HOSSAIN; RAHMAN, 2022; SAKHUJA et al., 2022). Thus, early diagnosis should not depend only on the frank manifestation of respiratory failure, but on the integration of clinical signs, risk factors, oropharyngeal physical examination, and anatomical imaging evaluation.

Contrast-enhanced computed tomography emerges as a central tool in the stratification of gravity, allowing the delimitation of purulent collections, extension to deep cervical spaces, signs of necrotizing fasciitis, mediastinal involvement, and the need for surgical drainage. However, its use should be conditioned to ventilatory safety: in cases of respiratory instability, imaging should not delay airway control (MAKKAR et al., 2022). This point is clinically decisive, as Ludwig's angina imposes a permanent tension between the need for accurate anatomical characterization and the urgency of intervention before complete obstruction.

Ventilatory management is the critical core of decision-making. Awake fiberoptic intubation is described as a particularly relevant strategy in patients with an early difficult airway, as it allows preservation of spontaneous ventilation and progressive visualization of respiratory structures, even in the face of limited mouth opening and cervical anatomical distortion (FELLINI et al., 2017). However, its applicability depends on technological availability, team experience, patient cooperation, and degree of supraglottic edema. In scenarios of advanced infection, profuse secretions, bleeding, or anatomical collapse, the technique may fail or become unsafe.

Videolaryngoscopy appears as a potential alternative in some contexts, but its effectiveness may be limited by severe trismus, macroglossia, oral floor edema, and cervical mobility restriction. Emergency tracheostomy, on the other hand, remains an indispensable strategy in cases of imminent obstruction, intubation failure, or impossibility of safe transoral access, although it also presents technical difficulties due to cervical edema, distortion of anatomical planes, and local infection (MAHEEN et al., 2019). Cricothyroidotomy, in turn, should be understood as a rescue measure in a "do not intubate, do not ventilate" situation, especially when ventilatory deterioration is abrupt. The literature, however, does not offer universal consensus on the ideal time for invasive intervention, nor on the superiority of one technique over another, reinforcing the need for individualized, early, and multidisciplinary decision making (FELLINI et al., 2017; LONG; DEMIRCI; KRUSE, 2018).

The absence of a universally accepted protocol represents one of the main weaknesses in care. Studies suggest that management should be guided by clinical severity, speed of progression, presence of stridor, anatomical extent of infection, team experience, and available resources. This decision-making heterogeneity is understandable, but it exposes the patient to the risk of therapeutic delay when the severity is underestimated. In this sense, early airway intervention should be considered not only in the face of installed obstruction, but also in the face of signs of anatomical and clinical progression suggestive of imminent deterioration (İSLAMOĞLU et al., 2018; SAKHUJA et al., 2022).

In addition to ventilatory control, the studies analyzed reinforce that effective treatment requires broad-spectrum intravenous antibiotic therapy, coverage for aerobic and anaerobic flora, early surgical drainage, and elimination of the odontogenic focus. The association between drainage and antibiotics was recurrent in reports with favorable evolution, especially when performed before mediastinal dissemination or the onset of severe sepsis (BHUIYAN; HOSSAIN; RAHMAN, 2022; ÜNAL; MOLLAOĞLU, 2025). Drainage should not only be understood as an infectious control measure, but also as a decompressive intervention capable of reducing tissue tension, local edema, and risk of respiratory progression.

The complications described in the selected studies show the systemic severity of the disease. Dissemination to the mediastinum, cervical necrotizing fasciitis, aspiration pneumonia, pleural empyema, sepsis, and respiratory failure are potentially fatal outcomes, especially when there is a diagnostic delay or fragmented management (MILLER; VON CROWNS; WILLOUGHBY, 2018; MAKKAR et al., 2022; SAKHUJA et al., 2022). Fatal reports reinforce that apparently localized odontogenic infections can progress to cervical necrosis, descending mediastinitis and death, demonstrating that Ludwig's angina should be treated as a time-dependent infectious syndrome.

The multidisciplinary approach appears as a cross-sectional element in studies with better outcomes. The integration between anesthesiology, oral and maxillofacial surgery, otorhinolaryngology, head and neck surgery, radiology, and intensive care allows for the alignment of priorities: protecting ventilation, controlling the infectious focus, defining the surgical moment, monitoring systemic progression, and planning safe extubation. This coordination becomes even more relevant because therapeutic success does not depend on a single intervention, but on the appropriate sequence between clinical recognition, respiratory stabilization, imaging, antibiotics, drainage, and intensive surveillance (LONG; DEMIRCI; KRUSE, 2018; FELLINI et al., 2017; ÜNAL; MOLLAOĞLU, 2025).

Finally, the available literature has important limitations. Case reports, small clinical series, and retrospective analyses predominate, with heterogeneity in terms of diagnostic criteria, patient severity, ventilatory control techniques, antimicrobial regimens, and time until surgical intervention. This fragmentation makes it difficult to formulate universal recommendations and prevents robust comparisons between strategies such as fiberoptic intubation, videolaryngoscopy, and tracheostomy. Even so, the convergence of the findings allows us to affirm that the prognosis of Ludwig's angina depends fundamentally on early recognition, anticipation of the difficult airway, aggressive control of the infectious focus, and coordinated action by experienced teams.

Thus, the results of this integrative review indicate that Ludwig's angina should be understood as a simultaneous anatomical, infectious, and ventilatory emergency. The main contemporary gap lies not only in the availability of therapies, but in the precise definition of the optimal time to apply them before deep cervical progression produces irreversible respiratory failure.

4 CONCLUSION

The present integrative review shows that Ludwig's angina remains a highly severe infectious emergency, characterized by rapid progression through the deep cervical fascial spaces and high potential for fatal respiratory deterioration. The prognosis is directly related to the early recognition of the disease, adequate clinical stratification, and timely ventilatory intervention, especially in the face of manifestations such as hardened submandibular edema, elevation of the oral floor, trismus, dysphagia, stridor, and imminent signs of respiratory failure. In this context, advanced airway control strategies, including awake fiberoptical intubation, videolaryngoscopy, and tracheostomy, play a central role, although the literature still does not present a universal consensus regarding the ideal technique or the safest time for invasive intervention.

The studies analyzed reinforce that the reduction of morbidity and mortality depends on an integrated multidisciplinary approach, associating broad-spectrum intravenous antibiotic therapy, early surgical drainage, elimination of the odontogenic focus, and intensive monitoring. However, the predominance of case reports, small retrospective series, and methodologically heterogeneous studies highlights an important limitation of the available evidence and hinders the standardization of care protocols related to ventilatory management in deep neck infections.

Thus, it is concluded that Ludwig's angina should be understood simultaneously as an infectious, anatomical and ventilatory emergency, in which the anticipation of the difficult airway is the main prognostic determinant. More than treating the established infection, therapeutic success depends on the ability to recognize signs of ventilatory impairment early and intervene before rapid cervical progression results in irreversible respiratory failure.

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CARDIAC PATHOLOGIES: HEMODYNAMIC ASSESSMENT AND COMPLICATIONS

PATOLOGIAS CARDÍACAS: AVALIAÇÃO HEMODINÂMICA E INTERCORRÊNCIAS

PATOLOGÍAS CARDÍACAS: EVALUACIÓN HEMODINÁMICA E INTERCURRENCIAS



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ABSTRACT

Cardiovascular diseases are the leading cause of mortality worldwide and remain a major challenge for public health in Brazil, especially in light of population aging and the high prevalence of cardiometabolic risk factors. In this context, hemodynamics, or interventional cardiology, plays a central role in the diagnosis and minimally invasive treatment of coronary syndromes and other cardiovascular pathologies. This chapter discusses the physiology of myocardial blood flow, the epidemiology of heart diseases, and the main clinical entities associated with coronary obstruction, with emphasis on atherosclerosis, angina, acute myocardial infarction, and heart failure. It also addresses the main procedures performed in hemodynamic services, such as cardiac catheterization, coronary angiography, coronary angioplasty, and stent implantation, emphasizing their indications and technical foundations. In addition, the text examines complications related to these procedures, especially vascular complications and events associated with arterial access routes, such as hematoma, spasm, pseudoaneurysm, radial artery occlusion, and contrast-induced nephropathy. Finally, the chapter reinforces the need for careful patient assessment, continuous monitoring, and early identification of clinical and laboratory predictive factors in order to reduce complications, improve patient safety, and enhance outcomes in hemodynamics.

Keywords: Cardiovascular Diseases. Hemodynamics. Interventional Cardiology. Percutaneous Coronary Intervention. Vascular Complications.

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RESUMO

As doenças cardiovasculares constituem a principal causa de mortalidade no mundo e permanecem como importante desafio para a saúde pública no Brasil, especialmente diante do envelhecimento populacional e da elevada prevalência de fatores de risco cardiometabólicos. Nesse contexto, a hemodinâmica, ou cardiologia intervencionista, assume papel central no diagnóstico e no tratamento minimamente invasivo das síndromes coronarianas e de outras patologias cardiovasculares. O capítulo discute a fisiologia do fluxo miocárdico, a epidemiologia das doenças cardíacas e as principais entidades clínicas associadas à obstrução coronariana, com destaque para aterosclerose, angina, infarto agudo do miocárdio e insuficiência cardíaca. Também são abordados os principais procedimentos realizados no serviço de hemodinâmica, como cateterismo cardíaco, cinecoronariografia, angioplastia coronariana e implante de stents, enfatizando suas indicações e fundamentos técnicos. Além disso, o texto examina as intercorrências relacionadas a esses procedimentos, especialmente complicações vasculares e eventos associados à via de acesso arterial, como hematoma, espasmo, pseudoaneurisma, oclusão radial e nefropatia induzida por contraste. Por fim, o capítulo reforça a necessidade de avaliação criteriosa dos pacientes, do monitoramento contínuo e da identificação precoce de fatores preditores clínicos e laboratoriais, visando reduzir complicações, aprimorar a segurança assistencial e qualificar os desfechos em hemodinâmica.

Palavras-chave: Doenças Cardiovasculares. Hemodinâmica. Cardiologia Intervencionista. Intervenção Coronária Percutânea. Complicações Vasculares.

RESUMEN

Las enfermedades cardiovasculares constituyen la principal causa de mortalidad en el mundo y continúan siendo un importante desafío para la salud pública en Brasil, especialmente ante el envejecimiento poblacional y la elevada prevalencia de factores de riesgo cardiometabólicos. En este contexto, la hemodinámica, o cardiología intervencionista, desempeña un papel central en el diagnóstico y tratamiento mínimamente invasivo de los síndromes coronarios y de otras patologías cardiovasculares. El capítulo discute la fisiología del flujo miocárdico, la epidemiología de las enfermedades cardíacas y las principales entidades clínicas asociadas con la obstrucción coronaria, con énfasis en la aterosclerosis, la angina, el infarto agudo de miocardio y la insuficiencia cardíaca. También se abordan los principales procedimientos realizados en los servicios de hemodinámica, como el cateterismo cardíaco, la cinecoronariografía, la angioplastia coronaria y el implante de stents, destacando sus indicaciones y fundamentos técnicos. Además, el texto examina las complicaciones relacionadas con estos procedimientos, especialmente las complicaciones vasculares y los eventos asociados a la vía de acceso arterial, como hematoma, espasmo, pseudoaneurisma, oclusión radial y nefropatía inducida por contraste. Finalmente, el capítulo refuerza la necesidad de una evaluación cuidadosa de los pacientes, del monitoreo continuo y de la identificación temprana de factores predictivos clínicos y de laboratorio, con el objetivo de reducir complicaciones, mejorar la seguridad asistencial y optimizar los resultados en hemodinámica.

Palabras clave: Enfermedades Cardiovasculares. Hemodinámica. Cardiología Intervencionista. Intervención Coronaria Percutánea. Complicaciones Vasculares.

1 INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of global mortality, accounting for approximately 31% of deaths worldwide, according to the World Health Organization (WHO, 2023). According to the *Global Burden of Disease* (GBD, 2019), the number of people with CAD in Brazil increased from 1.48 million in 1990 to more than 4 million in 2019.

In Brazil, these diseases cause about 360 thousand deaths annually, corresponding to almost a thousand deaths per day. According to the publication *Cardiovascular Statistics - Brazil 2023*, CVDs account for about one-third of national deaths, disproportionately impacting socioeconomically vulnerable populations that face barriers to accessing specialized health services (Brazilian Society of Cardiology, 2023). Among the CVDs of greatest epidemiological relevance are coronary artery disease (CAD), acute myocardial infarction (AMI), heart failure, and cardiac arrhythmias, all of which are associated with high morbidity and mortality.

In this scenario, hemodynamic services play an essential role in the diagnosis and treatment of acute and chronic cardiovascular diseases, providing minimally invasive interventions that reduce the need for open surgeries and improve clinical outcomes (Mesquita; Ker, 2021). Among the procedures offered, coronary angiography, coronary angioplasty with stent implantation, valvuloplasty, embolizations, closure of cardiac communications and the implantation of cardiac devices such as pacemakers and defibrillators stand out (Ribeiro, 2008).

In the diagnosis and management of cardiovascular emergencies, coronary angiography is considered the gold standard, since it allows anatomical visualization of the coronary tree by means of injection of iodinated contrast via the femoral, radial, ulnar or brachial route. In addition, hemodynamic services are of great importance in diagnosing and subsidizing early interventions and reducing complications, length of hospital stay, and mortality.

Thus, this chapter seeks to describe the main complications in hemodynamic services, as well as the cardiac pathologies investigated and treated by diagnostic or therapeutic percutaneous coronary intervention.

2 MYOCARDIAL FLOW PHYSIOLOGY

The heart is surrounded by its own membrane, the pericardium, and is located in the thoracic mediastinum, between the two pleural cavities. Approximately two-thirds of the heart mass is located to the left of the midline of the body. Anatomically, the organ is composed of four muscular chambers - two atria and two ventricles - and the associated valve structures.

The right side of the heart (right atrium and ventricle) receives venous blood from the body and pumps blood to the lungs through the pulmonary arterial system, characterized by low pressure. The left side (left atrium and ventricle) receives oxygenated blood from the lungs and pumps it into the high-pressure systemic circulation (Woods, 2005).

The atria are separated from the ventricles by fibrous tissue that surrounds the atrioventricular valves. The electrical impulse that promotes cardiac contraction crosses the atrioventricular node, in which there is a physiological delay necessary to ensure synchronism between atrial and ventricular contraction, allowing adequate filling of the ventricles before ejection. This electrical activity is followed by contraction (systole) and relaxation (diastole) of the cardiac muscle fibers, composing the cardiac cycle - which is repeated 60 to 100 times per minute, depending on the heart rate. This cycle is responsible for cardiac output, that is, the volume of blood ejected by the heart per minute. Cardiac muscle contraction is essential to maintain adequate hemodynamics and ensure metabolic supply to the tissues. Changes in this mechanical activity can compromise cardiac function, with potential progression to heart failure (Jatene *et al.*, 2022).

The coronary artery system is made up of the epicardial coronary arteries, which branch into arterioles - resistance vessels - and, later, into an extensive capillary network. Under physiological conditions, the main coronary arteries do not offer significant resistance to blood flow, acting as conductors to the microcirculation. Myocardial blood flow is dynamically adjusted by self-regulatory mechanisms, in order to balance the supply and consumption of oxygen, preventing the occurrence of ischemia (Ribeiro; Filho, 2008).

According to Woods (2005), coronary circulation depends on the continuous activity of the heart, which needs to ensure the supply of oxygen and metabolic substrates to its own tissues, while removing carbon dioxide and other metabolic excreta, maintaining aerobic metabolism and contractile capacity. Unlike other tissues, the myocardium needs to generate force to promote its own perfusion. In human cardiac anatomy, two main coronary arteries stand out - the right and the left - which originate from the aorta, in the region of the sinuses of Valsalva. These arteries usually emerge from the aorta at angles close to 90 degrees, penetrate the myocardial wall, and branch extensively. There is significant individual anatomical variation in this branching pattern. In general, the right coronary artery irrigates the right atrium and ventricle, while the left coronary artery is responsible for irrigating the left atrium and ventricle.

3 EPIDEMIOLOGY OF HEART DISEASE

Cardiovascular diseases (CVD) are a relevant public health problem, being the main cause of mortality and disability among adults of full working age. It is estimated that they correspond to about 31% of global deaths (Mansur; Favarato, 2021; WHO, 2017) and approximately 27.7% of deaths in Brazil (Brasil, 2025). In addition to their impact on public health, CVDs impose high economic costs on the country, reflected in the loss of potential years of life and a significant burden on the public health system, both due to the high demand for hospitalizations and the costs associated with prolonged treatment (Schmidt *et al.*, 2011; Siqueira; Siqueria-Filho; Land, 2017; Malta; Moraes Neto; Silva Júnior, 2011; Ribeiro *et al.*, 2016).

With population aging, increased longevity and also with the proportional reduction of infectious diseases, they have contributed substantially to the growth in the prevalence of chronic diseases, including cardiovascular diseases (Salomon *et al.*, 2012; Morera *et al.*, 2021). This scenario is aggravated by persistent socioeconomic inequalities, which are reflected in the distribution of risk factors and mortality from CVD (Johnson-Lawrence; Kaplan; Galea, 2013; Stringhini *et al.*, 2012). Studies on cardiovascular mortality trends in Brazil point to a reduction in death rates among the elderly, related to the postponement of deaths from chronic diseases (Martins *et al.*, 2020; Moreira *et al.*, 2021).

Historically, humanity has undergone important transformations in the patterns of illness and mortality. In the first half of the twentieth century, infectious diseases and hunger were the main causes of death, reflected in a low life expectancy. In that period, cardiovascular diseases accounted for only 10% of deaths. However, over the last century, demographic, socioeconomic, nutritional transformations and the strengthening of public health policies have contributed to the reduction of deaths from infectious diseases and malnutrition. As a result, chronic non-communicable diseases, such as acute myocardial infarction and stroke, have come to occupy a prominent position as the main causes of death on a global scale (Jatene *et al.*, 2022)

This change is understood in the context of the epidemiological transition, the process by which societies evolve from a profile dominated by infectious diseases and malnutrition to a profile characterized by chronic diseases. Factors such as urbanization, changes in lifestyle and diet, sedentary lifestyle, population aging, and prolonged exposure to cardiovascular risk factors (such as hypertension, dyslipidemia, obesity, and smoking) are determinants of this process (Omram, 1971; Martins *et al.*, 2020).

According to data from the *Global Burden of Disease* study (GBD, 2017), ischemic heart disease and cerebrovascular diseases together account for about 32% of global

deaths. In high-income countries, these diseases were responsible for 32% of deaths, while in low-income countries this figure was 15%. Among individuals over 70 years of age, CVD mortality exceeded 40%, with no significant difference between the sexes.

In Brazil, the epidemiological transition has profoundly altered the mortality profile. Until the 1960s, infectious and parasitic diseases predominated as the main causes of death, except in large urban centers such as São Paulo and Rio de Janeiro. The reduction in mortality from coronary heart disease was observed first in the United States, starting in 1968, in Europe in the 1970s, and only from the 1990s onwards in Brazil. Currently, coronary and cerebrovascular diseases are the main causes of death in the country for both sexes. Among women, coronary heart disease has surpassed cerebrovascular disease as the leading cause of death. Cardiomyopathies, on the other hand, occupy the fourth position among the causes of cardiovascular death, influenced by the high homicide rates among young men (Jatene *et al.*, 2022).

Data from DATASUS (2019) reveal that early mortality from diseases of the circulatory system increases with age, both in men and women. Male excess mortality tends to decrease with advancing age, a phenomenon possibly related to the protective action of estrogens, or the androgen/estrogen ratio, against atherosclerosis (Brasil, 2019).

Recently, the COVID-19 pandemic, which began in 2020, changed the scenario of chronic diseases in Brazil. The country has recorded more than 700 thousand deaths and approximately 37 million confirmed cases of the disease (Brasil, 2023). The mobilization of health resources and scientific efforts aimed at confronting the pandemic directly and indirectly impact cardiovascular care. Since the first reports, a relationship between SARS-CoV-2 infection and cardiovascular health has been observed, both due to the direct involvement of the virus in the cardiovascular system and the overload on health services, which compromised access and regular care for patients with CVD (Ribeiro *et al.*, 2021).

Reports from *Cardiovascular Statistics – Brazil* show that, in 2021, COVID-19 surpassed acute coronary syndrome and stroke as the main cause of death in the country. Despite the reduction in hospitalizations due to CVD between 2020 and 2021 - especially due to heart failure and cardiomyopathies - there was an increase in the severity of the cases treated, with an increase of 19.4% in admissions to intensive care units and 13.6% in hospital deaths. Such data suggest that less severe patients stopped seeking care, while more critical cases arrived at health services late, compromising clinical outcomes (Ribeiro *et al.*, 2021).

4 MYOCARDIAL FLOW PATHOLOGIES

4.1 ATHEROSCLEROSIS

Atherosclerotic coronary artery disease presents in different clinical forms, one of which is chronic coronary occlusion (OCC), characterized by total obstruction of the vessel lumen for a presumed period equal to or greater than three months. This condition is present in approximately 16 to 18% of patients with significant coronary heart disease (Di Mario, 2022).

Atherosclerosis (AS) is a chronic inflammatory disease marked by the progressive development of atheromatous plaques on arterial walls. These plaques are composed of lipids, fibrous tissue, and calcium, and their growth results from the interaction between atherogenic lipoproteins and inflammatory processes. Inflammation plays a central role in the formation, progression, and destabilization of these lesions, making AS the most common and clinically relevant vascular manifestation (Ridker, 2016).

In this context, lipoprotein(a) [Lp(a)] has been highlighted as an independent risk factor for atherosclerotic cardiovascular diseases. In addition to actively participating in the inflammatory response, Lp(a) interacts with cellular components of the arterial wall, contributing to endothelial dysfunction and smooth muscle cell proliferation. Lp(a) can act by amplifying or mitigating inflammation depending on the context, making it a potential therapeutic target for cardiovascular prevention and treatment strategies (Ajoolabady, 2024).

Ischemic heart disease of atherosclerotic origin results from stenosis or obstruction of the lumen of the coronary arteries, causing reduced blood flow (ischemia), hypoxia and, in more severe cases, myocardial necrosis. In this context, cardiovascular diseases (CVDs) are among the greatest global public health challenges, with atherosclerosis being its main cause. Ischemic heart disease, a direct consequence of this process, remains the leading cause of mortality from heart disease in the world (Lu; Daugherty, 2015; GBD 2017).

The current understanding of atherogenesis recognizes this process as active and dynamic, involving complex inflammatory mechanisms, rather than as a simple passive accumulation of cholesterol in the arteries. The immune response, both innate and adaptive, actively participates from the early stages to the clinical complications of atherosclerosis. According to Song *et al.* (2022), anti-inflammatory strategies have been investigated as effective alternatives in reducing cardiovascular risk, complementing the control of traditional risk factors. The effects of lipid-lowering drugs on inflammatory markers are also studied, as well as the use of classic anti-inflammatory drugs, immunomodulatory therapies directed to specific cytokines, and the development of vaccines with preventive potential.

Modulating inflammation has been shown to be a promising strategy in the prevention and treatment of atherosclerosis. Clinical evidence indicates that the control of the inflammatory process can prevent adverse cardiovascular events, reinforcing the importance of translational research for the development of new therapeutic approaches. Among the emerging strategies, the following stand out: the blocking of inflammasomes, the inhibition of cytokines, the modulation of the adaptive immune response, and the stimulation of mechanisms for the resolution of inflammation. Such interventions, together with lifestyle changes and the control of dyslipidemia, systemic arterial hypertension and diabetes mellitus, constitute an advance in the management of atherosclerotic risk (Soehnlein; Libby, 2021).

Coronary stenosis, caused by the deposition of atherosclerotic plaques, reduces arterial caliber. The degree of obstruction is measured in percentage terms, considering the relationship between the normal diameter of the vessel and the diameter of the stenosed segment. A 50% stenosis can reduce coronary reserve by up to 3 to 4 times; above 70%, this reserve is practically non-existent, severely compromising myocardial perfusion (Jatene *et al.*, 2022).

Partial or total reduction in coronary blood flow triggers myocardial ischemia, a condition that has a close correlation with clinical prognosis, especially in relation to the severity, location, and extent of the obstruction. In symptomatic patients, the main therapeutic goal is to relieve chest pain and improve quality of life. Atherosclerosis significantly impacts the functionality of patients, is associated with worsening quality of life, higher prevalence of depressive symptoms, and increased hospital admissions. Therapeutic interventions include myocardial revascularization, either through coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), with the aim of restoring blood flow, reducing symptoms, and improving functional capacity (Feres *et al.*, 2017)

According to Mariani *et al.* (2023), knowledge about the national reality is essential for Brazil's adequate positioning on the international scene, especially in relation to public policies and continuing education programs aimed at the treatment of coronary heart disease. Access to advanced therapies requires not only technical training, but also the availability of high-cost devices, which are not always accessible in the public network. In this sense, Silva *et al.* (2023), through the *LATAM CTO Registry* - a Latin American multicenter registry on chronic total coronary occlusion (CTO) recanalization in 26 Brazilian centers - demonstrated that PCI can be performed effectively and safely in Brazil, with a technical success rate of 84%, adverse events in 2.3% of cases, and mortality of only 0.75%.

These results reinforce the quality of Brazilian cardiology practice and its representativeness in the main institutions dedicated to the treatment of complex coronary obstructions.

Coronary artery disease, as previously mentioned, represents the most prevalent form of cardiovascular disease, and is strongly associated with severe outcomes such as acute myocardial infarction, heart failure, and death. Inflammation plays a central role in the pathophysiology of coronary heart disease, acting both in the onset and progression of the atherosclerotic process. In this context, the adipose tissue that surrounds the blood vessels, called perivascular adipose tissue, plays an important role as a metabolic mediator and vascular regulator (Nomura *et al.*, 2020; Goeller *et al.*, 2019).

In healthy individuals, perivascular adipose tissue secretes adipokines with anti-inflammatory and vasodilatory properties, contributing to the maintenance of vascular homeostasis. However, in pathological conditions, such as the presence of cardiovascular risk factors, this tissue begins to secrete adipokines and pro-inflammatory cytokines, promoting structural and functional changes in the vascular wall and favoring the formation and progression of atherosclerosis. Specifically in the coronary arteries, this compartment is called pericoronary adipose tissue (PAT), whose evaluation has been carried out through imaging tests, such as computed tomography (Nomura *et al.*, 2020; Goeller *et al.*, 2019).

Pericoronary adipose *tissue (PCAT) analysis* by computed tomography (CT) has been shown to be a promising marker of inflammatory status and coronary artery health. This approach is especially relevant with the increasing use of coronary computed *tomography angiography (CCTA)* in the evaluation of patients with suspected or diagnosed coronary artery disease (CAD). The CCTA allows a comprehensive investigation, including the quantification of the total atherosclerotic burden, the analysis of the severity of the strictures, the functional evaluation of the lesions by means of fractional flow reserve by CT (FFR-CT) or CT-induced pharmacological stress (CT *stress*), in addition to the characterization of the inflammatory component by means of PCAT (Uretsky; Aldaia, 2020). In this scenario, percutaneous coronary intervention is no longer a first-line approach in the diagnostic investigation of CAD, but is reserved for cases indicated after stratification by noninvasive methods.

4.2 ANGINA

Angina pectoris is a classic clinical manifestation of coronary artery disease (CAD), characterized by transient chest pain or discomfort, secondary to myocardial ischemia without necrosis. This pain is usually retrosternal and can radiate to the jaw, neck, left shoulder, and arm. It is commonly triggered by physical exertion, emotional stress, or

exposure to cold, and relieved with rest or nitrate use (Rajkumar *et al.*, 2024; Chotai *et al.*, 2025).

Angina can be classified as stable or unstable, according to the clinical pattern of pain. Stable angina presents predictably, with pain triggered by exertion and relief at rest. Unstable angina, on the other hand, is characterized by the recent onset of symptoms, worsening of the usual pattern, or occurrence at rest, and may progress to acute myocardial infarction. This instability is associated with changes in atherosclerotic plaque, such as rupture or erosion, followed by thrombus formation. Diagnosis and risk stratification are based on clinical evaluation and the use of complementary tests, such as electrocardiogram (ECG), exercise stress test, myocardial scintigraphy, and coronary angiography (Mansur *et al.*, 2012).

The ORBITA study (*Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina - 2024*) made important contributions to the understanding of the efficacy of percutaneous coronary intervention (PCI) in patients with stable angina. When randomizing 200 patients with significant single-vessel CAD using clinical treatment optimized for PCI or placebo procedure, it was observed that, after six weeks, there was no significant difference in the primary outcome between the groups. This finding raised questions about the relationship between symptoms, stenosis, and ischemia (Chotai *et al.*, 2025).

Subsequently, the ORBITA-2 study was conducted with methodological modifications, including less interference from antianginal drugs and longer follow-up time. Its results demonstrated that PCI, in patients with greater selection rigor and without previous intensive use of antianginal medication, provided significant symptomatic improvement, measured by angina scores, reinforcing the role of intervention in specific situations (Chotai *et al.*, 2025).

In the context of Chronic Coronary Syndrome (CCS), PCI continues to be discussed as a therapeutic strategy. Studies such as FAME 2 (*Fractional Flow Reserve versus Angiography for Multivessel Evaluation*) and ISCHEMIA (*International Study of Comparative Health Effectiveness with Medical and Invasive Approaches*) reinforce that PCI guided by invasive physiological assessment, especially fractional flow reserve (FFR) and instantaneous flow reserve index (iFR), is associated with a reduction in angina symptoms and hospitalizations. although it has not demonstrated a significant impact on mortality (Fearon *et al.*, 2025).

Additional analyses of FAME 2 (2012) showed that lower FFR values before PCI, as well as higher deltas between pre- and post-procedure FFR, correlated with greater symptomatic relief, suggesting a direct relationship between the degree of ischemia and the

clinical benefits of the intervention. These findings were reinforced by ORBITA-2 (2023), which showed that patients with reduced FFR or iFR values showed greater functional improvement and reduced angina after PCI.

The comprehensive clinical evaluation of patients with angina should consider not only typical or atypical chest pain, but also variables such as the anatomical location of the lesions, the number of vessels affected, the extent of the disease (assessed by the retraction pressure gradient), and the presence of microvascular dysfunction. The absence of abnormal heart sounds and atypical pain features also influence the clinical interpretation. These elements highlight the importance of an individualized, physiological evidence-driven approach to identifying patients with the greatest potential for benefit from PCI (Fearon *et al.*, 2025).

The main objectives of angina treatment are to control symptoms, improve quality of life, and prevent major cardiovascular events, a study by Fearon *et al.*, 2025 brings therapeutic strategies that include lifestyle changes, strict control of risk factors (such as hypertension, dyslipidemia, diabetes mellitus, and smoking), and the use of antianginal drugs, as beta-blockers, calcium channel blockers, and nitrates. In selected cases, PCI revascularization or coronary artery bypass grafting may be indicated. Evidence indicates that the association between optimized clinical treatment and revascularization provides more significant benefits in patients with high ischemic risk or significant functional impairment.

In the context of ST-segment elevation AMI (STEMI), PCI of an artery unrelated to infarction should follow criteria similar to those of elective PCI. On the other hand, the routine performance of PCI in intermediate or complex strictures during the primary procedure requires careful evaluation. According to Hussain *et al.* (2024), the decision should integrate clinical status, comorbidities, complexity of the lesion, and medical judgment, in order to determine the optimal strategy and timing for PCI in these patients.

4.3 ACUTE MYOCARDIAL INFARCTION (AMI)

Acute Myocardial Infarction (AMI) is a serious clinical condition characterized by the sudden interruption of blood flow in a coronary artery, usually due to the rupture of an unstable atherosclerotic plaque, followed by the formation of a thrombus. This obstruction leads to sustained ischemia and necrosis of myocardial areas, causing significant hemodynamic and electrical repercussions. Clinically, AMI is manifested by intense, oppressive, and persistent chest pain, often accompanied by sweating, nausea, dyspnea, and a feeling of imminent death (Calderaro, D. *et al.*, 2022).

Based on the electrocardiographic findings, AMI is classified into two main forms: ST-elevation (STEMI) and non-ST-elevation (NSTEMI). This distinction is crucial to define the initial therapeutic strategy. STEMI requires emergency reperfusion, preferably by percutaneous coronary intervention (PCI), ideally performed within 90 minutes of symptom onset. NSTEMI, on the other hand, is managed with antithrombotic therapy and clinical and laboratory stratification for an eventual early invasive approach (Ibanez *et al.*, 2018).

In recent decades, mortality from AMI has been significantly reduced due to advances in reperfusion strategies, the use of antithrombotic agents and neurohormonal blockers, as well as the standardization of evidence-based clinical protocols. However, long-term survival still depends on residual ventricular function, the presence of comorbidities, and adherence to treatment. In this context, cardiovascular rehabilitation and lifestyle changes play a central role in the prevention of new events (Biener, M. *et al.*, 2022).

Among the diagnostic resources, cardiac biomarkers represent a fundamental tool for the early detection and risk stratification of AMI. Cardiac troponin (TnI or TnT) is considered the most sensitive and specific marker currently available, allowing the identification of myocardial necrosis even at minimal levels. Its serum increase directly reflects the integrity of the myocyte and has a high prognostic value. Serial troponin dosing is recommended, especially in the first hours after symptom onset, in order to confirm the diagnosis (Biener, M. *et al.*, 2022).

In addition to troponin, other laboratory biomarkers have prognostic relevance in patients with AMI, such as:

- a) B-type natriuretic peptide (BNP and NT-proBNP): indicative of ventricular dysfunction and hemodynamic overload, associated with the risk of heart failure and mortality;
- b) ultrasensitive C-reactive protein (hs-CRP): an inflammatory marker that, when elevated, reflects a higher risk of post-infarction complications;
- c) myoglobin and CK-MB: less used today, but still useful in specific situations, such as early reinfarction or initial rapid evaluation;
- d) emerging biomarkers such as asymmetric dimethylarginine (ADMA), interleukin-6 (IL-6), galectin-3, and soluble ST2 (sST2), studied for correlation with inflammation, myocardial fibrosis, and cardiovascular prognosis (Sabatine, 2022).

Primary PCI is considered the standard treatment for patients with STEMI, with different strategies available, such as balloon angioplasty, uncoated metal stents, drug-eluting stents, thrombus aspiration, direct stent implantation, rotational atherectomy (rotablation), and cutting balloon angioplasty. In cases of multivessel coronary disease, the therapeutic decision must be individualized, and may include PCI only of the culprit vessel,

multivessel PCI in the same procedure, or PCI staged during hospitalization or after discharge (HUSSAIN *et al.*, 2024).

From a therapeutic point of view, multicenter studies have demonstrated the superiority of primary PCI over fibrinolysis in STEMI. The European EORP STEMI registry revealed that, while in 2001 only 20% of patients underwent primary PCI, by 2011 this number had already reached 80% in the member countries of the European Society of Cardiology (ESC), largely due to the *Stent for Life initiative* (Kaifoszova *et al.*, 2014).

International guidelines reinforce primary PCI as the treatment of choice in STEMI (IBANEZ *et al.*, 2018; STEG *et al.*, 2012). However, approximately 10% of patients do not receive early reperfusion, mainly due to late presentation, which contributes to in-hospital mortality of up to 15% (Zeymer *et al.*, 2021). When performed in a timely manner, PCI significantly reduces mortality compared to fibrinolysis, consolidating itself as the main advance in the treatment of coronary artery disease (CAD) in emergency settings.

The effectiveness of ICP in non-emergency contexts, however, has been the subject of debate. Clinical trials such as the *ISCHEMIA Trial* and the *Culprit-Only Revascularization Strategies* have shown benefits in patients with unstable CAD, especially in reducing major cardiovascular events. On the other hand, in patients with stable and asymptomatic CAD, invasive intervention has not demonstrated a significant impact on outcomes such as mortality or new infarctions, underscoring the importance of individualized risk stratification (Chackro, 2020). Thus, the benefit of PCI is proportional to clinical instability and ischemic load, and laboratory biomarkers are fundamental not only for diagnosis, but also as prognostic tools and therapeutic decision support.

In this sense, the meta-analysis by Fazel *et al.* (2020), which systematically reviewed 31 clinical trials, compared different reperfusion strategies in STEMI: fibrinolysis alone (n = 4,212), primary PCI (n = 6,139), and fibrinolysis followed by early PCI (n = 5,006). The outcomes of mortality, nonfatal reinfarction, stroke, and severe bleeding were evaluated using Bayesian analysis. The results showed that primary PCI was the strategy associated with the lowest risk of adverse events, with an odds ratio of 0.73 (95% CI: 0.61–0.89) for mortality compared to fibrinolysis. The invasive drug approach (fibrinolysis followed by early PCI) was the second most favorable, with an odds ratio of 0.79 (95% CI: 0.59–1.08). The study concluded that the invasive drug approach is safer and more effective than facilitated PCI and fibrinolysis alone, highlighting the importance of the interval between fibrinolysis and PCI as a determinant for the prognosis of the disease.

4.4 HEART FAILURE

Heart failure (HF) is a complex clinical syndrome, characterized by the inability of the heart to pump blood adequately to meet the metabolic demands of tissues, or to do so only at the expense of high filling pressures. This condition may result from structural or functional abnormalities that compromise ventricular filling, blood ejection, or both. From the pathophysiological point of view, HF establishes a vicious cycle of compensatory neurohormonal activation, mainly involving the sympathetic nervous system and the renin-angiotensin-aldosterone system. Although these mechanisms temporarily maintain tissue perfusion, they progressively contribute to ventricular remodeling, sodium and water retention, and deterioration of cardiac function. This process results in typical clinical manifestations, such as dyspnea, fatigue, orthopnea, peripheral edema, and exercise intolerance (Oliveira *et al.*, 2023)

The classification of HF is based on left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF), when $LVEF < 40\%$; preserved ejection fraction (HFpEF), when $LVEF \geq 50\%$; and intermediate form, when LVEF is between 40 and 49%. This stratification has prognostic and therapeutic relevance, directing specific pharmacological conducts. The diagnosis of the syndrome should be based on clinical evaluation, complemented by imaging tests, such as echocardiography, which allows the analysis of systolic and diastolic function. In addition, biomarkers, such as B-type natriuretic peptide (BNP) or NT-proBNP, have diagnostic and prognostic value, helping to differentiate causes of dyspnea and monitor the progression of the disease (Steg *et al.*, 2012).

The treatment of HF is multifactorial, encompassing lifestyle changes, sodium restriction, strict control of comorbidities (hypertension, diabetes mellitus, obesity, among others) and the use of drugs with proven efficacy in reducing mortality and hospitalizations. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, aldosterone antagonists, neprilysin inhibitors in combination with angiotensin receptor antagonist (sacubitril-valsartan) and, more recently, sodium-glucose cotransporter type 2 inhibitors (iSGLT2). In cases refractory to optimized clinical treatment, ventricular assist devices, cardiac resynchronization therapy, or, ultimately, heart transplantation are indicated, especially in young patients with a low burden of comorbidities (Oliveira *et al.*, 2023).

HF is a relevant public health problem, due not only to the high rates of hospitalization and mortality, but also to the functional, emotional, and economic impact on patients and caregivers. In this context, primary prevention, based on the control of cardiovascular risk factors and the early detection of subclinical cardiac dysfunction, represents a fundamental

strategy to contain the progression of the syndrome. It is important to emphasize that HF, in isolation, does not constitute a direct criterion for percutaneous coronary intervention (PCI). However, in patients with significant coronary artery disease or other associated cardiovascular conditions, HF may be a complication that justifies the indication of the procedure (Steg *et al.*, 2012).

Heart failure with preserved ejection fraction (HFpEF) corresponds to a specific clinical entity, defined by the presence of HF signs and symptoms associated with an LVEF $\geq 50\%$. The universal definition states that, in addition to maintaining the ejection fraction, elevated levels of natriuretic peptides and objective evidence of functional or structural abnormalities, with signs of pulmonary or systemic congestion, must be present (Kittlesen *et al.*, 2023).

The prevalence of HFpEF is on the rise, driven by population aging, increased obesity, and high incidence of cardiometabolic disorders. The diagnosis, however, is challenging, since associated comorbidities, such as pulmonary or renal disease, can confuse the interpretation of symptoms and clinical signs. Although clinical evaluation is essential, complementary tests, such as chest X-ray, echocardiography, and hemodynamic measurement (pulmonary artery or right heart catheterization), are often necessary for diagnostic confirmation. In some cases, stress tests associated with echocardiography or right heart catheterization allow to demonstrate increased filling pressures, especially in patients with unexplained intolerance to physical exercise (Bozkurt *et al.*, 2021).

In the context of HFpEF, percutaneous intervention is not considered a central therapeutic strategy. The priority remains in the optimization of clinical treatment, the control of associated comorbidities, and the adoption of measures that improve the patient's quality of life. Thus, detailed diagnostic investigation and individualized approach are essential for the proper management of this population (Bozkurt *et al.*, 2021).

5 HEMODYNAMICS SERVICE

The Hemodynamics Service, also called Interventional Cardiology, is a medical subspecialty focused on performing minimally invasive procedures aimed at the diagnosis and treatment of diseases of the cardiovascular system. This approach, less aggressive when compared to conventional surgeries, has gained increasing prominence in the face of the increase in the incidence of cardiovascular diseases, as it allows safe, effective interventions with shorter recovery time for patients. Among the main procedures performed in this service are cardiac catheterization, vascular arteriography, coronary angioplasty, electrophysiological studies with ablation of arrhythmias, embolization of vascular

malformations and implantation of endoprotheses. These techniques aim to restore blood flow, diagnose obstructions, and correct structural anomalies in a precise and minimally invasive way (Ribeiro; Filho, 2008).

Coronary angiography, also known as cardiac catheterization, is considered the gold standard for diagnosing coronary artery disease (CAD). It is an imaging test that, through the injection of iodinated contrast directly into the coronary arteries, allows the radiological visualization of the arterial lumen and the identification of stenosis or occlusions (Abizaid *et al.*, 2013).

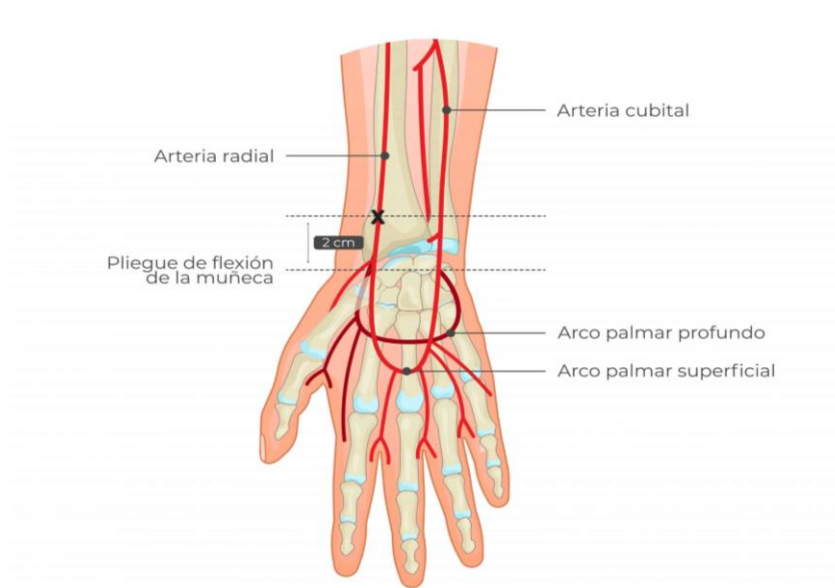
The initial milestone of percutaneous coronary intervention occurred in 1977, at the University of Zurich, when Andréas Roland Gruentzig performed the first percutaneous transluminal angioplasty in a patient with critical obstruction of the anterior descending artery, using a balloon catheter inserted via femoral access. This procedure inaugurated a new era in the treatment of ischemic heart disease, enabling the development of increasingly advanced techniques and devices of interventional cardiology (Ribeiro; Filho, 2008).

Coronary angioplasty aims to remodel the atherosclerotic plaque, transforming an obstructive lesion into a stable and non-obstructive condition, favoring myocardial perfusion and reducing ischemic symptoms. With the evolution of the technique, the use of stents, expandable devices responsible for maintaining the arterial lumen after dilation, was incorporated, which significantly reduced restenosis rates and increased therapeutic efficacy (Woods, 2005).

Arterial access is a critical step in percutaneous procedures, being defined according to the clinical characteristics of the patient and the experience of the medical team. Initially performed through the brachial approach, the approach evolved to the femoral approach and, more recently, to the radial approach, currently preferred because it offers greater safety, ease of compression and lower rate of hemorrhagic complications (Abizaid *et al.*, 2013).

Figure 1

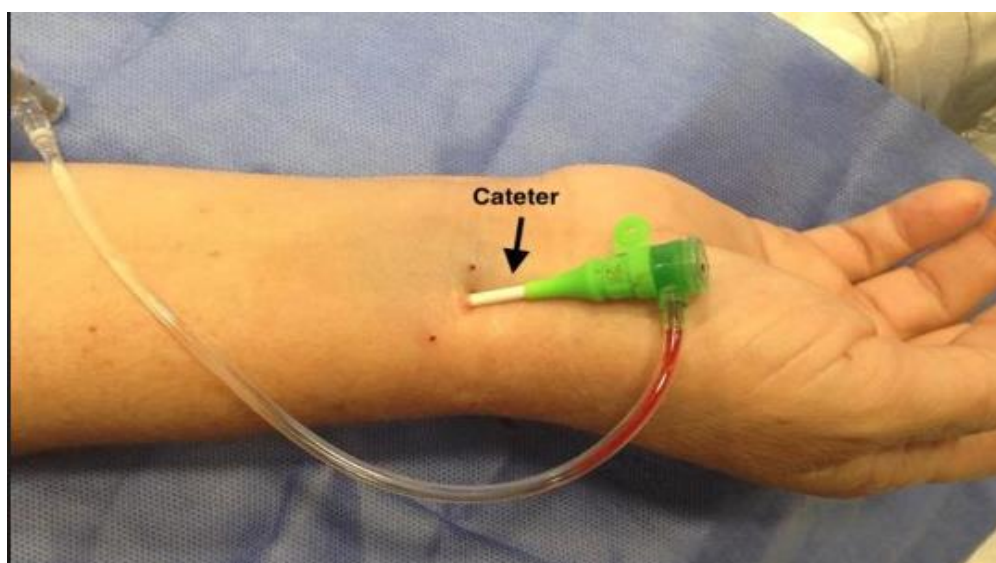
Anatomical location for radial artery puncture



Source: Adapted from Guedes A. (2012).

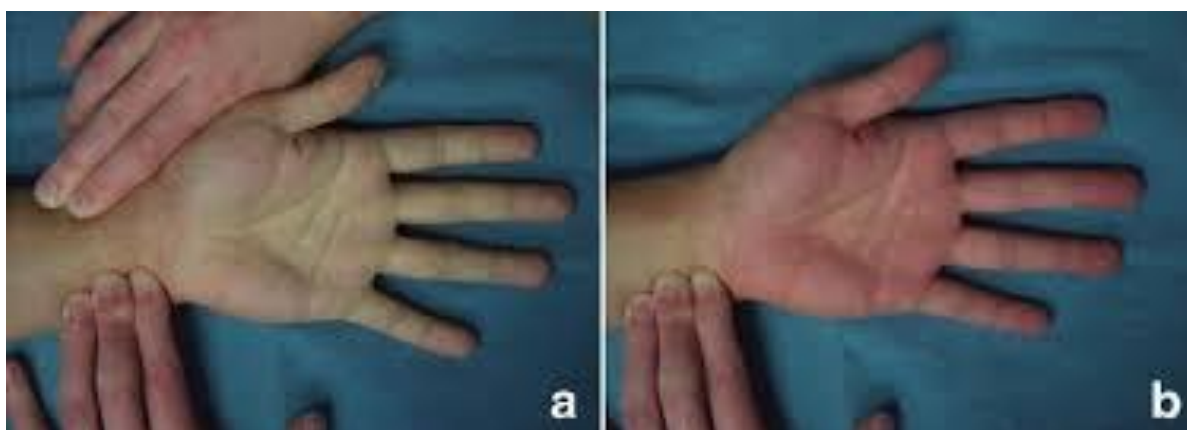
Figure 2

Radial access in hemodynamic services



Source: Adapted from medizy.com.

To choose the radial approach, it is recommended that the patency of the palmar arches be previously evaluated using the Allen test. The test is considered normal when there is return of palmar perfusion within 10 seconds after the release of the flow through the ulnar artery. This procedure can be performed with a pulse oximeter on the thumb, observing the presence or absence of the pulse wave. The results are classified into types A to D, with type D being a contraindication for the radial approach (Abizaid *et al.*, 2013).

Figure 3*Allen test*

Source: Adapted from medizzy.com.

Legend: Allen Test Method of Performance. A) Negative Allen's test, the return of the reddish color of the palm of the hand takes more than 10 seconds, indicating that the circulation parallel to the radial artery is not intact. B) Positive Allen test, the blood flow of the ulnar artery should reperfuse the vessels of the hand in less than 10 seconds, being identified by the return of the reddish color to the palm of the hand.

The radial artery puncture technique must follow standardized protocols in order to ensure safety and efficacy. Because it has a high density of adrenergic receptors, the radial artery requires specific measures to prevent spasms, such as the administration of analgesics and sedatives. Proper positioning of the patient is essential, and the right arm is often used on an acrylic support (Woods, 2005)

Local anesthesia is performed with 0.5 to 1.0 mL of 2% lidocaine. Next, the Seldinger technique is applied, using a short 22G or 20G catheter, with the bevel facing upwards, and a 0.021-in metal guide. After puncture, a 5 or 6 Fr hydrophilic sheath is introduced. To prevent thrombosis, 5,000 IU of heparin is administered; in cases of arterial spasm, nitroglycerin can be used in doses of 100 to 200 mcg (Abizaid *et al.*, 2013).

Radial coronary angiography uses the same pre-molded catheters applied in the femoral approach. For the left coronary artery, the JL 3.5 or 4.0 type catheter is used; to the right, the JR 4.0 catheter is used. Ventriculography is performed with a pigtail catheter. Catheter exchange occurs with the aid of a 0.035-in teflon guide with a J-tip (Abizaid *et al.*, 2013). After the procedure, compression of the radial artery is performed to obtain hemostasis, which can be achieved by different methods. The hemostatic process, as described by Woods (2005), involves the sequential activation of coagulation factors, resulting in the formation of a fibrin clot at the site of vascular injury and preventing blood leakage. Disturbances in this process can result in bleeding of different intensities, from petechiae and ecchymosis to severe hemorrhages.

In this sense, Petroglou (2018) compared manual and mechanical compression after transradial angiography, concluding that mechanical compression tends to be more effective, as it offers continuous and stable pressure, reducing hemostasis time, the occurrence of bleeding, and the risk of radial artery occlusion (RAO). Such evidence reinforces the importance of maintaining vessel patency, especially in view of the increased use of radial access in cardiovascular therapies.

In order to assist in this process, different hemostasis devices have been employed. Santos *et al.* (2018) reported the use of the TR Band device (Terumo Medical, Tokyo, Japan), similar to a transparent bracelet. Positioned directly over the introducer insertion hole, it is inflated with 15 mL of air through a syringe, promoting controlled compression. After removal of the sheath, the antegrade flow of the radial artery is maintained, ensuring adequate distal perfusion. The removal protocol provides for gradual deflation of 3 mL every 30 minutes, starting two hours after the procedure. In cases of bleeding, the balloon is re-inflated with 5 mL of air and the protocol is restarted after 60 minutes.

Santos *et al.* (2018) also describe an alternative hemostasis technique, conducted by a nursing professional with medical support, which consists of applying a roll of compressive gauze over the puncture site, fixed with a tape band. On the dressing, two strips of adhesive tape are applied crossed in an "X" shape, without fully involving the limb. After 3 to 4 hours, the dressing is removed, as long as there is no active bleeding, and the site is protected with a simple dressing consisting of gauze and tape.

5.1 CARDIAC CATHETERIZATION

Cardiac catheterization has its origins in 1844, when Claude Bernard performed pioneering experiments in catheterization of the jugular veins and carotid artery in horses, allowing hemodynamic measurements in cardiac chambers. In 1929, Werner Forssmann proved the feasibility of intracardiac access in humans by introducing a ureteral catheter into his own right atrium, paving the way for clinical techniques. The modern era of interventional cardiology was consolidated in 1958, with Mason Sones at the Cleveland Clinic, when he developed coronary cineangiography and initiated percutaneous interventions (Ribeiro; Filho, 2008).

5.1.1 Right Heart Catheterization

Right heart catheterization is performed intravenously - femoral, internal jugular, subclavian or antecubital - and enables hemodynamic evaluation of the right chambers and pulmonary circulation. Its main indications include:

- a) determination of cardiac output in advanced heart failure;
- b) diagnosis of pulmonary hypertension;
- c) detection of intracardiac shunts;
- d) investigation of cardiomyopathies, constrictive pericarditis, and cardiac tamponade (Jatene *et al.*, 2022).

The most frequent complications involve inadvertent arterial puncture, formation of pseudoaneurysm or arteriovenous fistula, lymphatic duct injury and, in rare cases, rupture of pulmonary vessels or episodes of hypoxia (Ribeiro; Filho, 2008).

5.1.2 Left Cardiac Catheterization and Coronary Angiography

Left heart catheterization, also called coronary angiography, is the gold standard for the study of coronary anatomy. The procedure begins with arterial puncture (femoral or radial), followed by careful introduction of catheters to the root of the aorta and selective catheterization of the coronary ostia. The injection of iodinated contrast, combined with serial radiographic projections, allows the identification of the arterial lumen, quantify the degree of stenosis, and evaluate vascular morphology (Jatene *et al.*, 2022).

Coronary anatomy is presented in two main systems:

- a) left coronary artery: originates from the left coronary sinus and bifurcates into the anterior descending artery (ADA) and circumflex artery (ACX), supplying a large part of the myocardium;
- b) right coronary artery (RCA): arises from the right coronary sinus, runs through the atrioventricular sulcus, and divides into the crux cordis into the posterior descending and posterolateral branches.

5.2 RADIOGRAPHIC PROJECTIONS AND VENTRICULOGRAPHY

For an accurate analysis, each artery must be evaluated in at least two distinct projections, avoiding overlapping segments. Ventriculography, often performed together, provides information on global and segmental systolic function, presence of intracavitary thrombi, and mitral regurgitation. It is contraindicated in patients with mechanical aortic prosthesis, known ventricular thrombus, decompensated heart failure, or acute pulmonary edema (Ribeiro; Filho, 2008).

5.3 AORTOGRAPHY AND PRINCIPLES OF LUMINOGRAPHY

Intraventricular aortography can be used to evaluate the aortic valves, the diameter of the aortic root, and to identify dissections. However, the additional use of contrast

increases the risk of induced nephropathy, and a careful risk-benefit assessment is necessary. Luminography, a fundamental technique in angiography, exclusively delineates the luminal contour of the vessels, without allowing direct analysis of the arterial wall (Ribeiro; Filho, 2008).

5.4 CORONARY ANGIOPLASTY

Coronary angioplasty, also called percutaneous coronary intervention (PCI), is a therapeutic strategy frequently performed after the diagnosis of relevant obstructive lesions during catheterization. The procedure can be performed in two main ways: with a balloon or with stent implantation (Ribeiro; Filho, 2008).

Balloon angioplasty consists of the introduction of a balloon catheter to the site of stenosis, where controlled balloon inflation occurs, promoting artery dilation and atherosclerotic plaque remodeling. This process generates a "controlled injury" to the arterial wall, redistributing plaque along the vessel and restoring blood flow. The clinical efficacy of this technique is high, with symptomatic relief in about 90% of treated patients (Abizaid *et al.*, 2013).

Angioplasty with *stent*, in turn, represents the evolution of percutaneous treatment, and is currently the most used method. The stent is a small expandable metal structure implanted inside the coronary artery, with the objective of maintaining the luminal diameter after dilation and avoiding restenosis. *Stents* can be classified as conventional (*bare-metal stents*) or pharmacological (*drug-eluting stents*), the latter coated with antiproliferative drugs that significantly reduce the incidence of vessel re-obstruction (Ribeiro; Filho, 2008).

Historically, the term "*stent*" was first used in 1916 by Dutch plastic surgeon Jan Esser, in reference to a dental prosthesis developed by English dentist Charles Thomas Stent. Initially, stents were produced with metal alloys such as nitinol, tantalum, platinum and stainless steel, materials that are easy to handle and have good biocompatibility. However, some limitations, such as low radiopacity, reduced flexibility, and high nickel content, potentially allergenic, have led to the search for new compositions (Abizaid *et al.*, 2013).

As an alternative, stents made of cobalt-chromium alloys appeared, which presented greater radiological visibility, thinner stems, and less nickel in their structure. Subsequently, platinum was incorporated into metal alloys, resulting in stents with superior properties, such as greater malleability, corrosion resistance, and lower risk of fracture. These innovations contributed to the technical improvement of the procedure and to the expansion of its safety and clinical efficacy (Abizaid *et al.*, 2013).

6 HEMODYNAMIC COMPLICATIONS

Despite technological advances and the wide use of coronary angiography as a diagnostic and therapeutic tool in the context of cardiovascular diseases, the procedure is not without risks, especially when performed in populations with greater clinical vulnerability. As described by Jatene *et al.* (2022), although coronary angiography is currently considered a safe test in elective scenarios, it is essential to carefully evaluate the risk-benefit ratio before performing it, especially in patients with factors predisposing to complications.

Among the main risk factors are: advanced age, presence of complex congenital heart diseases (especially in children), significant lesions in the left main coronary artery, multivessel coronary artery disease, advanced peripheral arterial disease, severe ventricular dysfunction with heart failure, diabetes mellitus using insulin and important valvular heart diseases, such as aortic stenosis. These factors require individualized planning in order to mitigate the risks inherent in the procedure (Jatene *et al.*, 2022).

Also according to Jatene *et al.* (2022), the most common complications associated with the test and their estimated frequency include: deaths (0.08%), acute myocardial infarction (0.05%), stroke (0.07%), cardiac arrhythmias (0.4%), vascular complications (0.5%), and adverse reactions to iodinated contrast (0.4%). Although relatively rare, these complications can have significant clinical implications, requiring close attention to pre-procedure preparation and post-intervention monitoring.

Perioperative drug management should also be carefully adjusted. Drugs such as metformin should be discontinued 24 to 48 hours before the procedure, with reintroduction only after 48 hours or after normalization of renal function, in order to avoid the risk of lactic acidosis. Direct anticoagulants, such as rivaroxaban, apixaban, and dabigatran, should be stopped at the same interval, with resumption 24 hours after the procedure. Antiplatelet agents, such as acetylsalicylic acid (ASA), should be maintained. In the case of patients using coumarin anticoagulants (such as warfarin), it is recommended to suspend them for five days before the procedure, with a target International Normalized Ratio (INR) between 1.5 and 1.8 at the time of the intervention. In these cases, full heparinization can be considered as a therapeutic bridge, especially in patients with high thromboembolic risk. It is important to note that, in emergency situations, these pharmacological protocols often cannot be followed, prevailing the clinical conduct aimed at preserving the patient's life and hemodynamic stabilization. Thus, the management of hemodynamic complications requires a trained multidisciplinary team, adequate hospital structure and well-established clinical protocols to ensure the safety and efficacy of the procedure (Ribeiro, Filho, 2008).

6.1 VASCULAR COMPLICATIONS

6.1.1 Clinical Complications of Patients Undergoing Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI), although widely disseminated and considered a safe and effective procedure for the treatment of coronary artery disease, may be associated with different clinical complications. The occurrence of these complications is often related to the clinical profile of patients, usually with multiple comorbidities, and to the emergency situations in which the technique is applied (Jatene *et al.*, 2022).

According to Ribeiro (2008), the most prevalent complications are associated with arterial puncture sites, especially femoral and radial punctures, manifesting in the form of hematomas, pseudoaneurysms and bleeding. Less frequently, events such as neurological lesions, lymphatic fistulas, catheter fragmentation, incoercible bleeding, and even stent migration may occur.

Cerebrovascular events, although uncommon, deserve to be highlighted due to their high severity and potential prognostic impact. These events may manifest during or immediately after PCI, and in some cases, diagnosis may be delayed by up to 36 hours. Vascular spasms and idiosyncratic reactions to iodinated contrast medium represent less frequent, but still relevant, causes of post-procedure neurological changes (Ribeiro; Filho, 2008).

Another complication of clinical relevance is contrast-induced nephropathy (CIN), characterized by acute worsening of renal function after exposure to iodinated contrast. CIN is at higher risk in patients with impaired baseline renal function, and its occurrence is related to factors such as total volume and type of contrast used, presence of comorbidities (especially diabetes mellitus), advanced age, episodes of hypotension, heart failure, and elevated serum creatinine levels before the procedure. Prevention strategies include adequate hydration, judicious use of contrast, choice of agents with less nephrotoxicity and, in selected cases, the use of medications with a nephroprotective effect.

Currently, it is observed that patients undergoing PCI have increasingly complex clinical and anatomical profiles, which reinforces the need to adopt additional safety measures. In this context, the use of ultra-low contrast agents is highlighted, with the objective of reducing the risk of renal complications without compromising diagnostic quality. The conscious performance of the professional regarding the selection of catheters, guidewires and auxiliary techniques is essential to minimize risks. In addition, the incorporation of advanced methods, such as intracoronary imaging (OCT- optical coherence tomography and IVUS - intravascular ultrasound) and invasive physiology, should be

prioritized whenever possible, partially replacing the need for contrast to ensure safer and more accurate results in PCI (Hennessey, 2023).

Technological advances and the availability of new navigation tools, such as dynamic coronary mapping and co-registration technologies, have been simplifying interventions and expanding the safety margin for high-risk patients, consolidating PCI as an increasingly effective and safe procedure (Hennessey, 2023).

6.1.2 Complications in the Access Road

Complications related to the arterial access route, whether femoral or radial, represent one of the main challenges in the post-procedure period of percutaneous coronary intervention (PCI). Strict care in the immediate postoperative period is essential for the early detection and appropriate management of these complications, which, if not identified in a timely manner, can progress to more severe conditions, requiring surgical intervention, blood transfusion, or even risk of death (Abizaid *et al.*, 2013).

According to Abizaid *et al.* (2013), among the most frequently observed complications at arterial puncture sites are: local hematomas, femoral artery pseudoaneurysms, retroperitoneal hematoma (particularly associated with femoral access), arteriovenous fistula, significant hemorrhages, arterial thrombosis, and local infections. The occurrence of these events is related to factors such as inadequate puncture technique, use of anticoagulants, advanced age, obesity, and lack of effective compression after removal of the vascular sheath.

Regarding the radial approach, although it has a lower rate of hemorrhagic complications compared to the femoral approach, there are contraindications that should be strictly observed. According to Abizaid *et al.* (2013), the radial approach should not be used in cases of Raynaud's disease, post-mastectomy upper limb lymphedema, presence of arteriovenous fistula (AVF) for hemodialysis, provision for the use of the radial artery as a graft in coronary artery bypass grafting, and lack of adequate collateral circulation between the superficial and deep palmar arches.

Kotowycz *et al.* (2012) describe that the radial and ulnar arteries are connected at the wrist by the deep and superficial palmar arches. Thus, if the radial artery is occluded, hand perfusion is usually maintained by increasing flow in the ulnar collateral circulation. To evaluate this circulation, the modified Allen test is used, which is considered a simple qualitative method. In this examination, the patient is instructed to clench the fist, while the examiner simultaneously compresses the radial and ulnar arteries. Then, the patient relaxes the hand, the ulnar artery is released, and the time required for the return of maximum palmar

flushing is recorded. Return within 5 to 10 seconds is considered normal, indicating adequate collateral circulation. Acute loss of radial artery patency after cardiac catheterization is often related to a thrombotic process, resulting from local endothelial injury and interruption of blood flow after sheath insertion.

Transradial access (ART) has been consolidated as the preferred route in PCIs due to the reduction of hemorrhagic complications. However, radial artery occlusion (RAO) can occur and often goes undetected clinically due to the dual blood supply to the hand. Munir *et al.* (2022) report that more than 50% of operators do not assess radial artery patency after PCI. In the initial phase of RAO, thrombi formation occurs due to endothelial injury and reduced blood flow after cannulation. Repeated manipulations of the catheter increase the risk of thrombosis. In general, RAO manifests soon after catheterization, but about 50% of patients undergoing ART procedures have spontaneous recanalization of the radial artery within three months. The incidence described in the literature ranges from 1.5% to 30.5%, with a mean of 5% to 12% of patients undergoing ART. Once occluded, the radial artery cannot be reused as an access route in future catheterizations or as an arterial graft in coronary artery bypass graft surgeries, in addition to making the ipsilateral ulnar artery vulnerable to the risk of hand ischemia.

Also according to Munir *et al.* (2022), advances in interventional cardiology require specific knowledge and skills for careful evaluation of access routes, especially in view of the growing adoption of the radial approach as a preferred choice. The preservation of radial artery patency is essential, especially in patients who require serial procedures. Strategies to minimize RAO include the use of smaller sheaths or even sheathless guides, adequate anticoagulation, and non-occlusive hemostasis. It is also recommended that the radial artery patency be systematically evaluated before hospital discharge, in addition to individualized clinical follow-up, in order to ensure greater safety and preservation of the access route for future procedures.

7 FINAL CONSIDERATIONS

Scientific evidence reinforces that cardiovascular diseases are one of the greatest challenges to public health, requiring increasingly resolute care responses. In this scenario, hemodynamic services play a strategic role by integrating accurate diagnosis and immediate intervention, which are decisive for reducing morbidity and mortality, especially in acute coronary syndromes.

Percutaneous coronary intervention has been consolidated as a therapeutic strategy for the identification and treatment of myocardial ischemia, bringing benefits to the individual

in restoring coronary flow and improving clinical outcomes. It is known that the precise investigation of the health professional in the face of patients with symptoms of coronary disease is essential for the good prognosis of the patient.

In percutaneous coronary intervention, the patient is exposed to surgical intervention in which the occurrence of vascular complications related to the percutaneous access route, even in established techniques such as the radial approach, shows that technological advances do not eliminate risks inherent to the procedure, especially in individuals affected by determinant diseases and established risk factors. In this sense, the identification of clinical and laboratory predictors of changes in arterial patency emerges as a key element for risk stratification and for more assertive clinical decision-making.

Thus, in hemodynamic services, it is essential to develop strategies and skills that reinforce the need for continuous qualification of care processes. Seeking improvements in processes through future investigations that validate predictive models and expand the applicability of findings, aiming to consolidate strategies that concretely impact patient safety and quality of care in interventional cardiology.

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WOMEN'S PERCEPTIONS OF THE SIGNS AND SYMPTOMS OF CLIMACTERIC ASSOCIATED WITH SEXUAL ACTIVITY

PERCEPÇÕES DE MULHERES SOBRE OS SINAIS E SINTOMAS DO CLIMATÉRIO ASSOCIADOS À ATIVIDADE SEXUAL

PERCEPCIONES DE LAS MUJERES SOBRE LOS SIGNOS Y SÍNTOMAS DEL CLIMATERIO ASOCIADOS CON LA ACTIVIDAD SEXUAL



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ABSTRACT

Objective: To investigate women's perceptions of climacteric signs and symptoms associated with sexual activity at a Basic Health Unit in the Federal District.

Method: This is a descriptive-exploratory study with a qualitative approach, conducted at a Basic Health Unit in the Federal District. Participants were 30 women aged 40 to 65 years, interviewed between February and April 2025. A semi-structured questionnaire containing sociodemographic data and open-ended questions about the physical and psychological changes of climacteric, sexuality, and the impact of symptoms on sex life was used. The interviews were analyzed using Bardin's Content Analysis.

Results: Three categories emerged: physical and psychological aspects related to menopause; difficulties and challenges in the area of sexuality; and social repercussions and coping strategies adopted by women. Participants reported symptoms such as hot flashes, irritability, anxiety, vaginal dryness, and weight gain, which directly affected self-esteem, well-being, and sexuality. In the social sphere, changes in family and marital relationships were observed. As coping strategies, spiritual support, dialogue, and the use of herbal teas were highlighted.

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Final considerations: the findings demonstrated that menopause is experienced in a complex way, with profound repercussions on sexual activity, and the need for a more sensitive and comprehensive approach in Primary Health Care.

Keywords: Climacteric. Women. Sexuality. Signs and Symptoms. Perception.

RESUMO

Objetivo: Investigar as percepções das mulheres sobre os sinais e sintomas do climatério associados à atividade sexual, em uma Unidade Básica de Saúde do Distrito Federal.

Metodologia: Estudo descritivo-exploratório, com abordagem qualitativa, realizado em uma Unidade Básica de Saúde do Distrito Federal. Participaram 30 mulheres na faixa etária de 40 e 65 anos, entrevistadas entre fevereiro e abril de 2025. Utilizou-se um roteiro semi estruturado contendo dados sociodemográficos e questões abertas sobre as alterações corporais e psicológicas do climatério, sexualidade e impacto dos sintomas na vida sexual. As entrevistas foram analisadas por meio da Análise de Conteúdo de Bardin.

Resultados: Emergiram três categorias: aspectos físicos e psicológicos relacionados ao climatério; dificuldades e desafios no campo da sexualidade; e repercussões sociais e estratégias de enfrentamento adotadas pelas mulheres. As participantes relataram sintomas como fogachos, irritabilidade, ansiedade e ressecamento vaginal, além do aumento de peso, que afetaram diretamente a autoestima, o bem-estar e a sexualidade. No campo social, observaram-se alterações nas relações familiares e conjugais. Como estratégias de enfrentamento, destacaram-se o apoio espiritual, o diálogo e uso de chás.

Considerações finais: Os achados demonstraram que o climatério é vivenciado de forma complexa, com profundas repercussões na atividade sexual, e a necessidade de uma abordagem mais sensível e integral na Atenção Primária à Saúde.

Palavras-chave: Climatério. Mulheres. Sexualidade. Sinais e Sintomas. Percepção.

RESUMEN

Objetivo: Investigar las percepciones de las mujeres sobre los signos y síntomas climatéricos asociados con la actividad sexual en una Unidad Básica de Salud del Distrito Federal.

Método: Estudio descriptivo-exploratorio con enfoque cualitativo, realizado en una Unidad Básica de Salud del Distrito Federal. Participaron 30 mujeres de 40 a 65 años, entrevistadas entre febrero y abril de 2025. Se utilizó un cuestionario semiestructurado con datos sociodemográficos y preguntas abiertas sobre los cambios físicos y psicológicos del climaterio, la sexualidad y el impacto de los síntomas en la vida sexual. Las entrevistas se analizaron mediante el Análisis de Contenido de Bardin.

Resultados: Surgieron tres categorías: aspectos físicos y psicológicos relacionados con la menopausia; dificultades y retos en el ámbito de la sexualidad; y repercusiones sociales y estrategias de afrontamiento adoptadas por las mujeres. Las participantes reportaron síntomas como sofocos, irritabilidad, ansiedad, sequedad vaginal y aumento de peso, que afectaron directamente su autoestima, bienestar y sexualidad. En el ámbito social, se observaron cambios en las relaciones familiares y de pareja. Como estrategias de afrontamiento, se destacaron el apoyo espiritual, el diálogo y el uso de infusiones.

Consideraciones finales: los resultados demostraron que la menopausia se experimenta de forma compleja, con profundas repercusiones en la actividad sexual, y la necesidad de un enfoque más sensible e integral en la atención primaria de salud.

Palabras clave: Climaterio. Mujeres. Sexualidad. Signos y Síntomas. Percepción.

1 INTRODUCTION

Over the decades, Brazil has been undergoing significant changes in its demographic transition, which directly impacts an aging population. Therefore, the health area has also undergone changes to serve this specific population, which has age-related pathologies and particular health issues (Santos *et al.*, 2021).

Regarding women's health, such a change in society reflects a greater number of women who face the climacteric/menopause phase. In this context, nursing consultations are a key element in health care, offering a better quality of life for climacteric women (Santos *et al.*, 2022).

Climacteric in the female population occurs during aging, in the age group of 40 to 65 years, being a phase that is characterized by the transition between the reproductive and non-reproductive period with a drop in steroidal hormones (Gonçalves *et al.*, 2023).

This hormonal transition phase encompasses the stages of premenopause, perimenopause, the phase closest to menopause, and menopause itself. During pre- and perimenopause, there is a progressive reduction in ovarian function, which causes changes in the menstrual cycle, making it irregular until its complete interruption. The absence of menstruation for 12 consecutive months characterizes the diagnosis of menopause, followed by the postmenopausal period. Generally, the climacteric begins around the age of 40 and can extend until approximately 65 years of age, with most women reaching menopause between the ages of 45 and 54 (Namazi *et al.*, 2019; Brazil, 2020; Santoro *et al.*, 2021).

In this phase, women have health promotion and prevention needs, since climacteric syndrome brings with it a set of associated signs and symptoms that affect daily life. These changes manifest as hot flashes (hot flushes), sweating, genital atrophy, vasomotor symptoms, vaginal dryness, decreased libido, insomnia, fatigue, and joint pain (Baccaro *et al.*, 2022; Silveira *et al.*, 2023).

In view of this, the changes that occur in a woman's body have a significant impact on her adaptation process, and sexuality is an aspect that must be taken into account in the quality of life of the climacteric period, considering that the symptomatology impairs their general well-being. Sexuality is not limited to sexual activity, it involves different ways of expressing vital energy, such as pleasure/displeasure, desires, needs, the ability to connect with people and even life itself, deserving your due attention (Freitas *et al.*, 2024).

In addition, all the changes faced during this period are of great importance, as they affect not only the physical, but also the psychological and social aspects of women, in order to impact their social relationships, marital life, which consequently negatively impacts their integral health (Silveira *et al.*, 2023).

During the climacteric, many of the physiological and emotional changes experienced by women are not fully understood by their social circle, including friends, family and partners, which can generate feelings of insecurity and isolation. The lack of support during this period can negatively impact self-esteem, adaptation, and communication about one's own feelings (Magüida *et al.*, 2024). Thus, the support of health professionals becomes essential.

Primary Health Care (PHC) plays a fundamental role as the gateway for these women to the Health System, offering welcoming, active and qualified listening, and also health promotion. All these actions contribute to the integrality of care, meeting the demands of women beyond their physical signs and symptoms, by providing support, guidance, and health education (Luz and Frutuoso, 2021).

This study is relevant to explore aspects that are still poorly understood about the signs and symptoms of the climacteric and its relationship with female sexuality. The scarcity of recent research on the subject reinforces the importance of the investigation, which may generate results capable of supporting both women and health professionals, in Brazil and in other countries.

In this scenario, a gap in knowledge is evidenced, associated with a theme that deserves greater attention, considering its direct impact on women's health and quality of life. In this context, a qualitative study was developed guided by the following guiding question: What are women's perceptions about the signs and symptoms of the climacteric associated with sexual activity? The objective of this study was to investigate women's perceptions of the signs and symptoms of climacteric associated with sexual activity, in a Basic Health Unit (BHU) in the Federal District (DF).

2 METHODOLOGY

This is a descriptive and exploratory study with a qualitative approach, developed in a Basic Health Unit (BHU) in an administrative region of the Federal District (DF). To carry it out, 30 women assisted by this UBS were interviewed.

The inclusion criteria consisted of: heterosexual women aged 40 to 65 years, in the climacteric. The exclusion criteria were: Women who had a mental disorder or health problems that prevented them from communicating or understanding the study instructions and/or who refused to participate in the research.

Data collection was carried out from February to April 2025. After the approval of the research project, a semi-structured script was applied with two parts: the first referred to sociodemographic profile data and included the following variables: age, education, salary

income, marital status and climacteric period in which they were: pre-menopause or post-menopause, sexual frequency and whether they used hormone replacement therapy.

The second involved five subjective and unstructured questions about the body and psychological changes of the climacteric, the difficulties and challenges in the field of sexuality and the impact of the signs and symptoms of the climacteric on women's sexual activity.

After agreeing and signing the Informed Consent Form, as well as the Authorization Term for the Use of Voice Sound for research purposes, data collection was carried out. The interviews, conducted by the field researchers in a single meeting, lasted an average of 30 minutes. Participants were invited to join the study before or after medical and gynecological nursing consultations. The conversations took place individually, in an office with closed doors, in order to ensure greater privacy and comfort for the women.

To ensure the anonymity of the participants, the letter "M" was adopted followed by sequential numbering in numerical digits. Qualitative data were obtained through recordings, fully transcribed and analyzed according to the content analysis technique proposed by Bardin (2016), which includes the interpretation and categorization of narratives, considering the subjectivity present in them. In addition, a field diary was used to record impressions about the context and the participants. For the treatment of data referring to the sociodemographic profile, simple descriptive statistics were applied.

The ethical principles established by Law No. 14,874 of 05/28/2024 were respected, with the approval of the Ethics Committee for Research with Human Beings in Health of the Foundation for Teaching and Research in Health Sciences – CEP/FEPECS under opinion 7.318.647 and CAAE: 84870424.0.0000.5553.

3 RESULTS

Regarding the sociodemographic profile, of the 30 climacteric women interviewed, eight (n=8) were between 40 and 49 years of age, eleven (n=11) women were between 50 and 55 years old, four (n=4) between 56 and 60 years old and seven (n=7) between 61 and 65 years old, respectively. The mean age was 53.86 years.

Regarding marital status, eleven (n=11) were married, one (n=1) had a stable union, four (n=4) divorced, three (n=3) widowed and eleven (n=11) single.

Regarding the level of education, seven (n=7) had incomplete elementary school, four (n=4) had incomplete high school, fifteen (n=15) had completed high school, one (n=1) had incomplete higher education, and three (n=3) had completed higher education.

Regarding wage income, eighteen (n=18) of them had an income of up to one minimum wage, seven (n=7) had an income of up to two minimum wages, one (n=1) an income of up to three minimum wages, three (n=3) of up to four minimum wages, and one (n=1) had an income of more than four minimum wages.

Regarding the climacteric phase, eleven (n=11) of the women admitted to being premenopausal and nineteen (n=19) postmenopausal. Among these, one (n=1) stated that she had already used hormone replacement therapy, while twenty-nine (n=29) had never used it.

Regarding sexual frequency, sixteen (n=16) of the women reported being active, while fourteen (n=14) reported being inactive. In the textual analysis of the reports, a word cloud was generated, in which the terms are graphically arranged. Words of greater size, positioned closer to the center, indicate greater relevance, according to the frequency of occurrence. It is a simple but useful lexical analysis, as it allows you to quickly identify the terms that stood out the most in the content, as illustrated in the following figure.

Figure 1

Lexical analysis of the content: <https://wordcloud.online/pt>



Source: Survey data, 2025.

After content analysis, the methodological categorization resulted in three thematic axes: Physical and psychological aspects related to the climacteric; Difficulties and

challenges in the field of sexuality and Social repercussions and coping strategies adopted by women in the climacteric.

3.1 PHYSICAL AND PSYCHOLOGICAL ASPECTS RELATED TO THE CLIMACTERIC

In the interviews, one of the initial questions addressed what the women were experiencing at that moment in their lives. It was noticed that many did not know the term "climacteric", and it was necessary to explain its meaning. In addition, the indistinct use of the words "menopause" and "climacteric" was common. The participants mentioned different symptoms, such as hot flushes, insomnia, fatigue, urinary incontinence and memory lapses, with hot flushes standing out as the most recurrent.

In this scenario, self-esteem is particularly vulnerable, being affected not only by physical transformations, but also by the effects of aging and social constructions linked to femininity and beauty standards. Among the body changes most mentioned by the participants are weight gain, skin dryness and changes in hair, nails and the skin itself. Weight gain was pointed out as the main factor in the reduction of self-esteem, in addition to other changes that, in a unique way, interfere in the perception, sensations and relationship that each woman maintains with her own body during the climacteric.

In addition to all these changes, the climacteric can cause significant emotional impacts, evidenced by reports of sadness, irritability, anxiety, and insecurity. Hormonal changes, added to the demands of adult life and the aging process, favor variations in mood, compromising the well-being and quality of life of these women. The testimonies of the participants on the subject strongly reinforce this reality.

About these manifestations, they expressed themselves as follows:

"Oh, I already feel that heat, a lot of headaches, everything I already feel [...] It's a heat like that, that suddenly hits us, it's really a strong heat, you get in a moment of stress, as soon as you are... well agonized [...] Sometimes it gets in the way because you feel that heat, you can't sleep and it disturbs sleep a lot." **M13**

"The worst: irritability. There are days when I want to hit my husband. It irritates me very easily. So the worst symptom is irritability. [...] My husband says it's freshness. [...] Sometimes I run to the bathroom and there's almost no time [...] Woman when my bladder is full, just by looking at the bathroom the pee already wants to come out. Sometimes I already start doing it in my panties." **M24**

"Yes, I put on weight. I created bucho. The skin became dry. Just today I was thinking "my skin is looking like a map, all dry". [...] Her nails were weak, very weak. It breaks just by me doing it like this (bends the nail). [...] Another thing, I'm breeding hair. Growing a beard. You can braid it. After veil appears every thing. If only we could be forever young, right?" **M4**

We think: when menopause comes, old age arrives, right? And I'm not liking it. And we know we're old, because when we go through, menopause ends, everything happens, right? Everything changes, the skin, everything dries out. Everything, the hair, I don't like. I had big hair, everything everything changes. Even to grow eyebrow hair, do you understand? It's more difficult." **M27**

"[...] It gives a lot of pressure, a lot of sadness, you get depressed. The woman gets very depressed, so the emotional part, you feel like crying. [...] There are certain subjects that you don't want to talk about, because you feel like crying. So it's difficult, menopause is just really feeling it, your head is racing, you don't know what you do." **M28**

"In the climacteric, at the beginning of everything we start with that feeling that we are going to die, feeling unwell and not knowing where we are going, right. He doesn't know if it's climacteric, depression or anxiety. So it was at the very beginning... I cried for nonsense [...] one day you're fine and another day you're bad. You go to the doctor and the doctor tells you: "No, you don't have anything". **M20**

3.2 DIFFICULTIES AND CHALLENGES IN THE FIELD OF SEXUALITY

Sex life can be affected in different ways, according to the individual experience of each woman. The hormonal changes typical of the climacteric have a direct influence on female sexuality, resulting, above all, in the reduction of sexual desire and discomfort during intercourse. Such changes have repercussions on marital dynamics, and can bring challenges to the couple's intimacy and satisfaction. In this scenario, the participants' reports show how the transformations of this period directly impact their sex life and their affective bonds.

"I was still in the trenches. Then later, when it ends (menopause), it's over at 50, when menopause is over. Then it decreases. The relationship, even in sensitivity. Touch. Those parts that play, it's not that thing anymore [...] In the beginning. He said that I was already in the fridge (laughs). That the person is "Oh, how do you want it if the woman doesn't want it, the woman is in a fridge." **M27**

"[...] Libido is also gone, you don't feel like having sex. And the husbands don't understand! [...] I wanted to be a more active woman, right? I have always enjoyed dating my husband. But now it's less, and I get a little sad, right. I think "oh, I'm going to lie here with him and I'm not going to do anything?" But it's a thing of life, right? I have to understand, right? Talk a lot. Dialogue, so we don't get bored, because what affects menopause the most is mood and life as a couple. [...] Sometimes, we have sex for the sake of it. And that already bothers me, I don't want to give it because I have to. I want to have sex because I like it." **M29**

"[...] We use a lot of lubricant when we have it, he puts it on, because we can't. The dry relationship doesn't work, you seem to have no pleasure, nothing. Really, it's terrible, menopause brings this kind of thing, especially in sexual intercourse." **M28**

"I don't feel like it (libido). It's all over. I don't feel like it. Before there was." **M6**

"It decreases libido a lot, it does more out of obligation. We don't have the same desire as before. [...] I was already dry before, but with the climacteric it became more so. [...] In the relationship I only have that discomfort, it gets very rigid, right? [...] The partner complains a little, but it's not too much." **M9**

3.3 SOCIAL REPERCUSSIONS AND COPING STRATEGIES ADOPTED BY WOMEN IN THE CLIMACTERIC

The climacteric has a relevant impact on women's social life, affecting their family, professional and community relationships. The physical, emotional, and hormonal transformations of this period can cause feelings of inadequacy, isolation, and even difficulties in participating in certain contexts, whether at home, at work, or in broader social interactions.

To face these challenges, each woman adopts her own strategies, among which family support, physical exercise, the use of teas and the experience of spirituality stand out. Such resources play an essential role in the management of this stage of life.

"A lot (laughs). My boys talk. It gets in the way with my children. I don't have patience for anything. Even with my granddaughter. One of these days I fought with her and her little sister said "Wow, I've never seen you talk to her like that". **M3**

"As soon as I started the climacteric, I felt a lot of impatience. A lot indeed. I fought with the boys, with my husband. But after 2 years now, it stabilized. **M9**

"I felt it (vaginal dryness), but at the time I went to the doctor, right? That was a lot. Then he gave me and my husband some ointment, some medicine and solved it." **M6**

"We have a colleague, a friend from the church. Then you can talk and also at the same time, the spiritual part. Through the spiritual part, you can also control yourself, maintain yourself. You talking to God and everything, right?" **M9**

"I also took a lot of home remedies. I take a lot of medicine, like, to get better. The mint, the stove we're on runs out, you know? You may be dying there, then it calms down. That's how I used to take it." **M11**

"Then I'm drinking that blackberry tea. I've been taught several things. Then, after I started drinking tea, thank God, it improved." **M21**

"Look, what I try to do is do a meditation... Because I think that even this issue of past traumas comes to the surface... look for groups, because they can feel lonely." **M29**

4 DISCUSSION

We sought to understand the perceptions, emotions and experiences of climacteric women regarding the psychological and physical transformations related to their sexual activity, through qualitative analyses. In general, it was found that this phase exerts a strong

influence and causes significant changes in the lives of women. The discussion of the results was divided into topics: Sociodemographic profile and characterization of the sample, Physical and psychological aspects related to climacteric; Difficulties and challenges in the field of sexuality and Social repercussions and coping strategies adopted by women in the climacteric.

4.1 SOCIODEMOGRAPHIC PROFILE AND CHARACTERIZATION OF THE SAMPLE

The comparative analysis of the sociodemographic profile of the women in this study with that of Silveira *et al.* (2023), conducted in Brasília with six participants, reveals a convergence in the results. In this study, the participants are mostly in the age group between 42 and 65 years. In Silveira *et al.* (2023), this range was from 47 to 66 years, which is also similar to the study by Castilhos *et al.* (2021), in which the majority were between 50 and 59 years of age, as well as in Brown *et al.* (2023), prevailing between 40 and 64 years old. This similarity in age groups confirms the predominance of women of non-reproductive age, in whom hormonal changes become more evident.

In addition, there was similarity between the studies regarding the climacteric phase, with postmenopause being the predominant phase in the study by Silveira *et al.* (2023), as well as in Castilhos *et al.* (2021). On the other hand, in Brown *et al.* (2023), premenopause was the most reported.

In the present study, married and single marital status predominated, indicating a balanced distribution between women with and without marital ties. Divorced, widowed and common-law participants were also identified. When compared to the study by Silveira *et al.* (2023), there is a difference in the profile of the participants, with only married marital status predominating, unlike Castilhos *et al.* (2021), where married and divorced women were the most reported, which can interfere with the way they experience the physical and emotional changes of the period.

In this study, it was observed that most of the interviewees had completed high school, followed by the levels of incomplete elementary school, incomplete high school, complete higher education and incomplete higher education. In comparison, in the study by Silveira *et al.* (2023), higher education predominated, followed by the secondary and basic levels. This difference reflects possible disparities in access to education between the groups studied. The level of education can influence the way the participants understand and relate to health information, interfering in their self-care practices and in the understanding of professional guidelines.

The women in the study by Silveira *et al.* (2023) reported fear of using hormone replacement therapy, mainly due to the fear of developing cancer. Such thinking is corroborated in Hirschberg *et al.* (2025), where participants reported concerns about side effects. On the other hand, in Silveira *et al.* (2023), some opted for treatment due to the intensity of the symptoms and the difficulty of living with them. On the other hand, in the present study, only one participant reported having used hormone therapy, but interrupted the treatment.

4.2 PHYSICAL AND PSYCHOLOGICAL ASPECTS RELATED TO THE CLIMACTERIC

In the present study, the main symptoms were accompanied by feelings of discomfort and loss of well-being. In Silveira *et al.* (2023), women reported similar discomforts, highlighting the presence of hot flashes and also the impact of bodily changes on the perception of femininity. In a study carried out in Rio Grande do Sul involving eight women, symptoms were associated with self-care practices such as the use of teas, exercises, and professional monitoring, which demonstrates a movement of positive resignification of this period (Bisognin *et al.* 2022).

This last finding suggests that the way each woman deals with symptoms is strongly related to the support network available and the way she understands the aging process. While some express acceptance and search for balance, others report feelings of denial and anguish in the face of bodily changes.

Recent studies point out that, during menopause or climacteric, many women report symptoms such as hot flashes, night sweats, insomnia, fatigue, irritability, mood swings, decreased libido, vaginal dryness and dyspareunia. In Brazil, there is a high prevalence of genitourinary symptoms, associated with mood disorders, rheumatological diseases, and poor health perception. Even so, many women describe these transformations as negative and difficult to accept (Brasil, 2025; Lu *et al.*, 2023). Corroborating some findings of this study.

Current research has demonstrated the findings on the prevalence of physical and psychological symptoms during the climacteric. In Mexico, a study of 143 climacteric women revealed that the most frequent symptoms were numbness, tingling, palpitations, insomnia, nervousness, depression, as well as muscle and joint pain (Martínez-Garduño *et al.*, 2022).

In Brazil, Santos *et al.* (2021) identified, among 385 menopausal women, the predominant occurrence of hot flashes, mood swings, irritability, sleep disorders, and dyspareunia. Similarly, more recent studies confirm these findings, highlighting the relationship between vasomotor symptoms, sleep alterations, and negative impact on quality

of life (Lu *et al.*, 2023; Alvarado-Aguilar *et al.*, 2024). These results reiterate that the climacteric represents a phase marked by intense physiological and emotional changes, requiring comprehensive attention to women's health.

The menopause period is characterized by complex physiological and hormonal changes that have a significant impact on women's quality of life, requiring specific care and a comprehensive health approach (León *et al.*, 2021; Fang *et al.*, 2024).

These transformations are often associated with the manifestation of vasomotor, psychological, and genitourinary symptoms, the intensity of which can affect physical, emotional, and social well-being. Recent literature shows that the understanding of menopause and the systematic assessment of the severity of symptoms are essential to support the implementation of care strategies centered on women, focusing on lifestyle changes, health promotion and prevention of chronic diseases (Lu *et al.*, 2023; Alvarado-Aguilar *et al.*, 2024). Such interventions contribute to mitigating the impact of hormonal changes and favoring healthy aging, reinforcing the importance of public policies and clinical practices sensitive to the demands of the climacteric.

In this study, there is evidence of weight gain, skin dryness and aging as elements that interfere with self-esteem, a situation similar to that described by Silveira *et al.* (2023), in which the participants reported a feeling of loss of beauty and vigor resulting from the experience of menopause, also highlighting weight gain. This perception is corroborated by a study involving 16 women in Rio Grande do Sul, where the reports express that, in addition to skin changes, there was a greater propensity to accumulate weight to the detriment of its loss (Curta; Weissheimerb 2020).

4.3 DIFFICULTIES AND CHALLENGES IN THE FIELD OF SEXUALITY

Sexuality stood out as a central theme in this study and presents results that emphasize the decrease in libido, discomfort in relationships and difficulty in dialogue with partners during the climacteric, elements that also appear expressively in Silveira *et al.* (2023). In the latter, the participants associated the loss of sexual desire with a lack of understanding of their partners and insecurities related to aging, demonstrating that these factors influence pleasure and intimacy. On the other hand, in Curta; Weissheimerb (2020), vaginal dryness and atrophy were pointed out as factors that negatively impact libido.

A study conducted in Turkey with 254 participants, including 127 postmenopausal women and their spouses, investigated female sexual function, sexual experiences, and marital adjustment. The results revealed sexual dysfunctions in 91.3% of the women and in 77.2% of their partners, and 74.1% of the women had a low level of marital adjustment

(Yildirim *et al.*, 2023). It was also observed that female sexual dysfunction was strongly associated with decreased relationship quality, also negatively impacting the sexual function of spouses. Similarly, the findings of the present study indicated that climacteric symptoms influence marital relationships, generating difficulties and dissatisfaction in the participants' relationships.

In Bisognin *et al.* (2022), although sexuality was not the main focus, it was mentioned in a complementary way, especially in the relationship between self-perception and well-being.

During climacteric, women face significant social pressure to maintain harmony in marital relationships, and are often seen as primarily responsible for the couple's sexual satisfaction. This expectation can lead to the internalization that decreased sexual interest is a personal problem to be corrected, often through hormonal treatments, even when sexual desire is already reduced (Yildirim *et al.*, 2023; Rafiei *et al.*, 2025).

In addition, a lack of understanding on the part of partners can aggravate the situation, resulting in conflicts and even separations. In the present study, it was observed that some participants reported difficulties in marital relationships associated with climacteric symptoms, corroborating the existing literature on the impact of menopause on marital dynamics.

It is perceived that sexuality goes far beyond the sexual act, constituting itself as a complex aspect of the human experience that involves self-knowledge and the way each woman perceives and values herself. Thus, sexuality is deeply linked to self-esteem and the maintenance of self-esteem, reflecting how much women are capable of recognizing and appreciating their own identity (Nogueira; Pachú, 2021).

However, there are still challenges for the effectiveness of comprehensive care for women's health, especially with regard to the approach to female sexuality. The topic continues to be surrounded by taboos and silences, which hinders dialogue between women and health professionals. Comprehensiveness of care presupposes the recognition of the particularities of each phase of the female life cycle and the sociocultural context in which the needs are produced, ensuring problem-solving and humanized actions (Nogueira; Pachú, 2021).

4.4 SOCIAL REPERCUSSIONS AND COPING STRATEGIES ADOPTED BY WOMEN IN THE CLIMACTERIC

In Silveira *et al.* 2023, it was identified that physiological changes that affect sexuality directly interfere with the marital relationship. Many women reported that their lives change

after the beginning of this phase, as their quality of life is impacted by the symptoms, leading them to feel in a position of inadequacy and lack of understanding on the part of other people. This data corroborates the findings of the present study, which also evidenced the feeling of helplessness of women in their social context, whether in the family, at work or in other living spaces.

In addition, Silveira *et al.* 2023 highlight that the experience of the climacteric results in a decrease in self-esteem, which reinforces the feeling of inadequacy and aging. This perception affects social life in a culture that exalts youth, contributing to women no longer perceiving themselves as someone capable of arousing desire or interest in the other, which generates repercussions in sexual life and in the marital relationship.

In Santos *et al.* 2022, it is observed that the lack of understanding of themselves makes climacteric women feel that they are experiencing something unknown, which is associated with the lack of family support and the difficulty of accepting and overcoming this phase of life. In the present study, this reality was also confirmed, as the participants reported feeling not understood by their family members.

In addition to the marital relationship, Santos *et al.* 2022 also shows that the separation from children during this period is a social consequence, an aspect also observed in this research, as the interviewees expressed feelings of irritability and lack of understanding on the part of their children.

In the present study, women reported facing symptoms with resilience and herbal medicines such as blackberry tea. Bisognin *et al.* (2022) emphasized the use of natural practices and popular knowledge as allies in health care. On the other hand, Curta; Weissheimerb (2020) identified the practice of physical exercise as an effective strategy for attenuating climacteric symptoms. These findings represent a wake-up call for health care providers. The clinical approach should not be limited to the prescription of pharmacological treatments, but should actively dialogue with the strategies that women already use. This implies asking about their support network, valuing their knowledge about natural practices and reinforcing the benefits of practices such as physical exercise, acting as a partner in the care plan built by the woman herself.

A randomized clinical trial carried out in China, involving 78 women in the climacteric phase, evaluated the effects of interventions based on personalized diets and physical exercises, applied in isolation and in combination in three distinct groups. The results showed statistically significant reductions in climacteric symptoms after the interventions, with significant improvement in insomnia, sexual disorders, hot flushes, sweating, irritability, depression, fatigue, palpitations, as well as muscle and joint pain. The group that received

the combination of diet and exercise showed the greatest improvements, indicating that integrated approaches enhance clinical benefits in the management of climacteric symptoms (Hao *et al.*, 2022; Chen *et al.*, 2023; Wang *et al.*, 2024). Differently from what was observed in this study, only one woman reported a change in eating habits and physical activity, which resulted in improvement of symptoms.

Currently, different therapeutic approaches have been studied for the management of climacteric signs and symptoms, especially in the treatment of vulvovaginal atrophy, a condition often associated with genitourinary syndrome of menopause. Recent evidence indicates that the use of technologies such as fractional CO₂ laser, fractional microablative radiofrequency, and non-ablative intravaginal radiofrequency presents promising results in tissue regeneration, improved lubrication, and increased sexual function (Lauterbach *et al.*, 2022; Garcia *et al.*, 2022; Sarmiento *et al.*, 2023; Pereira *et al.*, 2024).

In addition, the use of non-hormonal moisturizing vulvovaginal creams has been shown to be effective in reducing dryness and local discomfort, representing a safe alternative for women (Fang *et al.*, 2024). In the present study, it was observed that two participants reported the use of hormonal vaginal cream, reporting significant improvement in vaginal symptoms after its use.

It is widely recognized that lifestyle during the climacteric exerts a determining influence on women's health and well-being, being mediated by motivational, behavioral, and sociocultural factors that directly impact decision-making regarding self-care (Martínez-Garduño *et al.*, 2022; Lu *et al.*, 2023). The adoption of unhealthy habits, such as a sedentary lifestyle, inadequate diet, and excessive consumption of alcohol or tobacco, is an important risk factor, enhancing the repercussions of estrogen deficiency and increasing the incidence of cardiovascular, osteometabolic, and muscular diseases (Alvarado-Aguilar *et al.*, 2024; Fang *et al.*, 2024).

Thus, the implementation of a more balanced lifestyle, which involves regular physical activity, healthy eating and adequate stress management, is an essential strategy to mitigate the effects of the climacteric and promote active and healthy aging. In the present study, it was observed that one participant reported having adopted self-care measures aimed at improving her lifestyle habits, which contributed to the perception of well-being and symptom control.

In Silveira *et al.* (2023), pointed out the need for public policies and greater preparation of health professionals to offer information and adequate care to climacteric women. This reinforces that the care of women in this phase must be integral and continuous, encompassing physical, emotional and sociocultural dimensions. The nurse's work is

essential in this process, especially through educational actions, support groups and listening spaces that value the unique experience of each woman.

4.5 STUDY LIMITATIONS

The limitations of this study were mainly due to the restricted geographic area, since the research was carried out in only one Basic Health Unit in the Federal District, which may not represent the reality of other locations. In addition, the approach to intimate topics, such as sexuality, presented challenges during data collection, as it was possible to observe a certain embarrassment on the part of some women when dealing with these issues, which may have led to the omission of information.

4.6 CONTRIBUTIONS TO PRACTICE

This study contributes significantly to nursing practice by enabling a broader understanding of women's perceptions regarding the climacteric and its repercussions on sexual activity. The results show the need for more sensitive, humanized care based on qualified listening, considering the physical, emotional and social particularities experienced in this phase.

Based on the perceptions identified, it becomes evident the importance of nurses acting in an educational and empathetic way, promoting spaces for dialogue that favor the reception and exchange of experiences, in addition to providing adequate guidance on the symptoms and body changes of the climacteric. Valuing the symptoms reported by women is essential for care to be individualized and effective, since each experience is unique and reflects multiple aspects of physical and emotional health.

In addition, the study offers subsidies for the development of health education strategies focused on the theme, and can help Primary Health Care professionals to deal with issues related to female sexuality and the climacteric in an appropriate way. Thus, the results presented contribute to the improvement of the quality of care, reinforcing the role of nursing as an agent of promotion of women's integral health.

5 CONCLUSION

This study achieved its objectives as it investigated women's perceptions of the signs and symptoms of climacteric associated with their sexual activity. Through the qualitative approach, putting into practice the attentive listening of the participants' experiences, it was possible to verify that this phase is experienced in an expressive and complex way, with profound repercussions on the quality of life. The narratives revealed the participants'

suffering in the face of intense bodily, psychological and social changes, which directly impact the perception of themselves and their relationships.

The findings showed that physical symptoms, such as hot flushes and vaginal dryness, and emotional symptoms, such as irritability and sadness, are intertwined and strongly affect sex life. Decreased libido was often associated with discomfort during intercourse and difficulty in dialoguing with partners, which generates feelings of obligation and frustration.

This research was an instrument that can give voice to women, explaining the need for a more sensitive and comprehensive approach in Primary Health Care. The results reinforce the importance of creating spaces for reception and qualified listening that allow women to express their doubts and anxieties during the climacteric period, especially with regard to sexuality, a topic still surrounded by taboos. Thus, the study offers subsidies for the practice of nursing and other professions in the health area to be more humanized and effective, promoting a better quality of life in this transition phase.

The results of this study revealed aspects of the climacteric that deserve greater understanding, considering the impacts that this phase has on health. It is suggested that further research be carried out on the subject, with the aim of expanding knowledge and giving greater visibility to this group, which requires safe, qualified and specialized care.

In addition, the findings contribute to the understanding of the psychological and physical aspects and the effects that climacteric changes have on sexual activity and quality of life of women, according to the perception of the participants. These findings offer subsidies both for the women themselves and for the clinical practice of health professionals and public policy makers, favoring the improvement of comprehensive female health care during the climacteric.

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TOBACCO-ALCOHOL TOXIC-NUTRITIONAL OPTIC NEUROPATHY: A CASE REPORT

NEUROPATIA ÓPTICA TÓXICO-CARENCIAL POR TABACO-ÁLCOOL: RELATO DE CASO

NEUROPATÍA ÓPTICA TÓXICO-CARENCIAL POR TABACO Y ALCOHOL: REPORTE DE CASO



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ABSTRACT

Introduction: Tobacco-alcohol optic neuropathy is a toxic-nutritional condition that causes damage to the optic nerve. While tobacco exerts a predominantly toxic effect, alcohol acts through nutritional deficiency, impairing the bioavailability of essential nutrients such as folate and B-complex vitamins. The pathophysiology is associated with mitochondrial DNA damage and the accumulation of free radicals.

Case Report: A 67-year-old male patient, with a history of alcoholism and smoking for more than 30 years, presented with progressive visual loss in the right eye (RE) for two weeks. The left eye (LE) had previous amaurosis due to trauma. On examination, visual acuity in the RE was counting fingers at 1 meter. Complementary examinations revealed temporal pallor of the optic disc and a cecentral scotoma on computerized visual field testing. Following the diagnosis of tobacco-alcohol optic neuropathy, treatment was initiated with 5000 mcg of intramuscular vitamin B12 weekly for three weeks, in addition to counseling for smoking and alcohol cessation.

Results and Conclusion: After treatment, there was significant recovery of the visual field and improvement of visual acuity in the RE to 20/40. The visual prognosis of this condition depends directly on early diagnosis, duration of exposure to toxic substances, and the immediate cessation of alcohol and tobacco use in order to prevent irreversible damage.

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Keywords: Optic Neuropathy. Tobacco. Alcoholism. Vitamin B12. Cecocentral Scotoma.

RESUMO

Introdução: A neuropatia óptica por tabaco-álcool é uma condição de caráter tóxico-carencial que causa lesão ao nervo óptico. Enquanto o tabaco exerce um efeito predominantemente tóxico, o álcool atua de forma carencial, prejudicando a biodisponibilidade de nutrientes essenciais, como o folato e as vitaminas do complexo B. A fisiopatologia está ligada ao dano no DNA mitocondrial e ao acúmulo de radicais livres.

Relato do Caso: Paciente masculino, 67 anos, etilista e tabagista há mais de 30 anos, apresentou baixa visual progressiva no olho direito (OD) há duas semanas. O olho esquerdo (OE) apresentava amaurose prévia por trauma. Ao exame, a acuidade visual no OD era de conta dedos a 1 metro. Exames complementares revelaram palidez temporal no disco óptico e escotoma cecocentral na campimetria computadorizada. Com o diagnóstico de neuropatia tabaco-álcool, instituiu-se tratamento com 5000mcg de vitamina B12 intramuscular semanal por três semanas, além da orientação de suspensão do tabagismo e etilismo.

Resultados e Conclusão: Após o tratamento, houve recuperação significativa do campo visual e melhora da acuidade visual no OD para 20/40. O prognóstico visual desta condição depende diretamente do diagnóstico precoce, do tempo de exposição às substâncias e da interrupção imediata do consumo de álcool e fumo para evitar danos irreversíveis.

Palavras-chave: Neuropatia Óptica. Tabaco. Alcoolismo. Vitamina B12. Escotoma Cecocentral.

RESUMEN

Introducción: La neuropatía óptica por tabaco y alcohol es una condición de carácter tóxico-carencial que causa daño al nervio óptico. Mientras que el tabaco ejerce un efecto predominantemente tóxico, el alcohol actúa de forma carencial, perjudicando la biodisponibilidad de nutrientes esenciales, como el folato y las vitaminas del complejo B. La fisiopatología está relacionada con el daño al ADN mitocondrial y la acumulación de radicales libres.

Reporte de Caso: Paciente masculino de 67 años, alcohólico y fumador desde hacía más de 30 años, presentó disminución visual progresiva en el ojo derecho (OD) desde hacía dos semanas. El ojo izquierdo (OI) presentaba amaurosis previa debido a un traumatismo. En el examen, la agudeza visual en el OD era de cuenta dedos a 1 metro. Los exámenes complementarios revelaron palidez temporal del disco óptico y escotoma cecocentral en la campimetría computarizada. Con el diagnóstico de neuropatía óptica por tabaco y alcohol, se inició tratamiento con 5000 mcg de vitamina B12 intramuscular semanal durante tres semanas, además de orientación para la suspensión del tabaquismo y del alcoholismo.

Resultados y Conclusión: Después del tratamiento, hubo una recuperación significativa del campo visual y mejoría de la agudeza visual en el OD a 20/40. El pronóstico visual de esta condición depende directamente del diagnóstico precoz, del tiempo de exposición a las sustancias y de la interrupción inmediata del consumo de alcohol y tabaco para evitar daños irreversibles.

Palabras clave: Neuropatía Óptica. Tabaco. Alcoholismo. Vitamina B12. Escotoma Cecocentral.

1 INTRODUCTION

Tobacco-alcohol optic neuropathy is a condition that damages the optic nerve (NO) by a toxic-deficiency mechanism. Tobacco has a predominantly toxic effect and alcohol is predominantly deficient, since it affects the bioavailability of nutrients, especially B vitamins and folate, either by deficient absorption, by causing defects in metabolism or by hindering storage. The high incidence of smoking and alcoholism today reinforces the importance of describing clinical cases.

2 CASE DESCRIPTION

Male, 67 years old. She sought ophthalmologic care complaining of progressive visual impairment in her right eye 2 weeks ago. In her previous ophthalmological history, she reported perforating trauma in the left eye (LE) and cataract surgery in the right eye (RE); in addition to Covid for 45 days, alcoholism and smoking for more than 30 years as a previous pathological history. She denied other comorbidities and ophthalmological diseases in the family. On ophthalmologic physical examination, a corneal scar was observed in the left eye on ectoscopy with bilateral preserved ocular motility. Visual acuity without correction of the fingercount was 1 meter in RE and without light perception in LE, which did not change with refractive correction. Biomicroscopy of the anterior segment showed pseudophakia in RE and corneal scar in LE. Intraocular pressure of 12 mmHg bilaterally. Complementary tests for RE were requested, given the irreversibility of previous damage in LE.

Retinal mapping showed an oval optic nerve (NO), with mild temporal pallor, vessels emerging from the center, and papillary cupping of 0.3. Fluorescein angiography showed temporal hyperfluorescence in the optic disc (OD) due to a window defect in the late arteriovenous phase. Optical coherence tomography showed partial detachment of the posterior vitreous, adhered to the foveal region. Computerized campimetry showed an increase in blind spot with cecocentral scotoma. Based on the clinical history and the findings of the physical examination and complementary tests, the diagnosis of tobacco-alcohol neuropathy was established and, for the treatment, the administration of 5000mcg of intramuscular vitamin B12 weekly for 3 weeks was prescribed, in addition to the suspension of alcohol intake and smoking. Campimetry performed after treatment showed significant recovery of the visual field, with a decrease in the scotoma and improvement in visual acuity in RE to 20/40.

3 DISCUSSION

Tobacco-alcohol toxic-deficiency optic neuropathy mainly affects males, smokers and long-term drinkers. The pathophysiology primarily involves damage to mitochondrial DNA, impairing ATP production and accumulating free radicals that cause cell damage. Affected patients usually present with low visual acuity bilaterally, lesions in the maculopapillary bundle, central or cecocentral scotomas, and reduced color vision. The recommended treatment is supplementation with vitamin B12 and the immediate cessation of alcohol and smoking consumption. The prognosis depends on the time of exposure to the substances, an early diagnosis and the reversibility of nerve cell damage. The main differential diagnosis of this condition is Leber's hereditary neuropathy, which in its pathophysiology also involves a deficit in ATP production and accumulation of free radicals, but due to genetically inherited mutations in mitochondrial DNA, which is why this condition affects young people.

4 CONCLUSION

In view of the increasing incidence of smoking and alcoholism today, especially among young people, health professionals should pay attention to the signs of tobacco-alcohol toxic-deficiency optic neuropathy, which can acutely cause irreversible damage to vision, and advise patients about the other health impacts of the use of these substances.

Figure 1

Fundoscopic showing candle flame hemorrhage, drusen, oval optic nerve, with slight temporal pallor



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CLINICAL AND LABORATORY PARAMETERS AS PREDICTORS OF CHANGES IN ARTERIAL PATENCY AFTER PERCUTANEOUS INTERVENTION IN HEMODYNAMIC SERVICES

PARÂMETROS CLÍNICOS E LABORATORIAIS COMO PREDITORES DE ALTERAÇÕES NA PERVIABILIDADE ARTERIAL APÓS INTERVENÇÃO PERCUTÂNEA EM SERVIÇOS DE HEMODINÂMICA

PARÁMETROS CLÍNICOS Y DE LABORATORIO COMO PREDICTORES DE CAMBIOS EN LA PERMEABILIDAD ARTERIAL TRAS INTERVENCIÓN PERCUTÁNEA EN SERVICIOS DE HEMODINÁMICA



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ABSTRACT

Coronary artery disease (CAD) remains a major public health issue, with high incidence, mortality, and a significant impact on hemodynamic services. Its pathophysiology is directly associated with atherosclerosis and may progress to acute coronary syndrome through mechanisms such as plaque rupture, vasospasm, and embolism. In this context, coronary angiography and percutaneous coronary intervention play a central role in both diagnosis and minimally invasive treatment, although they may be associated with vascular complications such as bleeding, thrombosis, hematomas, and vasospasm. Early identification of clinical and laboratory factors at admission is essential for risk stratification and to facilitate the monitoring of patients undergoing these procedures. Key parameters of interest include age, sex, body mass index, metabolic comorbidities, use of antithrombotic therapy, and laboratory markers related to inflammatory response, myocardial injury, renal function, and hematological abnormalities. Thus, the integrated analysis of clinical and laboratory data may contribute to the prediction of complications, improvement of care, and enhancement of safety in hemodynamic practice.

Keywords: Coronary Artery Disease. Hemodynamics. Percutaneous Coronary Intervention. Vascular Complications. Clinical-Laboratory Biomarkers.

RESUMO

A doença arterial coronariana (DAC) mantém-se como importante problema de saúde pública, com elevada incidência, mortalidade e impacto sobre os serviços de hemodinâmica.

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Sua fisiopatologia está diretamente relacionada à aterosclerose, podendo evoluir para síndrome coronariana aguda por mecanismos como ruptura de placa, vasoespasma e embolia. Nesse contexto, a cinecoronariografia e a intervenção coronária percutânea desempenham papel central no diagnóstico e no tratamento minimamente invasivo, embora possam estar associadas a complicações vasculares, como sangramentos, trombose, hematomas e vasoespasma. A identificação precoce de fatores clínicos e laboratoriais na admissão é fundamental para estratificar o risco e favorecer a vigilância de pacientes submetidos a esses procedimentos. Entre os parâmetros de interesse, destacam-se idade, sexo, índice de massa corporal, comorbidades metabólicas, uso de terapia antitrombótica e marcadores laboratoriais relacionados à resposta inflamatória, lesão miocárdica, função renal e alterações hematológicas. Assim, a análise integrada de dados clínicos e laboratoriais pode contribuir para a predição de complicações, o aprimoramento da assistência e a segurança do cuidado em hemodinâmica.

Palavras-chave: Doença Arterial Coronariana. Hemodinâmica. Intervenção Coronária Percutânea. Complicações Vasculares. Biomarcadores Clínico-Laboratoriais

RESUMEN

La enfermedad arterial coronaria (EAC) sigue siendo un importante problema de salud pública, con alta incidencia, mortalidad e impacto significativo en los servicios de hemodinámica. Su fisiopatología está directamente relacionada con la aterosclerosis y puede progresar hacia el síndrome coronario agudo mediante mecanismos como la ruptura de la placa, el vasoespasma y la embolia. En este contexto, la angiografía coronaria y la intervención coronaria percutánea desempeñan un papel central tanto en el diagnóstico como en el tratamiento mínimamente invasivo, aunque pueden asociarse a complicaciones vasculares como hemorragias, trombosis, hematomas y vasoespasma. La identificación temprana de factores clínicos y de laboratorio al ingreso es fundamental para la estratificación del riesgo y para facilitar el seguimiento de los pacientes sometidos a estos procedimientos. Entre los parámetros de interés se incluyen la edad, el sexo, el índice de masa corporal, las comorbilidades metabólicas, el uso de terapia antitrombótica y los marcadores laboratoriales relacionados con la respuesta inflamatoria, el daño miocárdico, la función renal y las alteraciones hematológicas. Así, el análisis integrado de datos clínicos y de laboratorio puede contribuir a la predicción de complicaciones, la mejora de la atención y el aumento de la seguridad en la práctica de hemodinámica.

Palabras clave: Enfermedad Arterial Coronaria. Hemodinámica. Intervención Coronaria Percutánea. Complicaciones Vasculares. Biomarcadores Clínico-Laboratoriales.

1 INTRODUCTION

According to the *Global Burden of Disease* (GBD, 2019), the number of people with CAD in Brazil increased from 1.48 million in 1990 to more than 4 million in 2019. In the same period, 171,246 deaths attributed to CAD were recorded, which corresponds to 12% of all deaths in the country (GBD, 2019). This growth follows the increase in the prevalence of cardiovascular risk factors, such as diabetes mellitus, dyslipidemia, hypertension, obesity, smoking and sedentary lifestyle, phenomena that contribute to the increase in the demand for specialized cardiology care and hemodynamic procedures.

Cardiovascular diseases (CVDs) are the leading cause of global mortality, accounting for approximately 31% of deaths worldwide, according to the World Health Organization (WHO, 2023). In this scenario, hemodynamic services play an essential role in the diagnosis and treatment of acute and chronic cardiovascular diseases, providing minimally invasive interventions that reduce the need for open surgeries and improve clinical outcomes (Mesquit; Ker, 2021).

The pathophysiology of CAD is mainly based on the formation, progression, and instability of the atherosclerotic plaque, a process that can progress to erosion, rupture, and formation of an occlusive or subocclusive thrombus. Other pathophysiological mechanisms include vasospasm, coronary embolism, and arterial dissection. In addition, clinical conditions such as anemia, systemic arterial hypertension, tachyarrhythmias, aortic stenosis, and hypertrophic cardiomyopathy can precipitate imbalances between myocardial oxygen supply and demand, contributing to the development of acute coronary syndrome (Nicolau *et al.*, 2021; Oliveira *et al.*, 2021).

In the diagnosis and management of cardiovascular emergencies, coronary angiography is considered the gold standard, since it allows the anatomical visualization of the coronary tree by means of injection of iodinated contrast via the femoral, radial, ulnar or brachial route (Ribeiro, 2008). The puncture success rate depends on factors such as operator experience, anatomical and clinical characteristics of the patient, presence of comorbidities, use of anticoagulants, and fluoroscopy time. Among the most frequent complications are acute thrombosis of the radial artery, vasospasm, hematomas, ecchymosis, bleeding, pseudoaneurysms, arteriovenous fistulas, and other vascular alterations. Some complications appear early, but others may manifest late, increasing the length of hospital stay and the need for additional interventions (Woods, 2005).

In this context, a detailed clinical and laboratory evaluation at admission to the hemodynamics sector is important to identify patients at higher risk of complications early. This evaluation includes inspection of the puncture site, palpation of distal pulses,

identification of bulges or murmurs, and analysis of parameters such as age, gender, body mass index (BMI), hypertension, diabetes, use of anticoagulants, fluoroscopy time, and laboratory findings (Woods, 2005). Therefore, the investigation of clinical and laboratory biomarkers capable of predicting vascular changes related to the radial access emerges as a promising strategy to improve care protocols, reduce adverse events, and optimize care flows (Nicolau *et al.*, 2021; Gavidia *et al.*, 2024).

Thus, the present study seeks to describe the use of clinical and laboratory parameters in hemodynamic services to evaluate changes in the arterial patency of the upper limbs after diagnostic or therapeutic percutaneous coronary intervention.

2 HEMODYNAMICS

The Hemodynamics Service, also called Interventional Cardiology, is a medical subspecialty focused on performing minimally invasive procedures aimed at the diagnosis and treatment of diseases of the cardiovascular system. Among the main procedures are cardiac catheterization, vascular arteriography, coronary angioplasty, electrophysiological studies with ablation of arrhythmias, embolization of vascular malformations and implantation of endoprostheses. Such techniques aim to restore blood flow, diagnose obstructions and correct structural anomalies accurately and with reduced hemodynamic impact on the patient (Ribeiro; Filho, 2008).

Coronary angiography, also known as cardiac catheterization, is the gold standard for the diagnosis of coronary artery disease (CAD). It is an imaging test that, through the injection of iodinated contrast directly into the coronary arteries, allows the radiological visualization of the arterial lumen and the identification of stenosis or occlusions (Abizaid *et al.*, 2013). Because it is a less aggressive method, associated with fast, effective interventions and with a shorter recovery time, it has become fundamental in the face of the growing incidence of cardiovascular diseases.

The initial milestone of percutaneous coronary intervention occurred in 1977, at the University of Zurich, when Andreas Roland Grüntzig performed the first percutaneous transluminal angioplasty in a patient with critical obstruction of the anterior descending artery, using a balloon catheter inserted via femoral access. This procedure inaugurated a new era in the treatment of ischemic heart disease, enabling the development of increasingly advanced techniques and devices within interventional cardiology (Ribeiro; Filho, 2008).

Coronary angioplasty aims to remodel the atherosclerotic plaque, transforming an obstructive lesion into a more stable state with less hemodynamic impact, favoring myocardial perfusion and reducing ischemic symptoms. With the evolution of the technique,

the use of stents, expandable devices responsible for maintaining the arterial lumen after dilation, significantly reducing restenosis rates and increasing therapeutic efficacy (Woods, 2005) was incorporated.

Arterial access is a critical step in percutaneous procedures, and should be selected according to the clinical characteristics of the patient and the experience of the team. Initially performed via the brachial approach, it evolved to the femoral approach and, more recently, to the radial approach, which is currently preferred for greater safety, ease of compression, and lower rate of hemorrhagic complications (Abizaid et al., 2013). To choose the radial approach, it is recommended that the patency of the palmar arches be previously evaluated using the Allen test, which is considered normal when there is return of perfusion within 10 seconds after the release of ulnar flow. The procedure can be aided by the pulse oximeter on the thumb, observing the return of the pulse wave (Abizaid et al., 2013).

After the intervention, compression of the radial artery is performed to obtain hemostasis, achieved by different methods. As described by Woods (2005), the hemostatic process involves sequential activation of coagulation factors and fibrin clot formation at the site of vascular injury, preventing blood leakage. Disturbances in this process can result in bleeding ranging from petechiae and ecchymosis to severe hemorrhages. Among the devices used, the TR Band (Terumo Medical, Tokyo, Japan) stands out, similar to a transparent bracelet that, positioned over the introducer insertion site and inflated with 15 mL of air, promotes controlled compression, maintaining antegrade flow and ensuring distal perfusion during a gradual deflation protocol (Santos et al., 2018). An alternative technique involves the use of compressive gauze and adhesive tape strips applied in an "X" shape, fixing the dressing without fully involving the limb, also with a gradual removal protocol (Santos et al., 2018).

Cardiac catheterization has historical origins dating back to 1844, when Claude Bernard carried out pioneering experiments in catheterization of the jugular veins and carotid artery in horses, allowing the first intracardiac hemodynamic measurements. In 1929, Werner Forssmann proved the feasibility of intracardiac catheterization in humans by introducing a ureteral catheter into his own right atrium, a decisive milestone for subsequent clinical techniques. The modern era was consolidated in 1958, with Mason Sones at the Cleveland Clinic, when he developed coronary cineangiography and established the foundations of percutaneous intervention (Ribeiro; Filho, 2008).

Right heart catheterization, performed by venous, femoral, internal jugular, subclavian or antecubital route, allows hemodynamic evaluation of the right chambers and pulmonary circulation. Among its main indications are the determination of cardiac output in advanced

heart failure, the diagnosis of pulmonary hypertension, the detection of intracardiac shunts, and the investigation of cardiomyopathies, constrictive pericarditis, and cardiac tamponade (Jatene et al., 2022). The most frequent complications include inadvertent arterial puncture, formation of pseudoaneurysm or arteriovenous fistula, lymphatic duct injury and, rarely, rupture of pulmonary vessels or episodes of hypoxia (Ribeiro; Filho, 2008).

Left heart catheterization, also called coronary angiography, is the gold standard for coronary anatomical study. The procedure begins with femoral or radial arterial puncture, followed by the introduction of catheters to the root of the aorta for selective catheterization of the coronary ostia, visualizing the left and right sides of the heart and the right and left coronary arteries (Jatene et al., 2022). The injection of iodinated contrast, associated with serial radiographic projections, allows the identification of the arterial lumen, quantification of the degree of stenosis and evaluation of morphological details.

Radiographic projections are also fundamental in ventriculography, which helps in the evaluation of global and segmental systolic function, in the identification of intracavitary thrombi, and in the analysis of mitral regurgitation. It is contraindicated in patients with mechanical aortic prosthesis, known ventricular thrombus, decompensated heart failure, or acute pulmonary edema. Intraventricular aortography, on the other hand, allows the evaluation of aortic valves, aortic root diameter, and the identification of dissections, although the increase in contrast loading increases the risk of induced nephropathy, requiring a careful risk-benefit balance (Ribeiro; Filho, 2008).

Coronary angioplasty, also called percutaneous coronary intervention (PCI), is often performed after the diagnosis of significant obstructive lesions during catheterization. The procedure can be performed with a balloon or with stent implantation (Ribeiro; Filho, 2008). Historically, the term "stent" was first used in 1916 by plastic surgeon Jan Esser, in reference to the dental prosthesis of English dentist Charles Thomas Stent. The first models were made with metal alloys such as nitinol, tantalum, platinum and stainless steel, materials with good biocompatibility, but with limitations such as low radiopacity, little flexibility and high nickel content, potentially allergenic (Abizaid et al., 2013). The need for more robust devices has driven the development of stents in cobalt-chromium alloys, with greater radiological visibility, thinner stems, and lower nickel content. Subsequently, the incorporation of platinum conferred greater malleability, resistance to corrosion and lower risk of fracture, increasing the safety and efficacy of the procedure (Abizaid et al., 2013).

3 COMPLICATIONS IN HEMODYNAMIC PROCEDURES

Despite technological advances and the wide use of coronary angiography as a diagnostic and therapeutic tool in the management of cardiovascular diseases, the procedure is not without risks, especially when performed in groups of greater clinical vulnerability. As described by Jatene et al. (2022), although coronary angiography is considered a safe test in elective contexts, it is essential to thoroughly evaluate the risk-benefit ratio before performing it, especially in patients who have factors predisposing to complications. Among these factors are advanced age, complex congenital heart diseases (particularly relevant in children), significant lesions in the left main coronary artery, multivessel coronary disease, advanced peripheral arterial disease, severe ventricular dysfunction with heart failure, diabetes mellitus using insulin, and important valvular heart diseases, such as aortic stenosis. In view of this more fragile clinical profile, individualized planning and risk mitigation strategies are necessary, adapted to the particularities of each patient (Jatene et al., 2022).

Although rare, complications related to the test may have significant clinical relevance. Data presented by Jatene et al. (2022) demonstrate estimated incidences of death (0.08%), acute myocardial infarction (0.05%), stroke (0.07%), arrhythmias (0.4%), vascular complications (0.5%), and adverse reactions to iodinated contrast (0.4%). Although low percentages, these events reinforce the need for rigorous pre-procedure preparation, continuous surveillance during the intervention, and careful post-procedure monitoring, since the early identification of complications is decisive for a favorable clinical outcome.

Medication management in the perioperative period represents another fundamental pillar to reduce risks. Metformin should be discontinued between 24 and 48 hours before the test, and reintroduced only after 48 hours or after normalization of renal function, in order to avoid lactic acidosis. The direct anticoagulants, rivaroxaban, apixaban, and dabigatran, require interruption at the same interval, with resumption 24 hours after the procedure. On the other hand, antiplatelet agents, such as acetylsalicylic acid (ASA), should be maintained. In patients using coumarin anticoagulants, such as warfarin, it is recommended to suspend them for five days before the intervention, aiming to achieve an INR between 1.5 and 1.8. In these cases, the use of full heparin as a bridge may be considered, especially when there is a high thromboembolic risk. It should be noted, however, that clinical emergencies often make it impossible to rigorously apply these protocols, and it is necessary to prioritize conducts aimed at preserving life and hemodynamic stabilization.

Thus, the adequate management of hemodynamic complications requires appropriate hospital infrastructure, well-established clinical protocols, up-to-date technology and, above

all, a highly trained multidisciplinary team. The standardization of care practices, combined with the technical experience of professionals, is an essential element to ensure safety, reduce the occurrence of complications and optimize the results associated with procedures (Ribeiro; Filho, 2008).

3.1 CLINICAL COMPLICATIONS IN PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention (PCI), although widely disseminated and consolidated as a safe and effective procedure for the treatment of coronary artery disease, may be associated with a variety of clinical complications. The occurrence of these complications is often related to the clinical profile of patients, often with multiple comorbidities, and to the emergency situations in which the technique is applied, which enhances the complexity of the clinical scenario (Jatene et al., 2022).

As described by Ribeiro (2008), the most prevalent complications are associated with arterial puncture sites, especially in the femoral and radial accesses, manifesting as hematomas, pseudoaneurysms and bleeding. Less frequently, neurological lesions, lymphatic fistulas, catheter fragmentation, incoercible hemorrhages, and, in rare situations, stent migration may occur. Among the most severe complications, cerebrovascular events stand out, which, although uncommon, require high attention due to their prognostic repercussions. Such events may occur during or immediately after PCI, and may be diagnosed late, within 36 hours after the intervention. Vascular spasms and idiosyncratic reactions to iodinated contrast are less common, but still relevant, causes of post-procedure neurological manifestations (Ribeiro; Filho, 2008).

Contrast-induced nephropathy (CIN) represents another complication of significant clinical importance, characterized by acute deterioration of renal function after exposure to iodinated contrast agent. The risk of CIN is higher in patients with prior renal dysfunction, diabetes mellitus, older age, heart failure, episodes of hypotension, and increased creatinine levels prior to the procedure. Preventive strategies include adequate hydration, reduction of total contrast volume, selection of agents with lower nephrotoxicity and, in specific situations, the use of therapies with nephroprotective effect.

The current profile of patients undergoing PCI shows an increase in clinical and anatomical complexity, which reinforces the need to adopt additional safety strategies. In this context, the use of ultra-low contrast volumes is essential in order to reduce the risk of CIN without compromising diagnostic accuracy. The careful selection of catheters, guidewires and auxiliary techniques, combined with the operator's technical mastery, is an essential measure for risk mitigation. The incorporation of advanced intracoronary imaging methods,

such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS), as well as the use of invasive coronary physiology, should be prioritized whenever possible. These technologies, by providing detailed information about coronary anatomy and physiology, make it possible to reduce contrast dependence and increase the accuracy and safety of PCI results (Hennessey, 2023).

Recent technological progress, together with the availability of new navigation tools, such as dynamic coronary mapping and co-registration technologies, has contributed to the simplification of procedures and to the expansion of the safety margin, especially in high-risk patients. These innovations reinforce the role of ICP as an increasingly effective, accurate, and safe intervention (Hennessey, 2023).

Complications related to the arterial access route remain among the main challenges in the immediate post-procedure. Early detection and timely management of these complications are essential, since initially mild conditions can progress to severe situations, requiring blood transfusion, surgical intervention, or risk of death (Abizaid et al., 2013). The most frequently observed complications include local hematomas, femoral pseudoaneurysms, retroperitoneal hematoma, particularly associated with femoral access, arteriovenous fistula, arterial thrombosis, significant hemorrhages, and infections. Its occurrence is related to factors such as inadequate puncture technique, use of anticoagulants, advanced age, obesity, and ineffective compression after the removal of the sheath.

In the radial approach, although the rate of hemorrhagic complications is lower than in the femoral approach, there are contraindications that should be strictly observed. Among them, Raynaud's disease, post-mastectomy lymphedema in the upper limb, presence of arteriovenous fistula for hemodialysis, possibility of future use of the radial artery as a graft in myocardial revascularization surgery, and lack of adequate collateral circulation between the superficial and deep palmar arches (Abizaid et al., 2013). Kotowycz et al. (2012) describe that the radial and ulnar arteries are interconnected by the palmar arches, allowing that, in case of occlusion of the radial artery, the perfusion of the hand can be maintained by the ulnar circulation. The evaluation of this circulation is routinely performed using the modified Allen test, a simple and qualitative method that records the return time of palmar flushing, which is considered normal when less than 10 seconds.

Radial artery occlusion (RAO) is the most relevant complication of transradial access (ART) and often goes unnoticed due to dual irrigation of the hand. Munir et al. (2022) highlight that more than half of the operators do not assess radial patency after PCI. RAO is usually due to thrombosis secondary to endothelial injury caused by cannulation and reduced blood

flow during the procedure. Although it can manifest early, about 50% of patients have spontaneous recanalization within three months. The incidence, according to the literature, varies from 1.5% to 30.5%, and is, on average, between 5% and 12%. Once occluded, the radial artery cannot be reused as an access in future procedures or as an arterial graft in revascularization surgery, in addition to increasing the risk of ischemia in the event of concomitant involvement of the ulnar artery.

Recent advances in interventional cardiology reinforce the need for technical mastery and accurate clinical judgment for the appropriate selection of the access route. The preservation of radial patency becomes especially relevant for patients who require serial procedures. Preventive strategies include the use of smaller-caliber sheaths or non-sheathed access techniques, adequate anticoagulation, careful catheter manipulation techniques, and non-occlusive hemostasis. Systematic evaluation of radial patency before hospital discharge and individualized clinical follow-up are also recommended, ensuring greater safety and preservation of the access route for future interventions (Munir et al., 2022).

3.2 CLINICAL PARAMETERS ASSOCIATED WITH VASCULAR COMPLICATIONS

Vascular complications resulting from hemodynamic procedures represent a relevant clinical challenge, with a direct impact on patient morbidity and mortality. The incidence of these events is multifactorial, being influenced both by individual clinical characteristics and by technical aspects of the intervention. Among the factors related to the patient, advanced age, female gender, and presence of comorbidities stand out, which are associated with a higher risk of adverse events. In addition, the previous use of anticoagulants is an independent predictor of bleeding and complications at the vascular access site, reinforcing the importance of the appropriate choice of puncture route (Sugiharto *et al.*, 2023). Among the most frequent complications are bleeding, hematomas, pseudoaneurysms, and arteriovenous fistulas. An in-depth understanding of these aspects is essential for risk stratification and the adoption of effective preventive measures, with the aim of optimizing the clinical outcomes of patients undergoing percutaneous coronary interventions (Harvey *et al.*, 2020).

The clinical evaluation of patients with suspected or diagnosed acute myocardial infarction (AMI) is a complex process that requires integration of clinical, laboratory, and anatomical variables. According to Alnemer (2024), factors such as age, sex, smoking, body mass index (BMI), presence of comorbidities, and history of percutaneous coronary

intervention (PCI), when associated with specific biomarkers, play a determining role in the prognosis and in the definition of the therapeutic strategy.

Physiological aging is considered a central factor for the occurrence of adverse outcomes in AMI. Patients with hypertension, diabetes mellitus (DM), and chronic kidney disease (CKD) are at increased risk of complications due to greater myocardial involvement and additional difficulties in clinical management. In these cases, individualized assessments and personalized therapeutic strategies are essential to optimize results and reduce mortality (Alnemer, 2024).

In addition, the history of coronary *artery bypass grafting* (CABG) or previous PCI directly influences the clinical outcome, impacting hospital and post-hospital outcomes. In this scenario, individualized therapeutic planning and specialized follow-up play a crucial role. The relevance of incorporating laboratory biomarkers in clinical practice is also highlighted, as they allow the early identification of high-risk patients, contributing to the reduction of in-hospital mortality (Alnemer, 2024).

3.2.1 Gender

Risk factors for AMI are distributed differently between the sexes, influencing the clinical presentation, prognosis, and treatment strategies. Zhao *et al.* (2022) point out that men have lower life expectancy compared to women in all countries, a phenomenon attributed to the higher incidence of cardiovascular diseases. Women, on the other hand, have a higher prevalence of comorbidities, such as SAH, DM, and obesity. On the other hand, risky habits, such as smoking and excessive alcohol consumption, predominate among men.

From a biological, behavioral, and social point of view, men have accelerated aging, which is reflected in greater cardiovascular vulnerability (Zhao *et al.*, 2022). In a study conducted in Sweden with 213 middle-aged patients diagnosed with AMI, Nyström *et al.* (2022) identified marked differences between genders: while chest pain was the predominant symptom in both, women had a higher prevalence of hyperlipidemia and a higher stress load in the 12 months prior to the event, often related to economic difficulties and depressive symptoms. Men exhibited higher systolic blood pressure levels at hospital admission.

Women tend to present with AMI at an older age (57 ± 7 years) and often with atypical symptoms, resulting in late diagnosis and delays in treatment. In addition, psychosocial factors, such as stress, depression, sleep deprivation, and economic crises, have a more significant impact on female cardiovascular risk, reinforcing the need for differentiated approaches to prevention and management (Nyström *et al.*, 2022).

In a longitudinal study with patients hospitalized by AMI, Rohani *et al.* (2022) identified an overall mortality rate of 18.6%, being higher among women, whose average age was higher than that of men. Among the most prevalent risk factors, hypertension, DM, hyperlipidemia, smoking, and family history stood out. Multivariate analysis showed that mortality was higher in diabetic patients and lower among those with a history of hyperlipidemia. In addition, 85% of women were 55 years of age or older, compared to 62% of men.

In the retrospective study by Vallabhajosyula *et al.* (2020), which evaluated 90,648 hospitalizations for AMI associated with cardiogenic shock (AMI-CS) in individuals ≤ 55 years of age, found that women were less frequently submitted to PCI and mechanical circulatory support, despite the higher prevalence of comorbidities. This disparity was reflected in higher in-hospital mortality compared to men. Additional results showed higher mortality among young white women, suggesting an interaction between age, sex, and sociodemographic factors in the prognosis. Thus, although they present lower initial clinical severity, young women are subjected to less invasive conducts, with less favorable outcomes, a finding that reinforces the need for systematic incorporation of the gender variable in AMI prevention and treatment strategies.

3.2.2 Smoking

Smoking is one of the main modifiable risk factors for the development of cardiovascular diseases (CVD). Since the 1950s, scientific evidence has been consolidating its deleterious effects, recognizing it as the leading cause of preventable death among adults worldwide (Benjamin *et al.*, 2018). According to the World Health Organization (WHO, 2024), smoking is responsible for more than 8 million deaths annually, with one in five patients with CVD dying as a direct result of smoking.

Cardiovascular effects can be classified into short- and long-term. In the short term, nicotine induces transient elevation of blood pressure and heart rate through vasoconstriction, intensifying hemodynamic overload. At the same time, smoking promotes early endothelial injury, impairing vasodilator capacity and stimulating inflammatory and oxidative processes. In the long term, these mechanisms result in chronic endothelial dysfunction, systemic proinflammatory state, and hypercoagulability, which are central factors in atherogenesis. At the molecular level, the activation of pattern recognition receptors, such as Toll-like 9 (TLR9), NLRP3/AIM2 inflammasome activation, and the cGAS-STING pathway, directly associated with the progression of vascular lesions (Rahman *et al.*, 2025), stand out.

Recent studies have shown that early smoking initiation increases cardiovascular risks. Sheng *et al.* (2025), in an analysis of 2,345 NHANES participants (1999 - 2002), observed that smoking initiation before adolescence is associated with a higher risk of CVD and acceleration of biological aging, as assessed by epigenetic biomarkers of deoxyribonucleic acid (DNA) methylation. These findings reinforce that early smoking not only increases cardiovascular vulnerability, but also accelerates epigenetic aging, standing out as a priority in preventive strategies and public health policies.

3.2.3 Obesity

Obesity is defined as a chronic, multifactorial metabolic disease, characterized by excessive accumulation of body fat as a result of persistent positive energy balance. It is one of the main global public health problems, associated with chronic low-grade inflammation, metabolic dysfunctions, and hormonal and immunological changes. When the storage capacity of adipose tissue is exceeded, there is an increase in lipolysis, release of free fatty acids, and ectopic deposition of lipids in the liver, pancreas, and skeletal muscle, processes that culminate in lipotoxicity, oxidative stress, insulin resistance, and systemic inflammation (Khanna; Welsh; Rehman, 2024).

Adipose tissue, in addition to energy reserve, exerts an endocrine function, modulating metabolism and immunity through the secretion of adipokines. In obese individuals, however, the release of pro-inflammatory cytokines (IL-6, TNF- α , CRP, IL-18) predominates, in contrast to the anti-inflammatory profile of eutrophic individuals (IL-4, IL-10, TGF- β) (Khanna; Welsh; Rehman, 2024). Epicardial adipose tissue (EAT) has been evaluated as an independent marker of cardiovascular risk. Under physiological conditions, EAT acts protectively, providing local energy and secreting adiponectin. However, in obese and diabetic patients, EAT becomes an important source of inflammatory mediators, promoting myocardial electrical and structural dysfunction, coronary atherosclerosis, and heart failure (Konwerski *et al.*, 2022).

Powell-Wiley *et al.* (2021) reinforce that obesity contributes directly and indirectly to CVD, inducing microvascular remodeling, endothelial dysfunction, myocardial toxicity, and increased atherosclerotic burden since childhood. This effect is associated with oxidative stress and systemic inflammation, which favor lipid oxidation and the early formation of atherosclerotic plaques.

According to the WHO (2022), obesity has a multifactorial etiology, resulting from the interaction between genetics, environment, socioeconomic and behavioral factors. Currently, it is estimated that more than 650 million adults are obese, and could reach 1 billion by 2025.

In addition to CVD, obesity increases the risk of cancer, kidney and chronic respiratory diseases. The continuous growth of obesity is due to global changes in the food system and the prevalence of sedentary lifestyle, highlighting the need for public policies aimed at healthy nutrition and the promotion of physical activity. It should be noted, however, that the treatment of established obesity has low effectiveness in the total reversal of metabolic risk, reinforcing the importance of prevention (WHO, 2022).

3.2.4 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by persistent hyperglycemia and glucose intolerance, mainly due to peripheral insulin resistance and progressive failure of pancreatic β cells. Initially, there is a compensatory increase in insulin secretion; however, with the evolution of the disease, a relative deficiency of the hormone is established (WHO, 2021).

Uncontrolled hyperglycemia results in cumulative damage to the micro and macrovasculature, compromising the kidneys, retina, peripheral nervous system, and, especially, the cardiovascular system. T2DM currently represents one of the major global public health crises, being a central risk factor for atherosclerotic cardiovascular disease (ASCVD), heart failure, and chronic kidney disease. It is estimated that, in 2021, approximately 537 million adults (20 - 79 years) had diabetes, projected to reach 643 million in 2030 and 783 million in 2045. That same year, the disease was responsible for 1.6 million direct deaths, in addition to being implicated in 11% of deaths from cardiovascular causes (International Diabetes Federation, 2021).

A worrying aspect is the increase in the prevalence of DM2 in increasingly younger age groups, as a result of obesity and sedentary lifestyle. Study by Ma *et al.* (2022) emphasizes that the prevention of cardiovascular events in individuals with T2DM requires not only blood glucose control, but also strict management of blood pressure, lipid levels, and smoking cessation.

Despite advances in treatment, it is observed that the residual cardiovascular risk in DM2 is not fully explained by classic factors such as hypertension, dyslipidemia, and smoking. Recent evidence suggests that genetic predisposition, exacerbated insulin resistance, and hypoglycemic episodes also contribute to this additional risk. This understanding reinforces the need for investigation of specific biomarkers that can guide more personalized and effective therapeutic strategies (Ma *et al.*, 2022).

3.2.5 Hypertension

Systemic arterial hypertension (SAH) represents one of the greatest contemporary challenges in public health. It affects more than 1 billion people worldwide and constitutes the main risk factor for acute myocardial infarction, stroke, and heart failure (WHO, 2023). Despite the high prevalence, the rates of diagnosis, treatment and control remain unsatisfactory: only 54% of hypertensive adults have a confirmed diagnosis, 42% are undergoing treatment and only 21% have adequate blood pressure control.

Characterized as an asymptomatic disease, often described as a "silent killer" (Kario *et al.*, 2023), hypertension, when not diagnosed early, evolves to severe and irreversible cardiovascular outcomes. It is estimated that, in Latin America, more than two million annual cardiovascular deaths are associated with arterial hypertension, approximately half of which are premature, before the age of 70 (Sánchez *et al.*, 2024).

The pathophysiology of SAH involves vascular remodeling, endothelial dysfunction, and myocardial overload, mechanisms that increase the risk of both ischemic and hemorrhagic events. Evidence from the CLIDAS study (Otsuka *et al.*, 2024), conducted in Japan with 6,351 patients undergoing percutaneous coronary intervention (PCI), demonstrated that high blood pressure is associated with a higher occurrence of gastrointestinal bleeding after PCI, although no significant difference in the incidence of intracerebral hemorrhage was observed between the groups evaluated. This finding reinforces the role of brain autoregulation, which tends to protect patients with chronic hypertension from acute pressure fluctuations.

In view of the epidemiological magnitude of hypertension, prevention strategies, systematic screening, and integrated public policies are essential to reduce premature mortality and improve the quality of life of the population, especially in developing countries.

3.2.6 Dyslipidemia

Dyslipidemia, defined by quantitative and/or qualitative changes in the plasma lipid profile, is one of the main modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD) (Soppert *et al.*, 2020). Classic alterations include increased low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides (TG), which compromise lipid homeostasis and favor atherogenesis (Roth *et al.*, 2021).

Lipid metabolism is dynamic and interconnected, with lipoproteins as the main means of transport of hydrophobic lipids in the circulation. Among them, HDL-C stands out, responsible for the reverse transport of cholesterol, removing it from peripheral tissues and

returning it to the liver for excretion or recycling. Deficiencies in this process result in LDL-C accumulation and increased atherosclerotic plaque formation (Liu *et al.*, 2022).

In addition to the direct effects on atherogenesis, dyslipidemia contributes to endothelial dysfunction, chronic low-grade inflammation, insulin resistance, and oxidative stress, configuring a pro-atherogenic and pro-thrombotic environment (RHEE *et al.*, 2024). Recent evidence also points to the influence of the gut microbiota on the modulation of lipid metabolism and, consequently, on cardiovascular risk. The high prevalence of dyslipidemia makes it a global public health problem, requiring prevention and management strategies that combine lifestyle changes, lipid-lowering pharmacological therapies and, in specific cases, emerging therapies targeting specific lipid biomarkers. Adequate control of serum LDL-C and TG levels remains the central axis in the primary and secondary prevention of ASCVD.

3.2.7 Metabolic Syndrome

The Framingham Heart Study (FHS), started in 1948, is one of the most important milestones in understanding the epidemiology of cardiovascular diseases. This multigenerational study made it possible to identify classic risk factors, such as smoking, systemic arterial hypertension (SAH), high levels of total cholesterol and low-density lipoprotein (LDL-c), low levels of high-density lipoprotein (HDL-c), type II diabetes mellitus, advanced age, obesity, and sedentary lifestyle, laying the foundations for the primary and secondary prevention of heart disease (Mahmood *et al.*, 2013).

With the advances in research, new perspectives have been incorporated, expanding the understanding of the determinants of cardiovascular disease. Jurcut *et al.* (2017) highlight the relevance of adipose tissue-derived biomarkers, such as leptin, resistin, and adiponectin; inflammatory markers, such as ultrasensitive C-reactive protein (hs-CRP); prothrombotic state biomarkers, such as fibrinogen and plasminogen-1 activator inhibitor (PAI-1); in addition to the anomalous distribution of body fat (visceral fat and hepatic steatosis), insulin resistance (IR) and hyperinsulinemia (HI). In this context, the concept of metabolic syndrome was consolidated, defined as a set of interconnected clinical and biological factors that increase the risk of cardiovascular disease and type II diabetes.

Rus *et al.* (2023) point out that age and sex significantly influence the prevalence of metabolic syndrome, and men tend to have an increased risk compared to women, although in both genders this risk increases with aging. In addition, socioeconomic and behavioral factors, such as smoking, inadequate dietary patterns, and sedentary lifestyle, play a central role in its etiology. In this sense, the regular practice of physical activity emerges as an

important protective factor, reinforcing the need for prevention and early intervention strategies.

From a therapeutic point of view, Visseren *et al.* (2021) emphasize that the treatment of metabolic syndrome should prioritize lifestyle changes, with emphasis on weight reduction, balanced nutrition, and regular physical activity. Clinical management should also include the control of modifiable risk factors, such as arterial hypertension and dyslipidemia, in line with international guidelines. Early detection and prompt initiation of interventions are key to mitigating the risk of cardiovascular complications.

3.2.8 Heredity

Genetic inheritance has been shown to be a determining factor in cardiovascular risk. Despite advances in the knowledge of the molecular mechanisms involved in heart failure, therapeutic options still do not keep pace with the speed of discoveries. In this scenario, calcium-dependent protein kinase II/calmodulin (CaMKII) stands out, which is involved in pathological cardiac remodeling and arrhythmia induction. Experimental evidence suggests that modulation of this pathway may have a therapeutic effect, although the translation of experimental findings to clinical practice remains a challenge. Strategies under development include the use of small inhibitor molecules, genetic approaches, and novel drug delivery platforms, which aim to overcome historical barriers and enable innovative therapies for heart failure (Nassal *et al.*, 2020).

In the field of cardiogenetics, family history and genomic variations have been consistently associated with the risk of myocardial infarction (MI). Helgadottir *et al.* (2004) identified that variations in the 5-lipoxygenase activating protein contribute to greater inflammation of the arterial wall and increased leukotriene production, favoring the occurrence of DI. In another study, Do *et al.* (2014) demonstrated that rare alleles of the low-density lipoprotein receptor and apolipoprotein A5 are associated with increased risk for the event. In addition, Han *et al.* (2013), in a meta-analysis, observed that the rs671 polymorphism of mitochondrial aldehyde dehydrogenase 2 increases susceptibility to infarction. Anand *et al.* (2009), in a multicenter study with more than 8,000 individuals from five different ethnic groups, reported that 13 single nucleotide polymorphisms (SNPs) associated with apolipoprotein B levels increased the risk of MI, reinforcing the relevance of genetic factors in cardiovascular pathophysiology.

3.3 ANTITHROMBOTIC THERAPY AND VASCULAR COMPLICATIONS

In recent decades, percutaneous coronary intervention (PCI) has been consolidated as the main strategy for myocardial revascularization, being widely used in patients with advanced coronary artery disease. The efficacy of this procedure is directly related to appropriate antithrombotic therapy, involving antiplatelet and anticoagulant agents. It is a fundamental pharmacological intervention not only in the acute phase, but also in the long-term prevention of recurrent ischemic events (Castiello *et al.*, 2025).

According to a systematic review by Castiello *et al.* (2025), the optimization of antithrombotic therapy in patients undergoing complex PCI constitutes a significant clinical challenge. More intense or prolonged regimens may reduce ischemic load, but often increase the risk of bleeding, creating therapeutic dilemmas. The study reinforces the need to individualize strategies according to the clinical profile of the patient and the anatomical complexity of PCI, since standardized approaches do not adequately contemplate the heterogeneity of this population.

Currently, dual antiplatelet therapy (DAPT), consisting of aspirin plus a P2Y₁₂ inhibitor, remains the mainstay of secondary prevention. However, its duration and intensity must be carefully adjusted. In patients with complex PCI and high ischemic risk, prolonged DAPT may bring additional benefits, although accompanied by greater hemorrhagic risk. On the other hand, monotherapy with P2Y₁₂ inhibitors, especially ticagrelor, emerges as a promising alternative for patients at high risk of bleeding and moderate ischemic risk, reducing bleeding complications without loss of efficacy (Castiello *et al.*, 2025).

The meta-analysis by Laudani *et al.* (2025), involving 23 clinical trials and more than 45,000 patients, evaluated the early transition from DAPT to antiplatelet monotherapy in patients with acute coronary syndrome (ACS) undergoing PCI. The results showed superiority of P2Y₁₂ inhibitor monotherapy over aspirin alone, with a significant reduction in net adverse clinical events (NACE), encompassing ischemic and hemorrhagic outcomes. Aspirin monotherapy had a neutral effect, without the benefits observed with P2Y₁₂ inhibitors.

Another relevant aspect is radial artery occlusion (RAO), a complication associated with transradial access in PCI. Amirpour *et al.* (2023), in a pilot, double-blind, randomized clinical trial, included 30 patients with post-transradial angiography RAO, allocating them to apixaban (2.5 mg twice daily) or conservative management for 30 days. The recanalization rate was 70% in the treated group, suggesting the efficacy of apixaban in restoring arterial patency.

In a prospective study by Lounes *et al.* (2024), with 427 patients undergoing PCI, two modifiable factors strongly associated with RAO were identified: insufficient heparinization and occlusive hemostasis. Prevention involves adequate intraprocedural anticoagulation, "patent" hemostasis (preserving antegrade flow during compression), active surveillance to avoid hypercompression, in addition to technical measures such as the use of ultrasound for puncture, selection proportional to the radial diameter of the sheath and management of arterial spasm (analgesia, light sedation and intra-arterial vasodilators).

In the treatment of established RAO, most cases remain asymptomatic, with the potential for spontaneous repatence, especially in arteries of larger caliber. The findings of Lounes *et al.* (2024) corroborate those of Amirpour *et al.* (2023), suggesting that a short course of apixaban may favor recanalization. However, generalization of this approach should be cautious, since there is still a lack of robust evidence on safety, especially regarding the risk of bleeding.

Antithrombotic management in complex PCI is, therefore, a field in constant evolution. Decision-making should integrate clinical factors, procedural complexity, and up-to-date evidence in order to maximize ischemic benefits and minimize bleeding risks. The performance of qualified health professionals, capable of performing early assessments and implementing preventive measures, is crucial to mitigate complications such as bleeding, bruising, and RAO. Continuous research is indispensable to refine therapeutic strategies and improve clinical outcomes in this vulnerable population (Laudani *et al.*, 2025).

3.3.1 Antiplatelet Agents and Anticoagulants

Antiplatelet therapy is the mainstay of pharmacological treatment to prevent thrombotic or ischemic events in patients with ACS or undergoing PCI. Its use is indicated even in the face of hemorrhagic risks, and it is a challenge to define the ideal intensity of platelet inhibition considering individual patient factors and the clinical presentation of atherosclerotic disease. The modulation of antiplatelet therapy, by reducing (de-escalation) or increasing (escalation) the intensity, aims to balance the risk of thrombotic and hemorrhagic events. This modulation may involve changes in the type of drug, dose, or number of antiplatelet agents, with several emerging strategies described in the literature (Capodanno *et al.*, 2023).

Collet *et al.* (2024) reinforce that DAPT is effective in reducing atherothrombotic events, although it increases the risk of bleeding. Traditionally, it is recommended to maintain DAPT for 12 months after ACS, barring bleeding concerns. After this period, single antiplatelet therapy (SAPT), usually with aspirin, is indicated and is considered standard for

thrombotic prevention in patients with coronary artery disease, regardless of the need for revascularization.

Capodanno *et al.* Wang *et al.* (2023) emphasize that, in patients with no initial indication for oral anticoagulation, the individualization of antiplatelet therapy is decisive for prognosis. The intensity of inhibition should be adjusted according to the stage of the disease and clinical conditions, and may occur by de-escalation or escalation, including changes in the type of drug, the dose, or the number of agents used.

3.4 VASODILATOR THERAPY AND VASCULAR COMPLICATIONS

In recent decades, the transradial approach (TRA) has been consolidated as the main access for diagnostic and therapeutic procedures in hemodynamics, especially in percutaneous coronary intervention (PCI), due to its safety profile and the associated clinical and economic benefits. Compared to the femoral approach, RTA is related to a lower incidence of vascular and hemorrhagic complications, reduced mortality in high-risk patients, greater patient comfort, reduced length of stay, and decreased hospital costs (Silva *et al.*, 2023).

One of the most relevant complications associated with RTA is radial artery spasm (RAS), a condition that can compromise the progression of the procedure and cause severe pain. The pathophysiology of RAS involves an intense vasoconstrictor response mediated by mechanical stimuli during catheter manipulation, aggravated by factors such as reduced vessel caliber, female gender, anxiety, and local pain (Silva *et al.*, 2023). Prevention of spasm is based mainly on the intra-arterial administration of vasodilator agents — usually a "spasmolytic cocktail" composed of verapamil and nitroglycerin. Verapamil, a calcium channel blocker, promotes vascular smooth muscle relaxation, but may induce negative inotropic and chronotropic effects, limiting its use in patients with left ventricular dysfunction. Nitroglycerin, in turn, acts as a nitric oxide donor, leading to rapid vasodilation, but is contraindicated in cases of significant hypotension (Silva *et al.*, 2023).

Despite technological advances and improved techniques, the EAR still poses a significant technical challenge. In the study conducted by Da Silva *et al.* (2023), the 2,040 participants were randomized to receive nitroglycerin or placebo at two different times: (i) early administration, immediately after radial puncture, and (ii) late administration, at the end of the procedure. The primary endpoint was radial artery occlusion (RAO), assessed by Doppler ultrasonography up to 24 hours after the procedure and reassessed at 30 days.

The results showed the absence of a significant protective effect of prophylactic nitroglycerin on the overall incidence of RAS. However, a relevant benefit was observed in

cases conducted by operators in the initial phase of training, suggesting that the efficacy of pharmacological prophylaxis can be modulated by the technical experience of the hemodynamicist. These findings reinforce that the prevention of RAS depends on multiple factors, including not only the judicious use of vasodilating agents, but also the technical mastery of the operator, the appropriate selection of devices, and the adoption of non-pharmacological measures, such as minimizing arterial manipulation time and choosing smaller-caliber hydrophilic sheaths (Silva *et al.*, 2023).

Thus, recent literature emphasizes that the ideal approach to the prevention of RAS should integrate pharmacological and technical strategies, personalized according to the clinical profile of the patient and the experience of the team, with a view to preserving arterial patency and optimizing clinical outcomes.

3.5 LABORATORY PARAMETERS ASSOCIATED WITH VASCULAR COMPLICATIONS

Laboratory evaluations of vascular complications after procedures such as percutaneous coronary intervention (PCI) require an integrated approach between clinical findings, imaging methods, and laboratory parameters. However, laboratory tests play a prominent role both in the diagnosis of adverse events that have already been established, but also in the prediction and stratification of the risk of vascular complications. Among the parameters traditionally used, hemoglobin and hematocrit levels remain a fundamental marker in the detection of acute bleeding, allowing the monitoring of blood loss associated with vascular access or internal bleeding complications. However, more recent analyses suggest that the use of additional laboratory biomarkers may increase the predictive capacity of these tests (Cannon *et al.*, 2024).

The systemic inflammatory profile has been shown to be a relevant component in the risk assessment. The elevation of ultrasensitive C-reactive protein (hs-CRP), for example, reflects inflammatory and endothelial processes that increase vascular vulnerability and are associated with a higher risk of post-procedural complications. Markers such as erythrocyte sedimentation rate (ESR), although less specific, can complement this assessment (Hu *et al.*, 2021).

Parameters related to hemostasis and coagulation have also been explored. Changes in platelet levels at prothrombin time (PT) or activated partial thromboplastin time (aPTT) may signal a predisposition to bleeding or thrombosis. Similarly, D-dimer measurement can act as an indirect marker of coagulation activation and thrombus formation, being useful in stratifying the risk of severe vascular complications (Cannon *et al.*, 2024).

Another relevant aspect concerns kidney function. Elevated serum creatinine and reduced glomerular filtration rate (GFR) are strongly associated not only with the risk of contrast-induced nephropathy, but also with a higher incidence of bleeding complications and adverse cardiovascular events after PCI. Thus, the prior and serial evaluation of these parameters is considered strategic for clinical decision-making. Markers of metabolic stress and tissue hypoxia, such as serum lactate levels, may indicate inadequate perfusion due to extensive hemorrhages or shock, and are auxiliary tools both in the early diagnosis and in predicting the severity of vascular complications (Katrukra *et al.*, 2021).

It is observed that the prediction of vascular complications involves not only the monitoring of classical hematimetric parameters, but also the incorporation of inflammatory, hemostatic, renal and metabolic biomarkers, whose integrated interpretation provides valuable subsidies for risk stratification, therapeutic planning and reduction of morbidity and mortality in patients undergoing hemodynamic procedures.

3.5.1 Troponins

According to international guidelines, the diagnosis of myocardial infarction (MI) involves the measurement of cardiac troponins I (cTnI) and T (cTnT), recognized as highly specific and sensitive biomarkers of myocardial injury (Thygesen *et al.*, 2018). However, these markers have low efficacy in episodes of unstable angina. The main etiology of MI is related to inadequate oxygen supply, resulting in acute ischemia of cardiac tissue.

During the ischemic process, necrosis of cardiomyocytes occurs, with rupture of cell membranes and release of intracellular proteins into the bloodstream. This mechanism leads to a progressive increase in serum troponin levels, which peak between 10 and 20 hours in patients undergoing coronary reperfusion and between 24 and 50 hours in the absence of intervention. The elevation may persist for 10 to 14 days, longer than that observed for other biomarkers, such as creatine kinase-MB (CK-MB) and myoglobin. This prolonged release is explained by the strong binding of the troponin complex to the structures of the thin filaments in cardiomyocytes (Katrukra *et al.*, 2021).

Despite the high specificity of the cTnT and cTnI isoforms, their elevation is not restricted to AMI. Other conditions, reversible or irreversible, such as pulmonary embolism, sepsis, chronic renal failure, myocarditis, and endocarditis, can also cause increased serum levels. Thus, it is essential for researchers and health professionals to understand the different causes and mechanisms involved, in order to interpret laboratory results appropriately (Chauim, 2021).

The development of high-sensitivity methods for the measurement of cardiac troponins has made it possible to detect elevations even in non-ischemic contexts, expanding their clinical usefulness, but also generating challenges for differential diagnosis. Recent studies have shown that variables such as age, gender, and the presence of comorbidities significantly influence reference values. In patients with chronic renal failure, for example, the interpretation becomes even more complex (Tew *et al.*, 2024).

In a multicenter investigation, Neumann *et al.* (2024) evaluated the effectiveness of different cardiovascular biomarkers, high-sensitivity troponin I and T, NT-proBNP, BNP, and ultrasensitive C-reactive protein (hs-CRP), in predicting clinical events. The study, based on 28 population cohorts from 12 countries spread over four continents, followed participants for a median period of 11.8 years, considering stratification by age. The findings showed a consistent association between biomarkers and the occurrence of fatal and non-fatal cardiovascular events, as well as with total mortality.

According to the authors, the combined assessment of these markers provided additional gains in risk stratification compared to models based only on traditional risk factors. The predictive impact was most significant for heart failure and all-cause mortality in individuals aged 65 years and older. Although the increases in the prediction of risk for atherosclerotic disease have been limited, the results reinforce the relevance of biomarkers in the early identification of vulnerable individuals, in addition to highlighting their role in supporting the implementation of effective preventive strategies to reduce cardiovascular risks (Neumann *et al.*, 2024).

3.5.2 Creatine Kinase-MB (CK-MB)

Although troponin is the biomarker of choice for the diagnosis of AMI, the measurement of total CK, and especially of the CK-MB fraction, is still clinically relevant. A CK-MB/CK ratio greater than 6% indicates myocardial injury, while lower values suggest a non-cardiac origin. Elevated CK-MB levels in patients with STEMI undergoing primary angioplasty are associated with higher mortality. Despite the high sensitivity (90%), the specificity of CK-MB is considered relatively low, limiting its use alone (Popa *et al.*, 2023).

Regarding the time of release, CK-MB becomes detectable up to 12 hours after the onset of symptoms, peaking between 24 and 36 hours and returning to normal in 48 to 72 hours. Thus, it is not indicated for early diagnosis. However, its analysis can be useful for estimating the extent of infarction and predicting left ventricular dysfunction, especially when peak levels exceed 300 U/L (Dohi *et al.*, 2018).

3.5.3 Leukocyte Parameters

The identification of hematological parameters that are capable of inferring about the risk of complications in patients with cardiovascular diseases is relevant in the scenario of health services in order to support personalized therapeutic strategies. In this context, hematological biomarkers have received increasing attention, especially with regard to leukocyte counts (total and subpopulations) and their inflammatory indices, such as the Neutrophil-Lymphocyte Ratio (NLR), which may be associated with cardiovascular outcomes in patients undergoing percutaneous coronary intervention (PCI) (Alkarithi *et al.*, 2021).

The evaluation of the leukogram may be relevant, as these cells participate in the thrombotic process, being identified in thrombi of arterial and venous origin. The interaction of leukocytes with fibrin occurs through integrin $\alpha M\beta 2$ (Mac-1), a receptor involved in mediating the inflammatory response. Among the leukocyte subtypes, neutrophils stand out for their abundance in the circulation and for their ability to release bioactive mediators, such as matrix metalloproteinases, which act as platelet activation factor, cathepsin G, and elastase, which modulate coagulation by different pathways - from the activation of factors V, VIII, and X to the stimulation of platelet activation and the degradation of natural anticoagulants, such as antithrombin III, in addition to tissue factor (TF) pathway inhibitor cleavage. Monocytes, in turn, act as an important source of tissue factor in the intravascular environment, offering a cell surface conducive to triggering the coagulation cascade. There is also evidence that neutrophils can express tissue factor under certain conditions, although the results remain divergent (Alkarithi *et al.*, 2021).

In a recent study, Shah *et al.* (2017) reinforce that both total leukocyte count (CTL) and its subtypes have been widely investigated as predictors of outcomes in patients undergoing PCI. An elevated CTL, even before the procedure, is consistently associated with increased risk of major adverse cardiovascular events (MACE) and mortality. This relationship is attributed to the underlying systemic inflammation, which contributes to the progression of coronary artery disease and to an exacerbated response to periprocedural injury.

3.5.4 Erythrocyte Parameters

Erythrocytes, in addition to oxygen transport, have emerged as active elements in the pathophysiology of cardiovascular diseases, especially hemostasis and thrombosis. Evidence indicates that these cells also participate in the formation, structure, and function of the blood clot (Tutwiler *et al.*, 2018; Byrnes; Volberg, 2017).

Erythrocytes contribute to thrombin generation by pathways other than platelet-mediated pathways, since erythrocytes can express phosphatidylserine (PS) on their surface, which acts on thrombin synthesis through the meizothrombin pathway. This ability evidences the active role of erythrocytes in clot stabilization (Whelihan; Mann, 2013). In addition, Klatt *et al.* (2018) highlight that, in addition to their morphological transformations, erythrocytes interact in a complex way with platelets and plasma components, reinforcing their role in modulating coagulation.

Under conditions of mechanical stress, erythrocytes can take the form of polyhocytes, contributing to the compaction of the thrombotic network and increasing the resistance of the thrombus to lysis. In addition, molecular interactions, such as the FasL/FasR binding between erythrocytes and platelets, favor a procoagulant environment. Factor XIII also actively participates in the retention of erythrocytes in venous thrombi, influencing their composition and stability. Changes in erythrocyte membrane stiffness, as seen in sickle cell disease, amplify thrombotic risk and impact clinical prognosis (Alkarithi *et al.*, 2021). In this context, erythrocytes are important mediators of hemostasis and thrombosis, and the investigation of these processes can open perspectives in the prevention of complications and complications in PCI procedures.

3.5.5 Anemias

Anemia also plays a relevant role as a prognostic marker in cardiovascular diseases. In a community cohort study with the elderly, Cannon *et al.* (2024) noted that both anemia and iron deficiency in non-anemic individuals were associated with higher all-cause mortality, including cardiovascular disease, cancer, and respiratory conditions. In this study, 21% of the 4,020 participants had anemia, with hemoglobin concentrations < 12 g/dL in women and < 13 g/dL in men.

Blood transfusion, often used in cases of anemia associated with MI, is still a matter of debate. In a multicenter randomized clinical trial, Carson *et al.* (2022) compared liberal (Hb $\geq$ 10 g/dL) and restrictive (Hb < 8 g/dL) transfusion strategies, concluding that both can be safe, but have different implications. While the liberal strategy can improve oxygen delivery to the vulnerable myocardium, it also increases the risk of adverse effects, such as vascular inflammation and increased blood viscosity (Cannon *et al.*, 2024).

In addition, recent studies highlight the relationship between anemia and complications after percutaneous coronary intervention (PCI). In an investigation with 538 patients undergoing PCI, Hu *et al.* (2021) identified a significant association between anemia and a higher risk of in-stent restenosis (ISR). The presence of anemia, associated with

comorbidities such as diabetes mellitus and chronic kidney disease, significantly increased the incidence of SRI, indicating that low hemoglobin levels are an important risk factor in patients undergoing revascularization procedures.

3.5.6 Platelet Parameters

Platelets, cell fragments derived from bone marrow megakaryocytes, play a central role in hemostasis and thrombotic and inflammatory processes. In addition to their classic role in coagulation, they play a decisive role in all phases of atherosclerosis, a condition underlying coronary artery disease (CAD). In scenarios of endothelial dysfunction, platelets are the first blood cells to adhere to the vascular wall, promoting leukocyte recruitment and releasing adhesive, pro-inflammatory, and mitogenic factors that favor the progression of atherosclerotic injury (Shen *et al.*, 2025).

Both platelet count and functional reactivity of these cells vary according to the patient's clinical status. In acute myocardial infarction, for example, significant changes in these parameters reflect a higher risk of ischemic complications. Among the platelet indexes of routine use, the mean platelet volume (MPV) stands out, which represents the average size of platelets and reflects their degree of metabolic activity. Larger and denser platelets have higher granular and internal membrane content, which is associated with greater thrombogenic potential and, consequently, an increased risk of adverse cardiovascular events (Shen *et al.*, 2025).

In a study by Shen *et al.* (2025), involving 1,675 patients undergoing coronary angiography, analyzed associations between platelet indices and early coronary artery disease (PCAD), late-onset CAD (LCAD), and control group. After adjusting for traditional cardiovascular risk factors, it was observed that MV and platelet-to-large cell ratio (P-CSF) showed an inverse association with the presence of PCAD, while platelet-to-lymphocyte ratio (PLR) was positively correlated with the number of coronary lesions. In addition, CSF has been identified as an independent risk factor for coronary restenosis after percutaneous coronary intervention (PCI).

In this scenario, platelet indices, although widely available and low-cost, can provide additional information on risk stratification, disease severity, and clinical prognosis. Although there is still debate about their specific role in early coronary artery disease, these laboratory parameters emerge as valuable auxiliary tools in the context of the hemodynamics service, especially in the evaluation of vascular complications and in post-PCI monitoring.

3.5.7 Cell relationships derived from the Blood Count

Biomarkers derived from hematological parameters, such as platelet-to-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR or NLR), have stood out as prognostic tools in the context of cardiovascular diseases, especially in ST-segment elevation acute myocardial infarction (STEMI). These relationships reflect fundamental pathophysiological processes, such as systemic inflammation, immune response, and thrombotic state, allowing to assist in risk stratification and therapeutic follow-up of these patients (Précoma, 2022).

The PLR is a hematological index that expresses the interaction between inflammatory and thrombotic mechanisms. In the study of Precoma (2022), investigated the prognostic value of PLR in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI). The results showed that elevated pre-procedure PLR levels were associated with poorer in-hospital and long-term prognosis, including higher risk of all-cause mortality, cardiovascular mortality, major adverse cardiovascular events (MACE), and absence of adequate post-PCI reperfusion. Thus, the pre-procedural PLR proves to be a robust marker for the identification of patients at higher risk.

Similarly, NLR (or NLR) has emerged as an important predictor of mortality and cardiovascular adverse outcomes. The relationship is calculated by dividing the count of neutrophils and lymphocytes, cells that play opposite roles in the inflammatory and atherothrombotic process: neutrophils participate in the propagation of thrombosis and destabilization of atherosclerotic plaque, while lymphocytes contribute to the modulation of inflammation and stabilization of plaque (Sezer *et al.*, 2007; Dragu *et al.*, 2008).

A meta-analysis by UI Hussain *et al.* (2024), based on 35 studies, confirmed that elevated NLR is associated with a higher risk of all-cause mortality, cardiovascular mortality, MACE, prolonged hospital stay, occurrence of arrhythmias, angina, nonfatal infarction, no-reflow phenomenon, cerebrovascular accident (CVA), in addition to late outcomes such as in-stent thrombosis and need for revascularization. Other previous studies had already described this association. Tamhane *et al.* (2008) demonstrated that an elevated NLR before PCI correlated with higher long-term mortality, while Duffy *et al.* (2006) corroborated these findings, reinforcing the prognostic value of this biomarker.

In addition, the relevance of NLR transcends the cardiovascular context. Ullah *et al.* (2020) highlighted its usefulness in predicting adverse outcomes in patients with COVID-19, expanding the recognition of its clinical applicability as a nonspecific but sensitive inflammatory marker. Farkas (2022) points out that NLR synthesizes individual changes in the leukocyte count in a simple index, but with high prognostic capacity, especially in situations of physiological stress.

Recent studies also reinforce the role of circulating T lymphocytes in the evolution of myocardial ischemia. Boag *et al.* (2015) showed that lymphocyte dysfunction is associated with worsening of ischemia-reperfusion lesion after infarction, suggesting a central immunological role in the progression of cardiac damage.

Therefore, both LPR and NLR are easily obtained, low-cost, and immediately applicable hematological markers in clinical practice, providing relevant prognostic information in patients with STEMI undergoing PCI. The use of these indices can help in the early identification of individuals at higher risk of complications, allowing targeted therapeutic interventions and more rigorous monitoring, in line with the growing trend of using biomarkers in the management of cardiovascular diseases.

3.5.8 Creatinine

Percutaneous coronary intervention (PCI) involves the administration of iodinated contrast, which can lead to contrast-induced *nephropathy* (CIN), one of the most prevalent complications in this context. CIN is considered when there is an increase in serum creatinine ≥ 0.3 mg/dL (26.5 μ mol/L), an increase ≥ 1.5 times in relation to the baseline value, or a reduction in urine output to < 0.5 mL/kg/h in the period from 1 to 7 days after contrast exposure (Pranata; Wahyudi, 2023).

Modi *et al.* (2025) define CIN as a $\geq 25\%$ increase in serum creatinine from baseline or an absolute increment of 0.5 mg/dL (44 μ mol/L) within 48 to 72 hours after intravenous contrast exposure, provided there is no other identifiable cause for renal dysfunction. Serum creatinine levels usually peak between two and five days after the procedure, returning to baseline values in about 10 to 14 days in most cases.

CIN is associated with a higher risk of morbidity and mortality, especially in patients with chronic kidney disease, diabetes mellitus, or hypertension, in whom 20% to 30% may progress to persistent renal dysfunction. The need for dialysis is rare in individuals without diabetes (1%–3%), while in diabetics it can range from 10% to 15%, with about 20% remaining dependent on dialysis on a permanent basis (Pranata; Wahyudi, 2023; Modi *et al.*, 2025).

Prior evaluation of renal function, with emphasis on the measurement of serum creatinine and estimation of glomerular filtration rate (eGFR), is an essential step in the preparation for PCI. Patients with $\text{eGFR} < 60$ mL/min/1.73 m² should receive prophylactic intravenous hydration, initiated about 12 hours before the procedure and maintained for up to 24 hours after the intervention. Additional measures include discontinuation of nephrotoxic drugs, use of low or iso-osmolarity contrast, contrast volume restriction (maximum eGFR $\times$

3.7), choice of radial access route, volume minimization systems, and advanced intracoronary imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) with alternative contrast agents (Pranata; Wahyudi, 2023).

In selected cases, more sophisticated protocols can be applied, including hemodynamic monitoring guided by central venous pressure or left ventricular end-diastolic pressure, and association of hydration with diuretics such as furosemide, in order to optimize renal protection. Such strategies make it possible to reduce the incidence of CIN and minimize complications, ensuring procedural safety and better post-PCI recovery (MODI *et al.*, 2025). In this context, serum creatinine is a fundamental laboratory marker in the identification of patients susceptible to renal complications, and is indispensable for risk stratification and implementation of preventive measures in the context of the hemodynamics service.

3.5.9 Urea

Assessment of renal function in the pre-procedure period of a percutaneous coronary intervention (PCI) is important, as renal dysfunction is an independent predictor of adverse outcomes. Among the available tests, urea, in association with creatinine and other biomarkers of acute kidney injury (AKI), can provide relevant subsidies for risk stratification and clinical management of these patients (Laville *et al.* 2022).

Elevated serum urea levels have been pointed out as potential predictors of mortality and adverse cardiovascular events in individuals undergoing PCI, reflecting both the degree of renal dysfunction and associated metabolic changes (Laville *et al.* 2022). The Kidney Disease: Improving Global Outcomes guidelines (Ahmed *et al.*, 2024) reinforce the need for comprehensive assessment of kidney function for risk stratification in patients, as well as monitoring of proper kidney function. Although urea alone is not sufficient for clinical decision-making in PCI, its analysis integrated with other biomarkers can help in the early identification of patients who are more vulnerable to complications, increasing the safety of the procedure.

The use of iodinated contrast agent during PCI also poses an additional risk to renal function, and may trigger or aggravate AKI. Therefore, careful evaluation of renal function, both before and after the procedure, is essential to reduce the probability of unfavorable outcomes. Thus, the measurement of urea levels, associated with other laboratory parameters, should be valued as a complementary tool in the management of patients with cardiovascular disease, allowing for the anticipation of risks, guidance of preventive conducts, and favoring better clinical results.

3.5.10 Sodium (Na⁺) and Potassium (K⁺)

The human body is composed of approximately 20 elements, of which ten metals and ten non-metals. Among the essential metals are sodium (Na⁺), potassium (K⁺), magnesium (Mg), iron (Fe), zinc (Zn) among others, known as trace elements. Deficiencies or excesses of these metals are linked to disease, and their chemical properties, especially binding strength and mobility, explain both their biological roles and their toxicity (Sigel *et al.*, 2013).

Sodium (Na⁺) and potassium (K⁺) ions play an essential role in the generation of electrochemical gradients through biological membranes, which are fundamental for cellular excitability. In ion channels, K⁺ is favored by high hydration and permeability, while Na⁺ is restricted to less favorable coordination, ensuring selectivity. In biological systems, they exhibit variable coordination numbers, usually octahedral with oxygen-donating ligands such as hydroxyl and carboxylate. In addition, crystallographic structures demonstrate that these cations can act as cofactors in specific proteins, evidencing their relevance in maintaining biological activity (Pohl *et al.*, 2013)

In agreement with the study by Jomova *et al.* (2022), sodium (Na⁺) and potassium (K⁺) are electrolytes essential for cellular homeostasis, regulating osmotic pressure, pH, water transport, energy metabolism, enzymatic functions and electrical excitability. Sodium predominates in the extracellular medium (135 - 150 mmol/L), while potassium is the main intracellular cation (140 - 150 mmol/L), maintaining the electrochemical gradient necessary for membrane potential. These gradients are supported by Na⁺/K⁺ - ATPase, which consumes a large part of cellular energy, especially in the brain, and also plays a relevant role in kidneys, heart, and sperm motility.

Sodium homeostasis is controlled by ingestion, renal excretion, and hormonal action (aldosterone), and its dysregulation is associated with hyponatremia (excess water or loss of sodium) and hypernatremia (loss of water or excess sodium). In relation to potassium, homeostasis depends on the balance between intake, excretion and intracellular distribution, and is involved in frequent clinical conditions such as hypokalemia (levels <3.5 mmol/L), related to digestive and urinary losses or the use of diuretics, and hyperkalemia (levels >5 mmol/L), common in patients with renal failure or using drugs that reduce its excretion. Relating to cardiovascular diseases and complications in hemodynamic services, these two elements are associated with the development of arrhythmias and, in more severe cases, potentially fatal complications such as infarctions (Jackson *et al.*, 2014).

In addition, Jomova *et al.* (2022) describe that both deficiency and excess of essential metals can result in various disease states that arise in an organism. Some typical diseases that are characterized by a disturbed homeostasis of active redox metals include

neurological disorders (Alzheimer's, Parkinson's, and Huntington's diseases), mental health problems, cardiovascular disease, cancer, and diabetes.

3.5.11 Infectious Pathologies

Percutaneous coronary intervention (PCI) is performed under strict aseptic conditions; however, there is still a risk of infectious complications in these procedures. In this sense, Marin (2022) demonstrated the occurrence of transient bacteremia, with a prevalence between 4 and 8% of procedures, often related to the *Staphylococcus spp. germ.element*. Although asymptomatic in most cases, bacteremia can progress to severe conditions, including endocarditis, mycotic aneurysm, sepsis, and lesions at the arterial puncture site, conditions associated with high mortality. Such complications often require surgical intervention and prolonged antibiotic therapy.

The risk of infection is higher in patients with congestive heart failure, age over 60 years, diabetes mellitus, and obesity. In addition, technical factors such as multiple punctures, prolonged permanence of the sheath for hemodynamic management, and failures in the aseptic technique increase the probability of contamination. It is also observed that the femoral access presents a higher infectious risk than the radial access. It is recommended that any patient who presents with fever, chills, or signs of bacteremia within the first four weeks after PCI be carefully evaluated to exclude infectious complications (Marin, 2022).

In patients with ST-elevation acute myocardial infarction (STEMI), pneumonia after successful primary PCI represents a severe and often lethal complication. A study conducted at Jinhua Central Hospital, involving 619 patients with STEMI, investigated the occurrence of pneumonia in the first two weeks after the procedure. In this context, the systemic inflammatory response index (IRIS), calculated by the formula $(\text{neutrophils} \times \text{monocytes}) / \text{lymphocytes}$, was used as a predictive inflammatory marker (Yan; Wang, 2025).

The results demonstrated that high IRIS values (≥ 4.04) constitute an independent risk factor for the development of post-PCI pneumonia, surpassing in prognostic accuracy the isolated hematological parameters, such as leukocyte, neutrophil, monocyte, and lymphocyte counts. This finding reinforces that inflammatory biomarkers, such as IRIS, systemic immunoinflammation index (IBS), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR), play a crucial role in risk stratification (Yan; Wang, 2025).

Mechanistically, neutrophils contribute to the activation of the systemic inflammatory response, favoring instability and rupture of atherosclerotic plaques, as well as coronary thrombosis. The reduction in lymphocyte count, in turn, reflects an increase in lymphocyte apoptosis, compromising immune function and increasing susceptibility to infections.

Therefore, the integrated evaluation of these laboratory parameters allows greater precision in the early diagnosis and prognosis of infectious complications, representing an essential tool for the clinical management of patients undergoing PCI.

3.6 LABORATORY BIOMARKERS APPLIED TO THE HEMODYNAMICS SERVICE

3.6.1 Fluoroscopy Time

Percutaneous coronary interventions (PCIs) expose patients and medical staff to radiation doses. The magnitude of this exposure depends on multiple factors, including the duration of the procedure, the type of equipment used, the technique used, and the experience of the hemodynamicist. In addition, aspects such as beam projection and angulation, catheter type, patient anatomical variability, and lesion complexity directly influence the absorbed dose (Tarighatnia *et al.*, 2017).

In this context, the current equipment used in hemodynamics has integrated hardware and software systems that automatically record radiation exposure indicators. Among these parameters, the following stand out: cumulative air kerma (AK), cumulative dose-area product (DAP), total fluoroscopy time (TF), total cineangiography time (CT), and total number of kineangiographic sequences (Gurajala *et al.*, 2025).

As described by Gurajala *et al.* (2025), the air kerma (AK) corresponds to the energy transferred by radiation to an air mass, expressed in milliGrays (mGy). Its measurement is performed at the interventional reference point, located 15 cm before the isocenter of the X-ray beam, on the side of the emitting tube. AK is fundamentally related to the deterministic effects of radiation, characterized by clinical manifestations that occur when a certain dose threshold is exceeded. In addition, the dose-area product (DAP) results from the multiplication between the AK and the irradiated area, being expressed in Gy·cm², which is one of the best indicators of stochastic effects, as it simultaneously reflects the intensity of the radiation and the extent of the exposed field. Thus, it provides a more comprehensive assessment of radiological risk when compared with AK alone.

Fluoroscopy time (TF) is a complementary variable for exposure analysis, but it has limitations, since it does not include the time related to cineangiography, a stage responsible for a large proportion of the dose in several procedures. In this study, ET will be extracted from digital systems with the aim of investigating its usefulness as a possible parameter associated with the identification of vascular complications (Gurajala *et al.*, 2025).

Regarding the clinical and technical factors associated with radiation exposure, Tarighatnia *et al.* (2018) observed that, although the radial approach is consolidated by reducing bleeding complications, the radiation dose varies according to the patient's profile

and the technique adopted. Higher exposures were identified in men, in the left radial access, and in individuals with greater body surface area. These findings suggest increased anatomical complexity and prolongation of ET. For these scenarios, it is recommended to anticipate the possibility of a higher dose and apply mitigation strategies, including reduction of extreme angulations, optimization of workflow, judicious use of cineangiography, and reduction of total examination time.

In a multicenter study involving 6,967 patients who underwent coronary angiography (CA) with or without PCI via radial access, the following were identified as determinants of higher exposure: male gender, left radial access, and higher body mass index (BMI). Men had higher DBH and AK values, possibly due to higher atherosclerotic load, more complex anatomy, and higher mean body weight. The left radial access, despite its more straight path, was associated with higher ET and higher dose, often because it is used after difficulty with the right access and due to the operator's lower technical familiarity (Mantis *et al.*, 2022).

Additionally, Mantis *et al.* (2022) emphasize that anthropometric factors have a significant impact on dose, with an almost linear relationship between BMI, body surface area (BSA), and DBH and AK values. Thus, in men, the elderly, patients with high BMI or AUC, and those in need of left radial access, it is recommended to provide higher doses, inform the patient, and apply strict protective measures, such as minimizing the use of cineangiography, preference for continuous fluoroscopy, less angled projections, and, when indicated, fractionation of multi-vascular procedures.

Finally, although widely used as an indicator of complexity and exposure to radiation, fluoroscopy time alone is an imperfect marker of absorbed dose and does not allow direct assessment of clinical risk. The occurrence of adverse events after PCI depends on factors such as clinical profile, coronary anatomy, technique adopted, devices used, contrast volume, and anticoagulation regimen. Thus, ET should be interpreted as an auxiliary operational parameter, and not as an isolated predictor of outcomes.

3.6.2 Barbeau test

The Barbeau test (TB) is a non-invasive method used to evaluate the collateral circulation of the hand by analyzing the patency of the palmar arch and the ability of the ulnar artery to maintain distal blood flow when there is temporary occlusion of the radial artery. This test is based on digital plethysmography and allows verifying, quickly and affordably, whether the patient has adequate blood supply to support procedures performed by radial access. Thus, TB represents an important clinical tool for hemodynamic evaluation prior to

percutaneous interventions using the radial artery, contributing to the prevention of distal ischemia and other vascular complications (Serafino *et al.*, 2024).

In this context, the study by Di Serafino *et al.* (2024), conducted in three hospital centers in Italy and involving 480 participants, systematically applied TB by means of plethysmography, using a pulse oximeter with a pincer-type sensor positioned on the thumb. In this study, measurements were taken immediately before compression of the radial artery and after two minutes of continuous compression. The results were classified according to the behavior of the plethysmographic tracing:

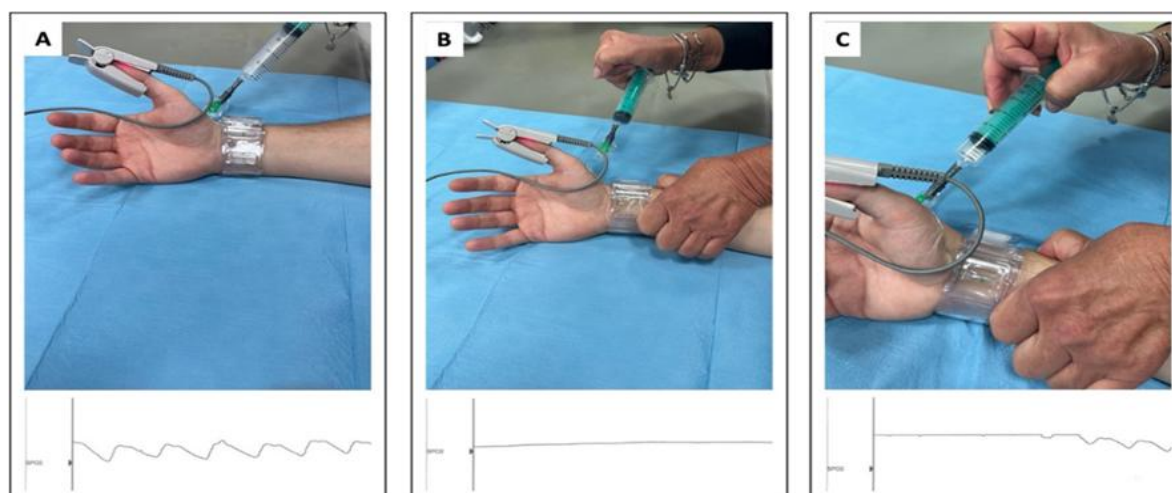
- a) A: maintenance of the tracing without damping after compression of the radial artery;
- b) B: presence of damping of the tracing;
- c) C: disappearance of the signal, followed by recovery within two minutes;
- d) D: absence of tracing recovery after occlusion.

These categories allow inferring the degree of contribution of the ulnar artery and palmar arch to the perfusion of the hand, providing important support for the preoperative evaluation of transradial procedures. In addition to TB, the authors also applied the modified radial plethysmography (mRBT) method, whose objective was to determine the ideal inflation volume of the hemostasis device used in the post-procedure (SERAFINO *et al.*, 2024).

The authors did not identify significant differences between the tests or devices evaluated in terms of radial patency preservation. However, they highlight that the Barbeau Test is a viable, simple, low-cost, and clinically useful method for pre- and post-procedure evaluation, especially due to its ability to contribute to hemodynamic safety and to the prevention of complications associated with radial access (Serafino *et al.*, 2024).

Figure 1

Modified reverse Barbeau test before the transradial procedure



Source: Di Serafino *et al.* 2024.

3.6.3 Attempts at arterial punctures

In percutaneous coronary intervention (PCI), transradial access (TRA) is the route that provides the medical operator with greater safety and a lower incidence of bleeding complications compared to transfemoral access. However, TRA is not without complications, and puncture attempts play a significant role in the development of possible complications, such as radial artery spasm frequent from transradial cardiac catheterization. The genesis of these complications is linked to the presence of adrenoreceptors in the radial artery wall, which when stimulated by catheter manipulation, wall stretching, and local trauma, contribute to increased vasoreactivity and vasoconstriction of smooth muscle (Roy *et al.*, 2021).

Roy *et al.* Wang *et al.* (2021) described that PCI-related factors, such as the number of puncture attempts, excessive catheter manipulation, duration of angiography/intervention, number of catheters used, caliber of catheters/devices, and local pressure time, are all associated with an increased risk of radial artery spasm. In addition, the authors emphasize that the hemodynamic team needs to be prepared and with adequate planning of evaluation and pre-procedure care, ultrasound available to obtain vascular access, appropriate use of catheters and sheaths, and adequate analgesia/sedation.

Alkagiet *et al.* (2021) demonstrates a 1-12% incidence of radial artery occlusion (RAO) outcomes. RAO usually occurs early (within 24 hours) after TRA, and in almost half of cases, there is spontaneous recanalization within 3 months. Among the risk factors for this complication, multiple puncture attempts stand out, which result in spasm and thickening of the medial intimal layer, leading to remodeling of the vascular wall and increased thrombogenicity. These changes, combined with impaired blood flow due to sheath insertion and perioperative vascular tissue injury, lead to thrombi formation and vessel occlusion. In this sense, transradial access is still a safe technique, but it presents risks of possible complications such as spasm and occlusion of the radial artery, highlighting situations. Therefore, understanding risk factors and implementing preventive strategies are crucial to optimize outcomes and patient safety.

3.6.4 Hematoma

Hematoma is a frequent vascular complication after coronary angiography procedures, resulting from the extravasation of blood into the subcutaneous tissue at the arterial puncture site. Although it is usually a low-severity event, it can progress to more severe complications, including expansive bleeding, compartment syndrome, compressive

neuropathies, and hemodynamic instability. For this reason, its systematic evaluation represents a key step in post-procedural monitoring (GAO *et al.*, 2020).

The formation of a hematoma at the puncture site may indicate dysfunctions related to hemostasis, inadequate pressure of the compressive device, or coagulation dysfunctions, particularly in patients using potent antiplatelets or anticoagulants. Early identification of the hematoma allows for rapid and effective interventions, such as compression adjustment, repositioning of dressings, or ultrasound evaluation in cases suggestive of associated complications (pseudoaneurysm, arteriovenous fistula, or active bleeding).

In coronary angiography procedures, the radial approach is currently recommended as the preferred route in patients with acute coronary syndrome (ACS), being associated with a reduction in major bleeding, vascular complications, and mortality when compared to the femoral approach. The study by Gao *et al.* (2020) indicates that these benefits are more significant in individuals classified as at high risk of bleeding, although they are not reproduced in the same way in low-risk patients. Bleeding remains one of the main perioperative predictors of mortality in invasive procedures, including coronary angiography, which reinforces the relevance of the appropriate choice of vascular access.

Thus, the patient's previous careful clinical and laboratory evaluation can be used to prevent or minimize hematomas at the puncture site, as well as this clinical parameter can be implemented as an indicator of the safety of the procedure, the efficacy of hemostasis, and the quality of care.

3.7 CLINICAL AND LABORATORY BIOMARKERS IN THE PREDICTION OF COMPLICATIONS IN HEMODYNAMICS

The use of clinical and laboratory parameters as tools for predicting complications in hemodynamic services still has important gaps in scientific knowledge. Although routine laboratory tests are widely available in hospital services, their systematic application to estimate the risk of vascular complications in patients undergoing catheterization remains limited. The investigation of specific biomarkers in this context has great potential, as it can assist in the pre-procedure evaluation, guide the choice of vascular access, and support the prevention of adverse events, thus contributing to patient safety and the efficacy of the procedure.

With the advancement of intervention technologies, transradial percutaneous coronary intervention (PCI) has become the strategy of choice, due to its lower complication rate, lower local trauma, ease of hemostasis process, less pain for the patient, and reduction in hospital stay. Even so, forearm hematoma is the most frequent complication, and may

generate relevant clinical risks, such as nerve compression and tissue necrosis due to the pressure exerted on local vessels and nerves. Although the incidence of hematoma is generally low, it tends to increase in procedures performed by less experienced operators, which reinforces the importance of prior evaluation and post-procedure monitoring (Writing Committee Members *et al.*, 2024).

The choice of the transradial approach requires a careful evaluation of the caliber, path, and elasticity of the radial artery, as well as the compensatory function of the ulnar artery. In this sense, prior analysis of the circulation of the hand, often performed by modified Allen test or pulse oximetry, is essential to verify the integrity of the palmar arch and reduce the risk of ischemic complications. In the post-procedure period, immediate clinical monitoring becomes essential to identify intercurrents early. Aspects such as the effectiveness of radial artery compression, skin staining, and distal hand and finger perfusion are direct indicators of the maintenance of local blood flow and allow for rapid interventions in cases of complication (ZHI *et al.*, 2024).

Laboratory evaluation represents a central step in the prevention and management of complications after PCI. Among the most relevant parameters, the analysis of renal function - particularly by means of urea and creatinine and glomerular filtration rate (GFR) - makes it possible to estimate the risk of contrast-induced nephropathy. Coagulation parameters, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count, offer subsidies to prevent hemorrhagic complications. In addition, the investigation of the presence of anemia, through the measurement of hemoglobin and hematocrit, contributes to defining individualized conducts that favor greater safety during and after the procedure. Together, these laboratory tests expand the predictive capacity of clinical data, allowing greater precision in risk stratification (ZHI *et al.*, 2024).

In this sense, there are still gaps regarding the use and applicability of integrated analyses of clinical and laboratory biomarkers in order to provide more robust and reliable indicators to predict changes in arterial patency in the upper limbs. In addition, the performance and experience of the multiprofessional team, especially nursing, plays an essential role in this process. Systematic clinical observation, combined with the use of parameters for decision-making, contributes to the early management of complications, ensuring individualized care and better clinical outcomes (ZHI *et al.*, 2024).

In this sense, precautionary measures must be clearly established with the multiprofessional team. The literature highlights that early observation and immediate management of arterial complications are crucial for the prevention of severe adverse outcomes. Zhi *et al.* (2024) emphasize the importance of structured surveillance in the

recovery period, highlighting three critical moments: (i) right after the end of PCI, when the physician assesses the presence of swelling at the puncture site during hemostasis; (ii) during the transfer to the recovery room, when the team must check the patient's level of consciousness and the local conditions of the puncture, intervening promptly in cases of bleeding or edema; and (iii) in the subsequent hours, in which serial measurement of the circumference of the arm is recommended, associated with the continuous observation of signs of bleeding and swelling.

In addition to local monitoring, the evaluation of arterial pulse should include the so-called "5 Ps syndrome" pain, pallor, absence of pulse, paresthesia and paralysis, whose early identification suggests ischemia and requires immediate intervention. Follow-up should be complemented by health education aimed at patients and their families. The guidelines cover local care, warning signs related to bleeding and ischemic complications, and specific instructions on the use of anticoagulants. This educational process, supported by illustrative materials and verbal instructions, contributes to greater understanding, adherence, and security in post-discharge care (Roy *et al.*, 2022).

Thus, it is observed that the integration between clinical data, laboratory biomarkers and specialized care conducts enhances the prediction of complications and the quality of care in hemodynamics.

4 FINAL CONSIDERATIONS

Percutaneous coronary intervention (PCI) or coronary angiography represent fundamental pillars in the diagnosis and treatment of cardiovascular diseases, however, they are not without risks, especially in clinically vulnerable populations. In-depth analysis of the complications associated with these procedures reveals the complexity of perioperative management and the need for individualized strategies to optimize clinical outcomes.

Risk factors for complications are multifaceted, ranging from demographic characteristics, such as advanced age and female gender, to comorbidities such as congenital heart disease, multivessel coronary artery disease, severe ventricular dysfunction, diabetes mellitus, and valvular heart diseases. Perioperative drug management requires rigor, with the careful suspension of drugs such as metformin and direct anticoagulants, and the maintenance of antiplatelet agents, emphasizing the importance of well-defined protocols, although challenging in emergency scenarios.

The complications of PCI can be classified into clinical and related to the access route. Clinical complications include hematomas, pseudoaneurysms, bleeding, cerebrovascular events, and contrast-induced nephropathy (CIN). CIN, in particular, is a concern in patients

with impaired renal function, requiring adequate hydration and judicious use of contrast. Technological evolution, with the use of low contrast doses and advanced intracoronary imaging methods (OCT and IVUS), has contributed to the reduction of these risks.

Regarding the complications of the access route, the transradial approach (ART) has been consolidated as preferential due to the lower incidence of hemorrhagic complications compared to the femoral approach. However, radial artery occlusion (RAO) remains a challenge, requiring attention to the puncture technique, adequate anticoagulation, and non-occlusive hemostasis. Radial artery patency assessment and post-procedure follow-up are crucial to preserve this pathway for future interventions.

Several clinical and laboratory parameters are associated with a higher risk of vascular complications. Advanced age, female gender, smoking, obesity, type 2 diabetes mellitus (DM2), systemic arterial hypertension (SAH), dyslipidemia, and metabolic syndrome are factors that contribute significantly to morbidity and mortality. Heredity also plays an important role, with genetic variations influencing the risk of myocardial infarction.

Antithrombotic therapy, essential in the prevention of ischemic events, requires a delicate balance between efficacy and risk of bleeding. Dual antiplatelet therapy (DAPT) is the mainstay, but its duration and intensity should be individualized. Strategies such as monotherapy with P2Y₁₂ inhibitors have emerged as promising alternatives for patients at high risk of bleeding. Optimization of heparinization and non-occlusive hemostasis are crucial to prevent RAO.

Finally, vasodilator therapy, such as verapamil and nitroglycerin, is employed to prevent radial artery spasm (RAS), a common complication in ART. The efficacy of pharmacological prophylaxis can be influenced by the operator's experience, highlighting the importance of integrating pharmacological strategies and personalized techniques. The monitoring of laboratory parameters, including inflammatory, hemostatic, renal and metabolic markers, offers valuable subsidies for risk stratification and clinical decision-making.

In summary, the safety and efficacy of coronary angiography and PCI depend on a holistic approach that considers patient complexity, procedural technique, pharmacological management, and continuous monitoring. Ongoing research and implementation of evidence-based protocols are imperative to improve outcomes and reduce complications in patients undergoing these vital procedures.

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USE OF DAPAGLIFLOZIN (FORXIGA) IN THE TREATMENT OF HEART FAILURE: CURRENT EVIDENCE AND CLINICAL EFFICACY

USO DA DAPAGLIFOZINA (FORXIGA) NO TRATAMENTO DA INSUFICIÊNCIA CARDÍACA: EVIDÊNCIAS ATUAIS E EFICÁCIA CLÍNICA

USO DE DAPAGLIFLOZINA (FORXIGA) EN EL TRATAMIENTO DE LA INSUFICIENCIA CARDÍACA: EVIDENCIA ACTUAL Y EFICACIA CLÍNICA



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ABSTRACT

Heart failure remains one of the leading causes of cardiovascular morbidity and mortality worldwide, being associated with high hospitalization rates, progressive functional

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impairment, and significant socioeconomic burden. In this context, dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has emerged as an important therapeutic strategy in the contemporary management of heart failure, demonstrating cardiovascular and cardiorenal benefits that extend beyond glycemic control. This study aimed to analyze current scientific evidence regarding the clinical efficacy of dapagliflozin in the treatment of heart failure, emphasizing its effects on cardiovascular mortality, hospitalizations, quality of life, functional capacity, and renal protection. This is an integrative literature review with a qualitative and descriptive approach, conducted through searches in PubMed, SciELO, and ScienceDirect databases using descriptors related to dapagliflozin, heart failure, and cardiovascular outcomes. Studies published between 2019 and 2023 were included, comprising randomized clinical trials, systematic reviews, meta-analyses, and international guidelines. The main findings demonstrated significant reductions in heart failure hospitalizations, cardiovascular mortality, and episodes of clinical worsening, in addition to improvements in quality of life and preservation of renal function across different phenotypes of the disease. The DAPA-HF and DELIVER trials were particularly highlighted as milestones in consolidating SGLT2 inhibitors as a fundamental therapeutic component in heart failure management. It is concluded that dapagliflozin represents an important advancement in the treatment of heart failure, promoting consistent clinical benefits and contributing to a more integrated and multidimensional therapeutic approach aimed at optimizing cardiovascular and cardiorenal outcomes.

Keywords: Heart Failure. Dapagliflozin. Forxiga. SGLT2 Inhibitors. Cardiovascular Outcomes. Cardiorenal Protection.

RESUMO

A insuficiência cardíaca permanece como uma das principais causas de morbimortalidade cardiovascular no mundo, associando-se a elevadas taxas de hospitalização, piora funcional progressiva e importante impacto socioeconômico. Nesse contexto, a dapagliflozina, inibidor do cotransportador sódio-glicose tipo 2 (SGLT2), emergiu como estratégia terapêutica relevante no manejo contemporâneo da insuficiência cardíaca, demonstrando benefícios cardiovasculares e cardiorrenais que extrapolam o controle glicêmico. O presente estudo teve como objetivo analisar as evidências científicas atuais acerca da eficácia clínica da dapagliflozina no tratamento da insuficiência cardíaca, enfatizando seus efeitos sobre mortalidade cardiovascular, hospitalizações, qualidade de vida, capacidade funcional e proteção renal. Trata-se de uma revisão integrativa da literatura, de abordagem qualitativa e caráter descritivo, realizada por meio de buscas nas bases PubMed, SciELO e ScienceDirect, utilizando descritores relacionados à dapagliflozina, insuficiência cardíaca e desfechos cardiovasculares. Foram incluídos estudos publicados entre 2019 e 2023, incluindo ensaios clínicos randomizados, revisões sistemáticas, meta-análises e diretrizes internacionais. Os principais achados evidenciaram redução significativa de hospitalizações por insuficiência cardíaca, mortalidade cardiovascular e episódios de descompensação clínica, além de melhora da qualidade de vida e preservação da função renal em diferentes fenótipos da doença. Destacaram-se especialmente os estudos DAPA-HF e DELIVER, considerados marcos na consolidação dos inibidores de SGLT2 como componente terapêutico fundamental na insuficiência cardíaca. Conclui-se que a dapagliflozina representa avanço importante no tratamento da insuficiência cardíaca, promovendo benefícios clínicos consistentes e contribuindo para uma abordagem terapêutica mais integrada, multidimensional e voltada à otimização dos desfechos cardiovasculares e cardiorrenais.

Palavras-chave: Insuficiência Cardíaca. Dapagliflozina. Forxiga. Inibidores de SGLT2. Desfechos Cardiovasculares. Proteção Cardiorrenal.

RESUMEN

La insuficiencia cardíaca sigue siendo una de las principales causas de morbilidad y mortalidad cardiovascular a nivel mundial, asociada a altas tasas de hospitalización, deterioro funcional progresivo e impacto socioeconómico significativo. En este contexto, la dapagliflozina, un inhibidor del cotransportador de sodio-glucosa tipo 2 (SGLT2), ha surgido como una estrategia terapéutica relevante en el manejo contemporáneo de la insuficiencia cardíaca, demostrando beneficios cardiovasculares y cardiorrenales que van más allá del control glucémico. Este estudio tuvo como objetivo analizar la evidencia científica actual sobre la eficacia clínica de la dapagliflozina en el tratamiento de la insuficiencia cardíaca, haciendo hincapié en sus efectos sobre la mortalidad cardiovascular, las hospitalizaciones, la calidad de vida, la capacidad funcional y la protección renal. Se trata de una revisión bibliográfica integradora, con un enfoque cualitativo y descriptivo, realizada mediante búsquedas en las bases de datos PubMed, SciELO y ScienceDirect, utilizando descriptores relacionados con la dapagliflozina, la insuficiencia cardíaca y los resultados cardiovasculares. Se incluyeron estudios publicados entre 2019 y 2023, incluyendo ensayos clínicos aleatorizados, revisiones sistemáticas, metaanálisis y guías internacionales. Los principales hallazgos mostraron una reducción significativa en las hospitalizaciones por insuficiencia cardíaca, la mortalidad cardiovascular y los episodios de descompensación clínica, así como una mejor calidad de vida y la preservación de la función renal en diferentes fenotipos de la enfermedad. Los estudios DAPA-HF y DELIVER fueron particularmente relevantes, considerados hitos en la consolidación de los inhibidores de SGLT2 como un componente terapéutico fundamental en la insuficiencia cardíaca. Se concluye que la dapagliflozina representa un avance importante en el tratamiento de la insuficiencia cardíaca, promoviendo beneficios clínicos consistentes y contribuyendo a un enfoque terapéutico más integral y multidimensional, centrado en la optimización de los resultados cardiovasculares y cardiorrenales.

Palabras clave: Insuficiencia Cardíaca. Dapagliflozina. Forxiga. Inhibidores de SGLT2. Resultados Cardiovasculares. Protección Cardiorrenal.

1 INTRODUCTION

Heart failure (HF) remains one of the main causes of cardiovascular morbidity and mortality on a global scale, configuring itself as an important public health problem due to the high frequency of recurrent hospitalizations, progressive functional limitation and substantial socioeconomic impact. Characterized by the inability of the heart to adequately meet the metabolic and hemodynamic demands of the body, the syndrome is associated with complex clinical manifestations, including dyspnea, fatigue, and intolerance to physical exertion. Despite the therapeutic advances observed in recent decades, HF still presents an unfavorable clinical evolution in a significant portion of patients, especially in the presence of reduced ejection fraction, renal impairment, and multiple associated comorbidities, evidencing persistent prognostic limitations even in the face of conventional pharmacological strategies (McMurray et al., 2019).

In this context, type 2 diabetes mellitus stands out as an important factor associated with the progression of heart failure and a significant increase in cardiovascular risk. The coexistence between metabolic dysfunction, chronic inflammation, hemodynamic alterations, and cardiorenal injury contributes to greater clinical complexity and worse outcome of these patients. In view of this pathophysiological interrelation, there has been a growing interest in therapeutic approaches capable of acting simultaneously on the cardiovascular, metabolic, and renal axes. Initially developed as hypoglycemic agents, sodium-glucose cotransporter type 2 (SGLT2) inhibitors have begun to demonstrate clinical effects that go beyond glycemic control, especially in the context of heart failure. Among them, dapagliflozin, commercially known as Forxiga®, has received increasing prominence due to its ability to modulate mechanisms related to natriuresis, reduction of volume overload, improvement of cardiorenal dynamics, and possible attenuation of cardiac remodeling, reflecting in favorable clinical outcomes regardless of the presence of diabetes mellitus (PETRIE et al., 2020).

The consolidation of dapagliflozin in the contemporary management of heart failure occurred mainly after the publication of the DAPA-HF study, considered a therapeutic milestone by demonstrating a significant reduction in the combined risk of worsening heart failure and cardiovascular death in patients with reduced ejection fraction. In addition to the decrease in relevant clinical events, a consistent impact on symptoms and functional outcome was observed, reinforcing the potential of dapagliflozin as a complementary therapy to traditional approaches already established in the treatment of HF (MCMURRAY et al., 2019). Subsequently, the findings of the DELIVER study expanded the clinical relevance of this drug by showing favorable results also in individuals with slightly reduced or preserved

ejection fraction, a scenario historically marked by limited therapeutic options and less robust pharmacological evidence (SOLOMON et al., 2022).

In addition to the effects on mortality and clinical decompensations, recent investigations have demonstrated relevant repercussions of dapagliflozin on the quality of life, functional capacity, and symptomatic perception of patients with heart failure. Evaluations based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) have shown clinically significant improvement in different domains related to cardiovascular health status, both in patients with reduced and preserved ejection fraction (KOSIBOROD et al., 2020; KOSIBOROD et al., 2023). At the same time, studies involving renal outcomes suggest an additional protective effect on renal function, a particularly relevant aspect in view of the recognized bidirectional interaction between heart failure and chronic kidney disease, often associated with worse clinical outcome and greater therapeutic complexity (JHUND et al., 2020).

In view of the increasing incorporation of SGLT2 inhibitors in international guidelines for the management of heart failure, it is essential to critically understand the contemporary evidence related to the clinical efficacy of dapagliflozin and its impact on the different phenotypic profiles of the disease. Recent updates from the European Society of Cardiology (ESC) have started to recommend this therapeutic class as an essential component in the treatment of heart failure, recognizing its consistency in reducing adverse cardiovascular events and optimizing the clinical evolution of patients (MCDONAGH et al., 2023). In this sense, the present study aims to review the current scientific evidence on the use of dapagliflozin in the treatment of heart failure, emphasizing its clinical efficacy, its therapeutic effects, and its relevance in cardiovascular and cardiorenal outcomes.

2 METHODOLOGY

The present study consists of an integrative literature review, of a descriptive nature and qualitative approach, developed with the purpose of critically analyzing the contemporary scientific evidence related to the use of dapagliflozin (Forxiga®) in the treatment of heart failure, emphasizing its clinical efficacy, prognostic repercussions, and impact on cardiovascular, functional, and cardiorenal outcomes in different phenotypes of the disease.

The bibliographic survey strategy was conducted through systematized searches in internationally recognized scientific databases, PubMed, SciELO and ScienceDirect, selected due to their wide relevance in the indexing of biomedical, cardiovascular and pharmacotherapeutic studies of high methodological rigor. To construct the search strategy,

descriptors in Portuguese and English associated with Boolean operators "AND" and "OR" were used, including the terms: "dapagliflozin", "Forxiga", "heart failure", "SGLT2 inhibitors", "reduced ejection fraction", "mildly reduced ejection fraction", "preserved ejection fraction" and "cardiovascular outcomes". The combined use of these descriptors sought to contemplate the growing phenotypic complexity of contemporary heart failure, ranging from patients with reduced ejection fraction to those with slightly reduced or preserved ejection fraction.

Scientific articles published between 2019 and 2023, available in full in Portuguese and English, that directly addressed the use of dapagliflozin in patients with heart failure, were included. The selection prioritized randomized clinical trials, multicenter studies, secondary analyses of large cardiovascular trials, systematic reviews, meta-analyses, and international guidelines related to sodium-glucose cotransporter type 2 (SGLT2) inhibitors and the contemporary management of heart failure. Among the main studies included, the DAPA-HF and DELIVER trials stand out, considered methodological milestones in the consolidation of SGLT2 inhibitors as a central therapeutic component in heart failure, particularly due to the robustness of their clinical designs, population breadth, and relevance of the cardiovascular outcomes evaluated. In addition, analyses related to quality of life, functional evolution, renal protection and therapeutic response in different clinical profiles of the syndrome were incorporated.

Duplicate studies, incomplete publications, studies without a direct relationship with the proposed theme, experimental studies without relevant clinical applicability, isolated case reports, and articles that did not present consistent clinical outcomes related to the therapeutic efficacy of dapagliflozin in heart failure were excluded. Studies with low methodological relevance or without adequate correlation with the central objectives of this review were also disregarded.

After the selection stage, eligible studies were submitted to critical analysis and comparative integration of evidence, considering aspects related to methodological design, population profile, heterogeneity of heart failure phenotypes evaluated, nature of clinical endpoints, and consistency of the therapeutic results observed. The analytical synthesis focused especially on major cardiovascular outcomes, including cardiovascular mortality, hospitalizations for heart failure, and episodes of clinical decompensation, as well as functional parameters, quality of life, and cardiorenal repercussions, components progressively valued in contemporary studies on heart failure. Thus, we sought to construct an integrated and critically contextualized interpretation of the recent literature, allowing us

to understand the role of dapagliflozin in the redefinition of modern therapeutic strategies applied to heart failure.

3 RESULTS AND DISCUSSION

The integrated analysis of the selected studies demonstrates that dapagliflozin has established itself as one of the main therapeutic innovations in the contemporary management of heart failure. The clinical trials analyzed show consistent benefits in different phenotypes of the syndrome, promoting a favorable impact not only on major cardiovascular outcomes, but also on functional parameters, quality of life, and cardiorenal protection. These findings contributed to significantly modify the traditional therapeutic approach to heart failure, which has historically focused predominantly on neurohormonal modulation.

The DAPA-HF study represented a relevant milestone in this process by demonstrating that dapagliflozin significantly reduced the combined risk of worsening heart failure and cardiovascular death in patients with reduced ejection fraction, regardless of the presence of diabetes mellitus (MCMURRAY et al., 2019). In addition to the reduction in hospitalizations and cardiovascular mortality, consistent clinical improvement was observed even in patients undergoing optimized pharmacological therapy. This suggests a complementary effect to the therapies traditionally used in the management of heart failure. Subsequent analyses derived from DAPA-HF demonstrated that the benefits remained consistent regardless of the background therapies employed, including beta-blockers, renin-angiotensin system antagonists, and mineralocorticoid receptor antagonists (DOCHERTY et al., 2020). These results strengthened the consolidation of SGLT2 inhibitors as a structural component of modern heart failure therapy.

Another aspect of high clinical relevance refers to the efficacy observed regardless of the glycemic status of the patients. Although initially developed as an antidiabetic agent, dapagliflozin has demonstrated similar benefits in individuals with and without type 2 diabetes mellitus, significantly expanding its clinical applicability in the cardiovascular context (PETRIE et al., 2020). This effect appears to involve mechanisms partially independent of glycemic control. Among the main mechanisms proposed are osmotic natriuresis, reduction of cardiac preload and afterload, improvement of myocardial metabolic efficiency, attenuation of systemic congestion, and preservation of renal function. Together, these effects suggest integrated action on multiple pathophysiological axes of heart failure.

Historically, patients with heart failure and preserved or slightly reduced ejection fraction had limited therapeutic options and less expressive clinical results when compared to those with reduced ejection fraction. In this scenario, the DELIVER study represented an

important advance by demonstrating a significant reduction in the risk of worsening heart failure and cardiovascular death in patients with ejection fraction above 40%, including individuals with preserved ejection fraction (SOLOMON et al., 2022). In addition, subsequent analyses showed consistent benefits also in patients with previously reduced ejection fraction and later recovered, reinforcing the therapeutic scope of dapagliflozin in different clinical presentations of the syndrome (VARDENY et al., 2022). Despite the robustness of the findings, it should be considered that some of the studies have relatively limited follow-up time and selected populations, which may influence the extrapolation of the results to patients with greater clinical complexity observed in daily care practice.

In addition to the effects on mortality and clinical decompensation, a relevant impact of dapagliflozin on quality of life and functional capacity was observed. Studies based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) have demonstrated significant improvement in symptoms, physical limitation, and global health perception in patients treated with the medication, both in heart failure with reduced and preserved ejection fraction (KOSIBOROD et al., 2020; KOSIBOROD et al., 2023). These findings have important clinical relevance, considering that heart failure is associated not only with high mortality, but also with progressive functional impairment and a substantial reduction in the quality of life of patients.

At the same time, the cardiorenal effects of dapagliflozin emerge as a central component in understanding its therapeutic efficacy. In DAPA-HF, patients with baseline renal impairment showed benefits similar to those observed in the general population, including reduction of cardiovascular events and slowing of loss of renal function over the course of clinical follow-up (JHUND et al., 2020). The preservation of renal function is of strategic relevance in heart failure, especially in view of the bidirectional interaction between cardiac dysfunction and chronic kidney disease. This association often contributes to a higher risk of recurrent hospitalizations, clinical progression, and mortality. Even so, the heterogeneity of the renal profiles evaluated in the studies and the lower representation of patients in advanced stages of chronic kidney disease remain aspects that require further investigation.

The results observed in the analyzed studies had a direct impact on the international guidelines for heart failure. Recent updates from the European Society of Cardiology have started to recommend SGLT2 inhibitors as an essential component of pharmacological therapy for heart failure, regardless of the presence of diabetes mellitus, consolidating dapagliflozin as one of the main therapeutic strategies in contemporary cardiology (MCDONAGH et al., 2023). However, challenges related to therapeutic implementation still

persist, including cost, access to treatment, medication adherence, and homogeneous incorporation of these recommendations in different health systems.

In addition, the systematic review and meta-analysis conducted by Ali et al. (2023) reinforced the magnitude of the clinical effects of dapagliflozin by demonstrating significant reduction in all-cause mortality, hospitalizations for heart failure, and cardiovascular death in a wide variety of patients with heart failure. The convergence between randomized controlled trials, secondary analyses, and meta-analyses strengthens the scientific consistency of the currently available evidence. Even so, the continuous production of data in more complex populations with prolonged follow-ups will be essential to expand the understanding of the effects of dapagliflozin in different clinical scenarios.

Thus, the findings analyzed in this review show that dapagliflozin transcends the role originally attributed to hypoglycemic agents, assuming a leading role in the contemporary management of heart failure. Its ability to act simultaneously on cardiovascular, functional, and cardiorenal outcomes reinforces the transition to a more integrated therapeutic model, aimed not only at reducing major clinical events, but also at modulating the pathophysiological complexity that characterizes modern heart failure.

4 CONCLUSION

The scientific evidence analyzed in this review demonstrates that dapagliflozin has established itself as an important therapeutic component in the contemporary management of heart failure, presenting consistent clinical benefits in different phenotypes of the disease, regardless of the presence of diabetes mellitus. The main randomized controlled trials, especially the DAPA-HF and DELIVER studies, have shown significant reductions in relevant cardiovascular outcomes, including worsening heart failure, recurrent hospitalizations, and cardiovascular mortality, as well as favorable repercussions on quality of life, functional capacity, and cardiorenal protection.

The available findings suggest that the therapeutic effects of dapagliflozin go beyond glycemic control, involving complex pathophysiological mechanisms related to natriuresis, reduction of hemodynamic overload, preservation of renal function, and modulation of cardiorenal dysfunction. This integrated action contributes to a more comprehensive therapeutic approach to heart failure, a condition characterized by high clinical complexity and important prognostic impact.

In addition, the incorporation of SGLT2 inhibitors into the main international guidelines reinforces the robustness of the currently available evidence and consolidates dapagliflozin as a fundamental strategy in the treatment of heart failure. However, despite the promising

results observed in contemporary studies, challenges remain related to applicability in clinically more complex populations, long-term follow-up, and therapeutic implementation in real clinical practice.

Thus, it is concluded that dapagliflozin represents a significant advance in the treatment of heart failure, promoting relevant cardiovascular, functional, and cardiorenal benefits. Its use shows the transition to a more integrated and multidimensional therapeutic model, aimed not only at reducing adverse clinical events, but also at improving the overall clinical evolution and quality of life of patients with heart failure.

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AUTISM SPECTRUM DISORDER IN THE CONTEXT OF PUBLIC SCHOOLS: CONTRIBUTIONS OF PHYSICAL EDUCATION TO THE DEVELOPMENT OF LANGUAGE: MEDIATION, BODY AND EMBODIED COGNITION

TRANSTORNO DO ESPECTRO AUTISTA NO CONTEXTO DA ESCOLA PÚBLICA: CONTRIBUIÇÕES DA EDUCAÇÃO FÍSICA ESCOLAR PARA O DESENVOLVIMENTO DA LINGUAGEM: MEDIAÇÃO, CORPO E COGNIÇÃO INCORPORADA

TRASTORNO DEL ESPECTRO AUTISTA EN EL CONTEXTO DE LA ESCUELA PÚBLICA: CONTRIBUCIONES DE LA EDUCACIÓN FÍSICA ESCOLAR AL DESARROLLO DEL LENGUAJE: MEDIACIÓN, CUERPO Y COGNICIÓN INCORPORADA



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ABSTRACT

This article analyzes the contributions of school Physical Education to the development of language in students with Autism Spectrum Disorder (ASD) in the context of public schools. This is qualitative research with a theoretical-bibliographic approach, grounded in Bardin's Content Analysis (2016), with a corpus composed of 38 scientific works selected from indexed databases SciELO, ERIC, Scopus and CAPES Journals Portal, published between 2020 and 2025, following a protocol compatible with PRISMA guidelines. The theoretical framework articulates Gardner's Theory of Multiple Intelligences (1995), critically repositioned in light of contemporary studies on embodied cognition and language, with Vygotsky's mediation perspective and recent literature on ASD, linguistic development, and school inclusion. Results indicate that Physical Education, when organized with pedagogical intentionality and grounded in inclusive principles, constitutes a relevant space for language mediation, enabling forms of expression that transcend orality including the articulated use of bodily practices and Augmentative and Alternative Communication (AAC) resources. The analysis reveals a productive tension between structured behavioral approaches and

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sociointeractionist perspectives, whose integration tends to produce more consistent outcomes in school contexts. It is concluded that the integration of body, movement, and language constitutes a relevant pedagogical axis for expanding the communicative repertoire of students with ASD, with direct implications for teacher education and inclusive education policies.

Keywords: Autism Spectrum Disorder. School Physical Education. Embodied Cognition. Pedagogical Mediation. Augmentative and Alternative Communication. Inclusive Education.

RESUMO

O presente artigo analisa as contribuições da Educação Física escolar para o desenvolvimento da linguagem em alunos com Transtorno do Espectro Autista (TEA) no contexto da escola pública. Trata-se de pesquisa qualitativa de abordagem teórico-bibliográfica, ancorada na Análise de Conteúdo proposta por Bardin (2016), com corpus constituído por 38 produções científicas selecionadas em bases indexadas SciELO, ERIC, Scopus e Portal de Periódicos da CAPES, publicadas entre 2020 e 2025, seguindo protocolo compatível com as diretrizes do PRISMA. O referencial teórico articula a teoria das Inteligências Múltiplas de Gardner (1995), reposicionada criticamente à luz de estudos contemporâneos sobre cognição incorporada e linguagem, com a perspectiva vigotskiana de mediação e com a produção recente sobre TEA, desenvolvimento linguístico e inclusão escolar. Os resultados indicam que a Educação Física, quando organizada com intencionalidade pedagógica e fundamentada em princípios inclusivos, constitui espaço relevante de mediação da linguagem, ao possibilitar formas de expressão que transcendem a oralidade incluindo o uso articulado de práticas corporais e recursos de Comunicação Aumentativa e Alternativa (CAA). A análise evidencia que tal potencial não se efetiva de modo automático, sendo condicionado pela qualidade da mediação docente, pelo planejamento sistemático das práticas corporais e pelas condições estruturais em que o trabalho pedagógico se desenvolve. Identifica-se, ainda, tensão entre abordagens comportamentais estruturadas e perspectivas sociointeracionistas, cuja articulação produz resultados mais consistentes no contexto escolar. Conclui-se que a integração entre corpo, movimento e linguagem configura eixo pedagógico relevante para a ampliação das formas de comunicação de alunos com TEA, com implicações diretas para a formação docente e para as políticas de educação inclusiva.

Palavras-chave: Transtorno do Espectro Autista. Educação Física Escolar. Cognição Incorporada. Mediação Pedagógica. Comunicação Aumentativa e Alternativa. Educação Inclusiva.

RESUMEN

El presente artículo analiza las contribuciones de la Educación Física escolar al desarrollo del lenguaje en alumnos con Trastorno del Espectro Autista (TEA) en el contexto de la escuela pública. Se trata de una investigación cualitativa de abordaje teórico-bibliográfico, anclada en el Análisis de Contenido propuesto por Bardin (2016), con un corpus constituido por 38 producciones científicas seleccionadas en bases indexadas SciELO, ERIC, Scopus y Portal de Revistas de la CAPES, publicadas entre 2020 y 2025, siguiendo un protocolo compatible con las directrices del PRISMA. El marco teórico articula la teoría de las Inteligencias Múltiples de Gardner (1995), reposicionada críticamente a la luz de estudios contemporáneos sobre cognición incorporada y lenguaje, con la perspectiva vigotskiana de mediación y con la producción reciente sobre TEA, desarrollo lingüístico e inclusión escolar. Los resultados indican que la Educación Física, cuando se organiza con intencionalidad pedagógica y principios inclusivos, constituye un espacio relevante de mediación del lenguaje, al posibilitar formas de expresión que trascienden la oralidad incluyendo la articulación con recursos de Comunicación Aumentativa y Alternativa (CAA). El análisis

evidencia que tal potencial no se efectiviza de modo automático, estando condicionado por la calidad de la mediación docente, la planificación sistemática de las prácticas corporales y las condiciones estructurales en que se desarrolla el trabajo pedagógico. Se identifica, además, una tensión entre enfoques conductuales estructurados y perspectivas socio interaccionistas, cuya articulación produce resultados más consistentes en el contexto escolar. Se concluye que la integración entre cuerpo, movimiento y lenguaje configura un eje pedagógico relevante para la ampliación del repertorio comunicativo de los alumnos con TEA, con implicaciones directas para la formación docente y las políticas de educación inclusiva.

Palabras clave: Trastorno del Espectro Autista. Educación Física Escolar. Cognición Incorporada. Mediación Pedagógica. Comunicación Aumentativa y Alternativa. Educación Inclusiva.

1 INTRODUCTION

Autism Spectrum Disorder (ASD) represents one of the most prevalent neurodevelopmental conditions in the contemporary school context. Data from the World Health Organization (WHO) indicate that approximately 1 in 100 children has some degree of impairment within the spectrum, which places public schools in front of concrete challenges with regard to the organization of effectively inclusive pedagogical practices (WHO, 2023). The communicative and interactional difficulties characteristic of ASD directly affect the possibilities of student participation in the learning processes, demanding from the different areas of the school curriculum more elaborate and intentionally articulated pedagogical responses.

In the context of Brazilian public schools and, in particular, in regions marked by deep structural inequalities, such as the Amazon, these challenges take on even more demanding contours. The distance between the legal frameworks of inclusive education and the concrete working conditions of teachers, the unequal access to continuing education, and the scarcity of specialized pedagogical resources configure a scenario that requires not only pedagogical prescriptions, but public policies that are consistent and committed to the reality of the schools where these students study and where these teachers work every day.

In the context of school Physical Education, this challenge takes on specific contours. The National Common Curriculum Base (BNCC) situates Physical Education in the field of body culture of movement, recognizing its formative potential in cognitive, social, affective and cultural aspects (BRASIL, 2018). From this perspective, Physical Education emerges as a privileged space for interaction, expression and construction of meanings, central dimensions for the development of the language of students with ASD. Studies converge on the understanding that the body is not a mere support for action, but is constituted as an instance of expression, communication and production of meanings (VYGOTSKY, 1998; WILLEMS; CASASANTO, 2011; FERREIRA; LIMA, 2024).

The realization of this potential does not result from the simple insertion of the student in Physical Education classes. It depends, in a decisive way, on the quality of teacher mediation, on the pedagogical intentionality of the proposed practices and on the structural conditions in which the work is developed (BARBOSA; SILVEIRA, 2024; HEALY; NACUA; FRAGALA-PINKHAM, 2018). In view of this scenario, this article aims to analyze the contributions of school Physical Education to the development of language in students with ASD in the context of public schools, based on a critical and systematized theoretical-bibliographic review.

2 THEORETICAL FRAMEWORK

2.1 AUTISM SPECTRUM DISORDER AND LANGUAGE DEVELOPMENT

Autism Spectrum Disorder (ASD) is characterized as a neurodevelopmental condition marked by persistent specificities in communication and social interaction, associated with restricted and repetitive behavior patterns (APA, 2022).⁹ It is a condition that manifests itself in unique ways in each subject, challenging standardized approaches and calling on the school to respond with creativity, listening and pedagogical intentionality. The heterogeneity of the spectrum imposes a relevant epistemological caveat: there is no single profile of student with ASD, and generalizations about the communicative difficulties of these students should be treated with methodological caution. Lord et al. (2022) reaffirm that phenotypic spectrum variability requires individualized pedagogical approaches, not uniform intervention protocols.

In the educational context, the characteristics of ASD have a direct impact on the development of language, especially in its pragmatic dimension that involves the social use of communication, the interpretation of intentions and the construction of meanings in interactions (GOMES; ALMEIDA, 2021). Pragmatic difficulties do not necessarily stem from limitations in the structural domain of language, but from the complexity of interactional situations and the unpredictability of communicative contexts (TAGER-FLUSBERG; PAUL; LORD, 2011; ADAMS et al., 2021). This distinction guides the focus of interventions towards the creation of structured and meaningful contexts of language use.

Recent studies indicate that language development in individuals with ASD is deeply related to opportunities for mediated social interaction. Environments that favor exchange, cooperation, and expression tend to enhance communicative advances (SILVA; MOTA, 2023; BARROS; LIMA, 2022). This perspective is in line with the historical-cultural approach of Vygotsky (1998), for whom higher psychological functions, including language, are constituted in mediated social interactions. It is also important to emphasize that communicative difficulties in ASD are articulated with sensory, cognitive and relational aspects: sensory hypersensitivity, for example, can limit participation in activities that involve physical contact or intense sounds frequent conditions in Physical Education classes (GOMES; ALMEIDA, 2021).

⁹ The adoption of the nomenclature "Autism Spectrum Disorder" in this work follows the terminology of the DSM-5-TR (APA, 2022), widely used in the scientific and educational field. It is recognized, however, that a significant part of the autistic community and researchers committed to the perspective of social identity prefer the term "autistic person" or "autistic spectrum condition", understanding autism as a constitutive trait of identity, and not as a disorder external to the subject. This distinction is politically relevant and should be considered by professionals working in the field.

A perspective that cannot be omitted in contemporary studies on ASD is that of neurodiversity, which understands autism not as a pathology to be corrected, but as a legitimate way of neurological functioning and being in the world (ARMSTRONG, 2012; SILVA; MOTA, 2023). This approach, articulated with Vygotsky's historical-cultural perspective, shifts the focus of the interventions: instead of seeking communicative normalization, it is about creating conditions for each student to expand their expressive repertoire based on their own possibilities. In the school context, this implies recognizing the unique forms of expression of students with ASD verbal, gestural, bodily and symbolic as pedagogical starting points, and not as deficits to be overcome. Such a repositioning is consistent with the National Policy on Special Education from the perspective of Inclusive Education (BRASIL, 2008) and with the principles of the Convention on the Rights of Persons with Disabilities, which affirm the right to difference and full participation in educational spaces (UN, 2006).

2.2 SCHOOL PHYSICAL EDUCATION AND MEDIATION IN THE INCLUSIVE PROCESS

School Physical Education has been resignified in recent decades, incorporating a broader perspective that considers the body as language, culture and expression. The BNCC reinforces this understanding by situating the area in the field of body culture of movement, shifting the axis from technical-motor practice to communicative and relational practice (BRASIL, 2018). In the context of inclusive education, by mobilizing games, play, cooperative practices and shared bodily experiences, this curricular component favors concrete situations of interaction in which communication is built in gesture, movement and in the relationship with the other (RODRIGUES; FERREIRA, 2022; COSTA; ANDRADE, 2023).

Pedagogical mediation occupies a decisive position in this scenario. The teacher acts as an organizer of meaningful experiences, adapting strategies, interpreting behaviors, and promoting interactions. In this role, the sensitivity to recognize and value unconventional forms of communication is as important as the mastery of pedagogical techniques: it is in the quality of the bond that the space for development opens or closes. For students with ASD, this mediation enables the construction of social bonds and the expansion of forms of communication, verbal and non-verbal (SANTOS; OLIVEIRA, 2021). However, the realization of this potential in the school routine still has limits: weaknesses in teacher training, absence of targeted pedagogical strategies and difficulties in adapting activities to the specific needs of students constitute recurrent challenges (BARBOSA; SILVEIRA, 2024). Inclusion that is achieved only through the physical insertion of the student, without

reorganization of pedagogical conditions, configures what Mantoan (2015) calls integration, as opposed to effective inclusion.

The inclusive perspective in Physical Education demands not only specific adaptations, but a structural reorientation of teaching practice that presupposes consistent initial and continuing education, institutional support and adequate material conditions (MENEAR; SMITH, 2021). The literature indicates that quality inclusive Physical Education is distinguished not by the type of activity proposed, but by the way the teacher structures the participation of students with ASD: simple practices can produce rich communicative experiences when organized with intentionality, predictability and attention to the forms of engagement of each student (COSTA; ANDRADE, 2023).

2.3 THE THEORY OF MULTIPLE INTELLIGENCES: HEURISTIC CONTRIBUTIONS AND EPISTEMOLOGICAL LIMITS

The theory of Multiple Intelligences, proposed by Howard Gardner in 1983 and revised in 1995, is a widely used reference in the educational field to support the diversity of ways of learning and expressing. For Gardner (1995), linguistic intelligence refers to the ability to use language effectively to express ideas, interpret meanings and establish social relationships, a conception that, in the context of ASD, offers an alternative pedagogical reading to the deficient model, recognizing that these students manifest different forms of expression and learning.

It is necessary, however, to critically situate this reference. Brody (2006) and Waterhouse (2006) demonstrated that the neurological evidence for the categorical separation of intelligences is insufficient to support the modular model proposed by Gardner, and Visser, Ashton and Vernon (2006) identified a high correlation between the postulated intelligences, contradicting the premise of independence between them. Acknowledging these limitations does not invalidate the pedagogical use of the framework, but it does require epistemological responsibility: for the field of Physical Education and ASD, the value of theory resides, above all, in its heuristic function: to broaden the teacher's view of the possibilities of learning and to legitimize different forms of expression without its theoretical fragility compromising the consistency of the central pedagogical argument.

Contemporary frameworks on embodied cognition offer more solid theoretical support. Willems and Casasanto (2011) indicate that language is not processed in isolated modules of the sensory-motor system, but is constituted in articulation with the subject's bodily experiences. This perspective, combined with the Vygotskian approach, theoretically grounds the relevance of Physical Education beyond its motor dimension, recognizing it as

a space for the constitution of language by the body in movement. For the purposes of this study, Gardner is mobilized in its heuristic-pedagogical dimension and Vygotsky allied to incorporated cognition as epistemological foundations for the analysis of the relationships between body, movement and language development.

3 METHODOLOGY

The present study adopts a qualitative design of a theoretical-bibliographic nature, anchored in the critical and interpretative analysis of consolidated scientific productions. As Minayo (2021) points out, qualitative research enables the interpretation of social phenomena in their symbolic and contextual dimension, configuring itself as an epistemologically legitimate alternative when the objective is to systematize the state of knowledge about a given educational phenomenon and extract implications for pedagogical practice. The researcher, linked to the public education network of the state of Pará and with direct action in teacher training processes aimed at inclusive education, positions herself from a perspective that articulates theoretical rigor and commitment to the reality of the schools where this work is developed. In the field of Special and Inclusive Education, rigorous theoretical-bibliographic reviews have demonstrated the ability to identify gaps, tensions, and convergences in the knowledge produced, contributing to the formulation of research agendas and guidelines for educational policies (LORD et al., 2022; BARBOSA; SILVEIRA, 2024).

The corpus was constituted through a systematized search in the SciELO, ERIC, Scopus and CAPES Journal Portal databases, with a time frame between 2020 and 2025, privileging the most recent and internationally indexed production on the subject. The descriptors used were: Autism Spectrum Disorder; School Physical Education; language; pedagogical mediation; linguistic intelligence; inclusive education, in Portuguese and English, combined by the Boolean operators AND and OR. The inclusion criteria included: (a) peer-reviewed publications; (b) thematic adherence to the object of study; (c) full-text availability; and (d) publication within the delimited period. The following exclusion criteria were adopted: course completion papers, dissertations not published in journals, editorials, and texts without an explicit empirical or theoretical framework.

The selection process followed a systematized protocol compatible with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, adapted for theoretical-bibliographic reviews, as detailed in Table 1. The initial survey resulted in 312 records, of which 187 were pre-selected by title and abstract, 74 read in full and 38 included in the final corpus after rigorous application of the eligibility criteria.

Table 1*Corpus selection protocol (adapted from PRISMA)*

Step	Description	Criteria applied	N
1	Identification — Search in the SciELO, ERIC, Scopus and CAPES Portal databases (2020–2025)	Descriptors combined by Boolean operators AND/OR in Portuguese and English	312
2	Sorting by title and abstract	Thematic adherence to the object of study; publication in a peer-reviewed journal	187
3	Eligibility – reading the full text	Full-text availability; explanation of the theoretical or empirical framework; exclusion of TCCs, unpublished dissertations, editorials	74
4	Inclusion in the final corpus	Full application of the eligibility criteria; relevance to the thematic categories of analysis	38

Source: prepared by the author (2025).

The analysis was carried out through Bardin's Content Analysis (2016), in three stages: pre-analysis, with floating reading and organization of the corpus; exploration of the material, with coding and thematic categorization; and treatment of the results. The thematic categories were: (a) communication and pragmatics of language in ASD; (b) pedagogical mediation and teaching intentionality; (c) bodily practices as a space for expression and language; and (d) structural conditions for inclusion in school Physical Education. It is recognized, as a delimitation, the absence of primary empirical data collection, which positions the work as an applied theoretical analysis.

Table 2*Summary of the main references of the corpus analyzed*

Author(s)/Year	Objective	Method	Key findings
BARROS; LIMA (2022)	Communication in an inclusive school environment for students with ASD	Qualitative research; Case Study	Structured inclusive environments progressively expand communicative forms
SILVA; MOTORBIKE (2023)	Social interaction and language development in ASD	Integrative review	Mediated interaction enhances advances in verbal and nonverbal language
COSTA; ANDRADE (2023)	Pedagogical intentionality in inclusive PE with ASD	Field research; Note	Teacher intentionality defines the quality of communicative experiences

RODRIGUES; FERREIRA (2022)	Pedagogical mediation and participation of students with ASD in PE	Qualitative; Interviews and observation	Qualified mediation expands verbal and non- verbal communicative repertoire
BARBOSA; SILVEIRA (2024)	Gaps in teacher training for inclusion in PE	Survey with teachers	Formative weaknesses limit the realization of inclusive potential
FERREIRA; LIMA (2024)	Imitation, repetition and interaction in communicative development with ASD	Qualitative longitudinal study	Meaningful repetition and functional imitation favor communicative expansion
SOUZA et al. (2024)	Mediated communication opportunities for students with ASD	Systematic review (2019– 2024)	Quality of mediated interactions is a determining variable of progress
HEALY; NACUA; FRAGALA- PINKHAM (2018)	Physical activity interventions for children with ASD	Systematic review	Communicative benefits depend on qualified mediation
LORD et al. (2022)	ASD profiles with a focus on language and communication	International narrative review	Spectrum heterogeneity requires individualized approaches
ADAMS et al. (2021)	Social Communication Intervention for ASD at School Age	Randomized controlled trial	Structured and mediated interventions produce consistent pragmatic gains

Source: prepared by the author (2025).

4 RESULTS AND DISCUSSION

4.1 LANGUAGE, INTERACTION AND ASD: CONVERGENCES AND TENSIONS IN RECENT LITERATURE

The analysis of the corpus allows us to identify expressive convergence: the language development of students with ASD is constituted in the conditions of social interaction and in the forms of pedagogical mediation present in the school environment, and not as an individual and autonomous process (APA, 2022; SILVA; MOTA, 2023; SOUZA et al., 2024). Interventions focused exclusively on the acquisition of formal linguistic structures are limited in scope, especially with regard to the pragmatic development of communication.

The observation reveals a relevant tension between two perspectives. On the one hand, behavioral approaches such as Applied Behavior Analysis (ABA) emphasize the systematic structuring of stimuli and responses, with consistent empirical evidence in clinical contexts (ADAMS et al., 2021). On the other hand, socio-interactionist approaches favor immersion in significant communicative contexts, with less emphasis on structured protocols (SILVA; MOTA, 2023; BARROS; LIMA, 2022). This tension implies concrete pedagogical

choices regarding the organization of Physical Education classes, and its non-problematization constitutes a recurrent gap in national studies. It is worth emphasizing that this is not an irreducible opposition: approaches that combine structure and meaning, predictability and openness to the communicative unforeseen, tend to offer more consistent results for students with ASD in school contexts (ADAMS et al., 2021; SILVA; MOTA, 2023).

The studies analyzed indicate that students with ASD are not characterized by the absence of language, but by their own modes of communicative manifestation. Recognizing these forms implies shifting the pedagogical gaze from a corrective perspective to an approach that welcomes and enhances the available communicative expressions. In addition, structured, sensorially adequate environments with predictable routines reduce the obstacles to communication — evidence of direct implication for Physical Education, whose context often involves high sensory unpredictability (GOMES; ALMEIDA, 2021).

The absence of studies with empirical designs capable of verifying the specific effects of Physical Education practices on the language development of students with ASD is identified as an expressive gap in the national literature. The international literature already has more robust intervention studies (ADAMS et al., 2021; HEALY; NACUA; FRAGALA-PINKHAM, 2018), configuring methodological asymmetry that the area will need to face. The communicative advances observed are neither linear nor homogeneous, reinforcing the need for individualized approaches and systematic monitoring of progress (LORD et al., 2022).

4.2 SCHOOL PHYSICAL EDUCATION AS A SPACE FOR LANGUAGE MEDIATION

The results indicate that school Physical Education can constitute a space for language mediation, especially when it organizes practices that expand the forms of expression beyond orality. This possibility is not homogeneous, nor can it be attributed to the curricular component itself — its effectiveness depends on the pedagogical conditions in which the practices are developed (RODRIGUES; FERREIRA, 2022; COSTA; ANDRADE, 2023).

Cooperative and playful activities produce concrete communication situations in which students need to negotiate meanings, respond to the actions of others and sustain forms of interaction. In these contexts, language is not a prerequisite for participation, but as part of the engagement process itself — a pedagogically relevant condition for students whose pragmatic difficulties limit access to conventional communicative contexts (OLIVEIRA; CASTRO, 2022). Symbolic games, role-plays, rhythmic activities, and cooperative games are strategies of particular relevance, as they require expressing intentions, negotiating

rules, and interpreting the actions of the other communicative functions that correspond exactly to the most committed pragmatic dimensions in the spectrum (SOUZA et al., 2024; FERREIRA; LIMA, 2024).

The presence of students with ASD in Physical Education classes, by itself, does not guarantee inclusive processes. Communicative advances depend on the forms of adaptation of practices and the quality of teacher mediation (BARBOSA; SILVEIRA, 2024; SANTOS; OLIVEIRA, 2021), which calls into question discourses that attribute to Physical Education an intrinsic inclusive potential without problematizing the concrete conditions in which this potential is realized. The analysis also shows that the use of visual resources — sequence cards, pictograms, anticipation of activities — enhances engagement and expands the possibilities of communicative participation, qualifying teacher mediation by reducing the unpredictability of the context (GOMES; ALMEIDA, 2021; RODRIGUES; FERREIRA, 2022).

In this context, the articulation between body practices and Augmentative and Alternative Communication (AAC) resources deserves to be highlighted. The AAC comprises a set of strategies, techniques, and technologies from communication boards with pictograms to electronic devices with voice synthesis that expand the expressive possibilities of students with difficulties in oral communication (DELIBERATO, 2021; VON TETZCHNER; MARTINSEN, 2000).

In the context of Physical Education classes, the integration between movements, functional gestures and AAC symbols can create multimodal communicative systems that favor both participation and language development. A student with ASD who uses a communication board to anticipate the stages of a cooperative activity is not only accessing information: he is exercising an active communicative function in the context of the class, building meaning in interaction with the teacher and colleagues. For this articulation to be effective, it is necessary for the Physical Education teacher to know the AAC systems in use by their students and to incorporate them into the pedagogical planning, a competence that is still little developed in the initial training courses in the area (BARBOSA; SILVEIRA, 2024; MENEAR; SMITH, 2021).

Finally, Physical Education offers unique conditions for the development of non-verbal forms of communication gestures, postures, rhythms, looks and body actions are legitimate forms of expression that expand the communicative repertoire of students with ASD in a way that other disciplines, more centered on verbal language, rarely manage to offer (OLIVEIRA; CASTRO, 2022; FERREIRA; LIMA, 2024).

4.3 TEACHER MEDIATION AND BODY PRACTICES: INTEGRATION BETWEEN BODY AND LANGUAGE

The results situate teacher mediation as a central variable in the articulation between body practices and language development of students with ASD. Mediation is concretized in the way the teacher organizes interactions, proposes activities, adapts demands, and monitors student participation (SOUZA et al., 2024). Pedagogical planning is a structuring variable: the absence of specific strategies reduces predictability, weakens the regulation of interactions, and restricts opportunities for communicative engagement (SILVA; MOTA, 2023).

The body emerges not as an auxiliary resource, but as a dimension through which the student with ASD expresses himself and constructs meanings. Gestures, actions, postures, rhythms and facial expressions expand the possibilities of participation of students with limited access to conventional orality. This understanding is supported both by the Vygotskian perspective and by research on embodied cognition, which demonstrates the functional articulation between sensorimotor systems and linguistic processes (WILLEMS; CASASANTO, 2011). Meaningful repetition, functional imitation and structured interaction are relevant dimensions of this process (FERREIRA; LIMA, 2024), progressively built in the experiences in which the student participates, observes and responds to the actions of the other.

The quality of teacher mediation is expressed in the ability to interpret unconventional forms of communication of students with ASD and use them as a starting point for the expansion of the communicative repertoire. This process requires pedagogical sensitivity, knowledge about the spectrum and willingness to reorganize practices skills rarely developed sufficiently in Physical Education degree courses (BARBOSA; SILVEIRA, 2024; MENEAR; SMITH, 2021). The results support, together, the thesis that the integration between body, movement and language mediated by intentional teaching action configures a relevant pedagogical axis for the development of language in students with ASD. This integration is not only methodological: it is also ethical, as it recognizes in the body that moves, that gesticulates and that inhabits the collective space of the class, a legitimate and valuable way of being and communicating in the world. Achieving it requires consistent teacher training, rigorous planning, and institutional conditions that respect the complexity of inclusive pedagogical work.

5 FINAL CONSIDERATIONS

The present study analyzed the contributions of school Physical Education to the development of language in students with ASD in the context of public schools. The theoretical-bibliographic analysis allows us to affirm that Physical Education, when organized with pedagogical intentionality and based on inclusive principles, constitutes a relevant space for language mediation, by enabling forms of expression that transcend orality and by creating conditions for the progressive expansion of the students' communicative repertoire.

Three central analytical axes emerge from the results. First, the language development of students with ASD is a socially constituted process, which depends on the quality of mediated interactions in the school environment, which positions Physical Education, with its interactive and expressive potential, as a curricular component of strategic relevance for inclusion. According to this potential, it is not automatically effective, being conditioned by the quality of teacher mediation, by the systematic planning of practices and by the structural conditions in which the pedagogical work is developed, including the articulation with AAC resources, still insufficiently incorporated into the training of Physical Education teachers. Third, the body constitutes an active dimension in communicative processes, supported both by the historical-cultural approach and by contemporary research on embodied cognition.

From the point of view of limitations, it is recognized that the absence of primary empirical data collection restricts the ability to contextualize verification of the statements produced. It is recommended that future research adopt collaborative action research designs or intervention studies with variable control, capable of articulating theoretical production, transformation of pedagogical practices and empirical verification of the effects on language development in public school contexts in regions with less access to specialized resources.

The implications of this study for teacher training are straightforward. The preparation of Physical Education teachers to work with students with ASD requires not only the mastery of adaptation strategies, but the development of a pedagogical posture that recognizes the communicative singularities of these students, articulating theoretical foundations of inclusion, knowledge about ASD, specific knowledge of the area and familiarity with AAC systems. It is concluded that the integration between body, movement and language is a relevant pedagogical axis for the inclusive education of students with ASD. This conclusion, however, cannot be read as yet another abstract prescription addressed to teachers already overworked in structurally fragile public schools. On the contrary, it requires managers, policymakers, and researchers to assume their responsibility: to ensure quality initial and

continuing teacher training, adequate material conditions, and an empirical research agenda committed to the reality of the schools where these students study and where these teachers work every day.

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TYPE 2 DIABETES MELLITUS AND SYSTEMIC ARTERIAL HYPERTENSION: ETIOLOGICAL, PATHOGENIC, AND PATHOPHYSIOLOGICAL ASPECTS

DIABETES MELLITUS TIPO 2 E HIPERTENSÃO ARTERIAL SISTÊMICA: ASPECTOS ETIOLÓGICOS, PATOGÊNICOS E FISIOPATOLÓGICOS

DIABETES MELLITUS TIPO 2 E HIPERTENSIÓN ARTERIAL SISTÉMICA: ASPECTOS ETIOLÓGICOS, PATOGÉNICOS Y FISIOPATOLÓGICOS



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ABSTRACT

Non-communicable chronic diseases represent a major challenge to public health due to their high prevalence, impact on morbidity and mortality, and association with modifiable risk factors such as physical inactivity, inadequate diet, smoking, obesity, and alcohol consumption. Among these diseases, systemic arterial hypertension and type 2 diabetes mellitus stand out because of their increasing frequency and direct relationship with cardiovascular, renal, and metabolic complications. Systemic arterial hypertension has a multifactorial etiology involving genetic predisposition, sympathetic hyperactivity, activation of the renin-angiotensin-aldosterone system, and endothelial dysfunction, whereas type 2 diabetes mellitus results from the interaction between insulin resistance, progressive pancreatic beta-cell dysfunction, and chronic low-grade inflammation. The diagnosis and monitoring of these conditions require careful clinical evaluation and specific laboratory tests, such as blood pressure measurement, fasting blood glucose, glycated hemoglobin, and oral glucose tolerance test. Treatment is based on lifestyle modification, the use of antihypertensive and antidiabetic drugs, as well as continuous follow-up in programs such as HIPERDIA. Therefore, an integrated understanding of these disorders is essential for adequate control, prevention of complications, and improvement of patients' quality of life.

Keywords: Non-Communicable Chronic Diseases. Systemic Arterial Hypertension. Type 2 Diabetes Mellitus. Pathophysiology. Diagnosis. Monitoring.

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RESUMO

As doenças crônicas não transmissíveis representam importante desafio para a saúde pública, em razão de sua elevada prevalência, impacto na morbimortalidade e associação com fatores de risco modificáveis, como sedentarismo, alimentação inadequada, tabagismo, obesidade e etilismo. Entre elas, a hipertensão arterial sistêmica e a diabetes mellitus tipo 2 se destacam pela frequência crescente e pela relação direta com complicações cardiovasculares, renais e metabólicas. A hipertensão arterial sistêmica apresenta etiologia multifatorial, envolvendo predisposição genética, hiperatividade simpática, ativação do sistema renina-angiotensina-aldosterona e disfunção endotelial, enquanto a diabetes mellitus tipo 2 resulta da interação entre resistência à insulina, disfunção progressiva das células beta pancreáticas e inflamação crônica de baixo grau. O diagnóstico e o acompanhamento dessas condições exigem avaliação clínica criteriosa e exames laboratoriais específicos, como medida da pressão arterial, glicemia de jejum, hemoglobina glicada e teste oral de tolerância à glicose. O tratamento baseia-se na mudança de estilo de vida, no uso de fármacos anti-hipertensivos e antidiabéticos, além do seguimento contínuo em programas como o HIPERDIA. Assim, a compreensão integrada desses agravos é fundamental para o controle adequado, a prevenção de complicações e a melhoria da qualidade de vida dos pacientes.

Palavras-chave: Doenças Crônicas Não Transmissíveis. Hipertensão Arterial Sistêmica. Diabetes Mellitus Tipo 2. Fisiopatologia. Diagnóstico. Monitoramento.

RESUMEN

Las enfermedades crónicas no transmisibles representan un importante desafío para la salud pública debido a su elevada prevalencia, impacto en la morbimortalidad y asociación con factores de riesgo modificables, como el sedentarismo, la alimentación inadecuada, el tabaquismo, la obesidad y el consumo de alcohol. Entre ellas, la hipertensión arterial sistémica y la diabetes mellitus tipo 2 destacan por su creciente frecuencia y por su relación directa con complicaciones cardiovasculares, renales y metabólicas. La hipertensión arterial sistémica presenta una etiología multifactorial que involucra predisposición genética, hiperactividad simpática, activación del sistema renina-angiotensina-aldosterona y disfunción endotelial, mientras que la diabetes mellitus tipo 2 resulta de la interacción entre la resistencia a la insulina, la disfunción progresiva de las células beta pancreáticas y la inflamación crónica de bajo grado. El diagnóstico y el seguimiento de estas condiciones requieren una evaluación clínica cuidadosa y exámenes de laboratorio específicos, como la medición de la presión arterial, glucemia en ayunas, hemoglobina glucosilada y prueba oral de tolerancia a la glucosa. El tratamiento se basa en cambios en el estilo de vida, el uso de fármacos antihipertensivos y antidiabéticos, además del seguimiento continuo en programas como HIPERDIA. Así, la comprensión integrada de estas enfermedades es fundamental para el control adecuado, la prevención de complicaciones y la mejora de la calidad de vida de los pacientes.

Palabras clave: Enfermedades Crónicas No Transmisibles. Hipertensión Arterial Sistémica. Diabetes Mellitus Tipo 2. Fisiopatología. Diagnóstico. Monitoreo.

1 INTRODUCTION

Chronic Non-Communicable Diseases (NCDs) are currently one of the main challenges for global public health. According to the World Health Organization (WHO, 2024) and the Ministry of Health (BRASIL, 2021), these diseases are responsible for approximately 74% of deaths in Brazil and for more than 70% of deaths globally. This group encompasses conditions of high social, clinical, and economic burden, with emphasis on cardiovascular diseases, neoplasms, chronic respiratory diseases, and diabetes mellitus, which share widely prevalent modifiable risk factors, such as sedentary lifestyle, inadequate diet, smoking, harmful alcohol consumption, and overweight (WHO, 2024).

The National Health Survey (PNS, 2019) showed that more than half of the Brazilian adult population is diagnosed with at least one NCD, which reinforces the magnitude of the problem and its complexity in the national epidemiological scenario (IBGE, 2020). Although important advances have been made in recent decades, such as the expansion of epidemiological surveillance and the implementation of specific public policies, such as the Strategic Action Plan to Combat NCDs 2021-2030, relevant inequalities still persist in access to prevention, timely diagnosis, and continuous treatment. Such inequities affect, more expressively, populations in situations of social vulnerability, compromising the principles of equity, universality, and integrality of the Unified Health System (SUS) (MALTA et al., 2020).

Among NCDs, Cardiovascular Diseases (CVDs) stand out as the main single cause of mortality in Brazil and in the world, in addition to representing an important factor of morbidity and reduction in quality of life. This group includes conditions of great clinical relevance, such as acute myocardial infarction (AMI), cerebrovascular accident (CVA), heart failure (HF), and arrhythmias. Although many of these conditions can be prevented through health promotion strategies and control of risk factors, their incidence remains high (PAHO, 2025).

In this context, systemic arterial hypertension (SAH) is the main risk factor for CVD, being recognized as a true silent pandemic. It is estimated that about one in four Brazilian adults lives with the disease, with a prevalence of 27.9% in the capitals, especially affecting women and individuals with less education. Defined by persistently high blood pressure levels, equal to or greater than 140/90 mmHg, SAH is often asymptomatic, which favors its underreporting and late diagnosis, although it is associated with important cardiovascular, renal, and cognitive complications (BRASIL, 2023; MIGOWSKI; COSTA, 2024).

At the same time, type 2 Diabetes Mellitus (DM2) stands out as one of the most prevalent and worrisome metabolic diseases of contemporary times, with growing projections worldwide. In Brazil, it is estimated that 16.6 million adults live with diabetes, and

approximately 31.9% are unaware of the diagnosis (IDF, 2024). It is a multifactorial condition, associated with aging, obesity, sedentary lifestyle, and inadequate eating habits, with a high potential to cause micro and macrovascular complications, such as retinopathy, nephropathy, neuropathy, amputations, and major cardiovascular events (IDF, 2021; WHO, 2023).

It is also noteworthy that most of the complications associated with SAH and DM2 can be prevented or minimized through early diagnosis, longitudinal follow-up, and therapeutic adherence. However, because these are diseases of insidious and often silent course, late diagnoses and interventions performed in advanced stages are frequent. This scenario reinforces the need for effective strategies for tracking, risk stratification, and continuous monitoring, especially in the context of Primary Health Care (PHC), the main gateway to the SUS and a strategic level for care coordination (IDF, 2021; WHO, 2023).

Thus, the objective of this chapter is to describe the main etiological, pathogenic, and pathophysiological aspects of type 2 diabetes mellitus and systemic arterial hypertension, highlighting their relevance as chronic non-communicable diseases, their risk factors, the pathophysiological mechanisms involved, and the possibilities of treatment, with emphasis on multidisciplinary action and health care programs.

2 CHRONIC NON-COMMUNICABLE DISEASES - NCDs

Chronic Non-Communicable Diseases (NCDs) are a set of clinical conditions of a prolonged nature, which are not caused by infectious agents and, therefore, do not present a risk of transmission between individuals. Such diseases result from the complex interaction of genetic, physiological, environmental, and behavioral factors, and are characterized by a generally silent onset, slow evolution, and often an asymptomatic course in the early stages (WHO, 2024).

NCDs mainly encompass cardiovascular diseases (such as acute myocardial infarction and stroke), various types of cancer, chronic respiratory diseases (including chronic obstructive pulmonary disease - COPD and asthma) and diabetes mellitus. These four groups of diseases together represent the greatest burden of morbidity and mortality in the global public health scenario, not only because of their high prevalence, but also because of the economic and social impacts associated with their management and the productive losses they cause (MIGOWSKI; COSTA, 2024; WHO, 2024).

Although they can affect individuals at any stage of life, the incidence and prevalence of NCDs increase significantly with population aging, which makes them especially frequent among adults and the elderly. According to estimates by the World Health Organization

(WHO), approximately 18 million deaths attributed to NCDs occur before the age of 70, surpassing all other combined causes of death in this age group. Of this total, about 82% are registered in low- and middle-income countries, which highlights the deep inequality in the distribution of risk and access to health care (STOPA et al., 2022; BRAZIL, 2021; WHO, 2024).

Data from the WHO (2021) indicate that approximately 75% of deaths unrelated to the COVID-19 pandemic, on a global scale, were caused by NCDs. In this context, cardiovascular diseases remain the leading cause of death, with more than 19 million deaths recorded in 2021, followed by cancers (10 million), chronic respiratory diseases (4 million), and diabetes (more than 2 million, including cases resulting from renal complications). Together, these four categories account for approximately 80% of all premature deaths attributed to NCDs (MALTA et al. 2014; WHO, 2024).

In Brazil, the *Epidemiological Bulletin of Premature Mortality (30 – 69 years) due to Chronic Non-Communicable Diseases in Rio Grande do Sul* (2024) reveals the persistence of the impact of these diseases on the population. In 2013, 20,855 premature deaths were recorded attributed to the four main NCDs, of which 12,133 (58.2%) occurred among men and 8,722 (41.8%) among women. In 2023, the total number of premature deaths was 20,410, of which 11,466 (56.2%) were males and 8,940 (43.8%) were females. Among the diseases studied, cancer remained the main cause of premature mortality in both sexes, followed by cardiovascular diseases (RIO GRANDE DO SUL, 2024).

A particularly alarming fact refers to the proportional growth in deaths from diabetes mellitus (DM), which increased from 7.1% to 9.4% between 2013 and 2023, which represents an increase of approximately 32.2% in the absolute number of deaths. This trend was observed both in males, with an increase of 41.5%, and in females, with an increase of 21.1%, which indicates a significant increase in the burden of the disease in the state's population. On the other hand, cardiovascular diseases showed a reduction in the proportional participation of premature deaths, although they remain the second leading cause of early mortality (RIO GRANDE DO SUL, 2024).

Most of the risk factors associated with NCDs are preventable and are directly related to the population's lifestyle. Among the main behavioral determinants are inadequate eating habits, sedentary lifestyle, use of tobacco products, abusive consumption of alcoholic beverages and exposure to environmental pollution. Such factors contribute to significant metabolic alterations, such as increased blood pressure, elevated blood glucose, dyslipidemia, and overweight, characterizing the so-called metabolic risk factors. These, in turn, are strongly associated with the development of NCDs, especially cardiovascular

diseases, which lead the global indicators of avoidable mortality (BRASIL, 2021; WHO, 2024; VIGITEL, 2023).

Among the NCDs with the highest prevalence and impact, systemic arterial hypertension (SAH) stands out, considered one of the main modifiable risk factors for cardiovascular, cerebrovascular, and renal events. It is estimated that more than 1.28 billion adults between 30 and 79 years of age live with hypertension in the world, and two-thirds of them live in low- and middle-income countries. Also according to the WHO, 46% of people with hypertension are unaware of the diagnosis, only 42% receive treatment, and only 21% have the condition under adequate control (MALTA et al., 2022; WHO, 2023).

SAH represents a relevant public health problem. Data from the Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL), referring to the year 2023, point to a self-reported prevalence of SAH of 27.6% among Brazilian adults. This prevalence increases progressively with age, being higher among women, individuals with a lower level of education, and residents of the Southeast and South regions of the country (BRASIL, 2021; VIGITEL, 2023).

Diabetes mellitus is one of the most relevant public health challenges in Brazil, which currently occupies the sixth position among the countries with the highest absolute number of cases of the disease worldwide. According to data from the Brazilian Diabetes Society (SBD), approximately 16.6 million Brazilians between 20 and 79 years old live with the disease. The self-reported prevalence of diabetes among adults is 11.1% in women and 9.1% in men, with an increase proportional to age and lower schooling. In addition, about 32% of cases remain undiagnosed, which aggravates the complications associated with the disease. Mortality attributed to diabetes more than doubled between 1992 and 2019, from 12.8 to 30.2 deaths per 100 thousand inhabitants, and its economic burden is significant, especially in the Unified Health System (SUS), where a large part of hospital costs is related to cardiovascular complications. The growing prevalence and the financial and social impact reinforce the urgency of public policies that integrate prevention, early diagnosis, and effective treatment (SBD, 2024; MALTA et al., 2022).

In Nova Candelária (RS), a municipality located in the northwest region of the state, chronic non-communicable diseases (NCDs) continue to be important causes of morbidity and mortality. According to DATASUS data for the year 2024, the mortality coefficient due to NCDs was 193.42 per 100 thousand people and the hospital admission rate was 1,611.86 per 100 thousand people, evidencing the impact of these diseases on the health of the local population. Diseases of the circulatory system and diabetes had the same mortality coefficient, which was 64.47/100 thousand people. Also in 2024, the rate of hospitalization

for diseases of the circulatory system reached 967.12 per 100 thousand inhabitants, and the rate of hospitalizations related to diabetes was 128.95 per 100 thousand inhabitants, indicating the need to intensify preventive actions and clinical management in primary health care (BRASIL, 2025).

2.1 SYSTEMIC ARTERIAL HYPERTENSION - SAH

2.1.1 Etiology

Systemic Arterial Hypertension (SAH) is a multifactorial clinical condition, whose etiology results from a complex interaction between genetic, environmental, and behavioral factors. The most prevalent form, accounting for 90% to 95% of cases, is classified as primary or essential hypertension and is characterized by the absence of a single identifiable cause. Evidence points to a significant familial predisposition, since individuals with a family history of the disease are at increased risk for its development. Such predisposition is associated with genetic polymorphisms that influence the regulation of the renin-angiotensin-aldosterone system (RAAS), the control of vascular tone, and sodium metabolism (CAREY et al., 2022; PADMANABHAN; DOMINICZAK, 2021).

In addition to genetic determinants, environmental and behavioral factors play a crucial role in the onset and progression of hypertension. Among the main ones are excessive sodium intake, obesity, sedentary lifestyle, alcohol abuse, smoking, chronic stress and inadequate eating patterns. Advanced age is also considered a relevant risk factor, since the aging process compromises arterial compliance, favoring the progressive elevation of blood pressure (AMORIM et al., 2024; COSTA et al., 2018).

Inadequate lifestyle habits are among the main preventable factors associated with high blood pressure. Among them, excessive sodium consumption, which can lead to sodium and water retention, increased plasma volume and, consequently, increased blood pressure. The World Health Organization recommends that the daily consumption of sodium should not exceed 2000mg, which is equivalent to 5g of sodium chloride/day (PAHO, 2023). In this sense, DASH (*Dietary Approaches to Stop Hypertension*) diets have shown important results in reducing blood pressure levels (BARROS et al., 2024).

Obesity/overweight also represents one of the modifiable risk factors for the development of hypertension. In this context, anthropometric parameters are important for clinical evaluation and patient monitoring. Waist circumference (WC) measurement provides independent and additive information to the body mass index (BMI) to predict morbidity and risk of death, so this simple measurement should be considered an important "vital sign" in clinical practice (BARROSO et al., 2020). It should be noted that overweight/obesity are

associated with increased peripheral vascular resistance, cardiac output overload, and endothelial dysfunction, mechanisms that, together, favor the increase in blood pressure levels (AMORIM et al., 2024; BARROSO et al., 2020; MALTA et al., 2022).

Another preventable cause is a sedentary lifestyle, which contributes to weight gain, insulin resistance, and endothelial dysfunction, in addition to negatively impacting blood pressure regulation, while the regular practice of physical activity exerts a protective effect, helping to reduce blood pressure. In addition, habits such as alcohol abuse and smoking are strongly related to hypertension. Alcohol, when ingested in large quantities, can raise blood pressure levels, while smoking induces vasoconstriction and damage to the vascular endothelium (AMORIM et al., 2024). In addition, chronic stress also contributes to the increase in blood pressure since this state stimulates the continuous release of hormones such as adrenaline and cortisol, capable of causing transient increases in blood pressure and, in the long term, contributing to the onset of hypertension (OLIVEIRA et al., 2021).

National studies, such as Vigitel (2023), indicate that a large part of the population has two or more combined risk factors, which combined and with synergistic action intensify the risk of early development of SAH. The prevention, control, treatment, and monitoring of hypertension are associated with lifestyle interventions, with a proven impact on the incidence and severity of the disease (BRASIL, 2023; MALTA et al., 2022)

In contrast to the primary form, secondary hypertension has a defined etiology and corresponds to a smaller portion of cases. Its causes are potentially treatable and include nephropathies, endocrine disorders (such as primary hyperaldosteronism and pheochromocytoma), long-term use of certain drugs (such as corticosteroids and oral contraceptives), and obstructive sleep apnea (CAREY et al., 2022; PADMANABHAN; DOMINICZAK, 2021).

2.1.2 Pathogenesis

Systemic arterial hypertension (SAH) is a chronic clinical condition characterized by persistent elevation of blood pressure levels, resulting from a set of functional and structural alterations that compromise, in an integrated manner, the cardiovascular, renal and neurohormonal systems. Its pathogenesis is complex and multifactorial, involving interrelated pathophysiological mechanisms that contribute to the sustained increase in blood pressure. Among the main ones, the exacerbated activation of the renin-angiotensin-aldosterone system (RAAS), increased activity of the sympathetic nervous system, endothelial dysfunction, and renal sodium and water retention stand out. These changes converge to the promotion of peripheral vasoconstriction, increased systemic vascular

resistance, and increased intravascular volume, creating a favorable scenario for chronic hypertension maintenance and progressive vascular remodeling (AMORIM et al., 2024; ALBUQUERQUE, 2024).

From a clinical point of view, SAH has an insidious evolution and is often asymptomatic in its early stages, which hinders early diagnosis and favors underreporting of cases. In most situations, detection occurs incidentally, during routine medical consultations. When present, the most frequently reported signs and symptoms include headache, dizziness, palpitations, tinnitus, visual blurring, dyspnea, and chest pain, especially in situations of hypertensive crisis or when there is target organ impairment (BARROSO et al., 2021; AMORIM et al., 2024; ALBUQUERQUE, 2024).

Hypertension-related headache, often called "hypertensive headache", tends to occur predominantly in the occipital region and is generally described as pulsatile, with variable intensity. It can intensify in the face of acute elevations in blood pressure, particularly in hypertensive crises. However, it should be noted that such a manifestation is not pathognomonic of SAH, as it can be associated with several other clinical conditions, which requires careful diagnostic investigation (SMITH et al., 2023).

In the cardiovascular context, left ventricular hypertrophy (LVH) is one of the main morphofunctional repercussions of chronic hypertension. This process results from the sustained increase in the hemodynamic overload imposed on the heart, leading to thickening of the ventricular wall and changes in its filling and ejection capacity. Echocardiography is the method of choice for detecting LVH, allowing the evaluation of the magnitude of cardiac structural and functional changes. The presence of this condition is strongly associated with an increased risk of adverse events, such as heart failure, arrhythmias, and stroke, and is therefore recognized as a marker of target organ damage and indicative of the need for more rigorous therapeutic intervention (ALBUQUERQUE, 2024).

Maintenance of SAH without adequate control triggers a continuous process of injury to multiple target organs. In the cardiovascular system, it favors the development of myocardial ischemia (angina pectoris), acute myocardial infarction, and ventricular dysfunction, which can culminate in congestive heart failure. In the renal system, persistently elevated blood pressure promotes glomerular sclerosis and arteriolar nephrosclerosis, resulting in progressive loss of renal function and possible progression to chronic kidney disease. In the ophthalmological field, hypertension can cause significant changes in the retinal microcirculation, characterizing hypertensive retinopathy, whose evolution can lead to partial or total loss of vision. In addition, SAH is one of the most relevant modifiable risk

factors for stroke, whether in the ischemic or hemorrhagic form (ALBUQUERQUE, 2024; AMORIM et al., 2024).

2.1.3 Pathophysiology

The pathophysiology of Systemic Arterial Hypertension (SAH) is characterized by a complex and interdependent set of functional and structural alterations that mainly involve the cardiovascular, renal, sympathetic nervous and endocrine systems. Among the vascular mechanisms, endothelial dysfunction stands out as one of the central factors in the genesis and progression of the disease. The endothelium, consisting of a single layer of cells that lines the blood vessels internally, plays a fundamental role in the regulation of vascular tone through the balanced release of vasodilator substances, such as nitric oxide (NO), and vasoconstrictors, such as endothelin-1. In hypertensive individuals, there is a reduction in the bioavailability of NO and a relative increase in vasoconstrictor mediators, resulting in an increase in peripheral vascular resistance. Such an imbalance favors the reduction of arterial compliance and vascular remodeling, with progressive loss of elasticity of the vessels, culminating in a sustained increase in blood pressure (ALBUQUERQUE, 2024; BRYAN, 2022).

Another relevant mechanism is the exacerbated activation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II, the main effector of this system, has a potent vasoconstrictor action, intensifies the activity of the sympathetic nervous system, stimulates the secretion of aldosterone, and induces renal sodium and water retention. These combined actions increase intravascular volume and systemic vascular resistance, in addition to promoting vascular inflammation and endothelial injury. Evidence also indicates that angiotensin II acts on macrophages, stimulating cholesterol synthesis and contributing to the formation of atherosclerotic plaques, which reinforces its role in both the development of SAH and its cardiovascular complications (SU et al., 2021; ALBUQUERQUE, 2024).

Renal function plays a determining role in pressure homeostasis, regulating extracellular volume and fluid and electrolyte balance. Excessive sodium and water retention, often mediated by aldosterone, raises blood volume and, consequently, blood pressure. On the other hand, chronic hypertension can induce progressive damage to nephrons, establishing a pathological cycle in which kidney injury aggravates the hypertensive condition and this, in turn, accelerates the deterioration of renal function (REZENDE et al., 2021; YE et al., 2022; SANTOS et al., 2024).

In addition, sympathetic nervous system hyperactivity and chronic inflammatory status play significant roles in the maintenance of hypertension. Exacerbated sympathetic

stimulation causes tachycardia, peripheral vasoconstriction, and increased catecholamine release, increasing hemodynamic overload on the heart and vessels. Chronic inflammation, on the other hand, favors endothelial dysfunction, oxidative stress, and structural remodeling of the myocardium and vasculature, contributing to the hypertensive phenotype and increased risk of cardiovascular complications in the long term (LOPES et al., 2021). An integrated understanding of these pathophysiological mechanisms is essential to support more comprehensive therapeutic interventions, as well as to identify biomarkers that aim to predict the occurrence of cardiovascular events or complications resulting from major hypertension and reduce mortality associated with hypertension (YE et al., 2022).

2.1.4 Diagnostics and monitoring

The diagnosis of Systemic Arterial Hypertension (SAH) is based on the repeated and standardized measurement of blood pressure, associated with a comprehensive clinical evaluation and, when indicated, complementary tests. According to the current guidelines, the measurement should be performed with a calibrated sphygmomanometer, following strict technical criteria: the patient should remain at rest for at least five minutes, sitting, with legs uncrossed, feet flat on the floor, back relaxed and supported, arm positioned at heart level, without having ingested caffeine, smoked or practiced intense physical exercise in the previous 30 minutes (BRANDÃO et al., 2025; BARROSO et al., 2021; WHELTON et al., 2024).

The diagnosis is established when the pressure levels are equal to or greater than 140 mmHg for systolic pressure and/or 90 mmHg for diastolic pressure, measured on at least two different occasions, with the patient in ideal conditions. The classification of SAH, according to the stage of pressure elevation, is essential to define the severity of the condition and guide therapeutic management. Table 1 shows the BP classification (BRANDÃO et al., 2025; BARROSO et al., 2021; SMITH et al., 2023).

Figure 1

Classification of blood pressure according to the measurement in the office from 18 years of age

Classificação da PA	PAS (mmHg)		PAD (mmHg)
PA normal	< 120	e	< 80
Pré-hipertensão	120–139	e/ou	80–89
HA Estágio 1	140–159	e/ou	90–99
HA Estágio 2	160–179	e/ou	100–109
HA Estágio 3	≥ 180	e/ou	≥ 110

DBHA: Diretriz Brasileira de Hipertensão Arterial; HA: hipertensão arterial; PA: pressão arterial; PAD: pressão arterial diastólica; PAS: pressão arterial sistólica.

^aA classificação é definida de acordo com a PA no consultório e pelo nível mais elevado de PA, sistólica ou diastólica.

^bA HA sistólica isolada, caracterizada pela PAS ≥ 140 mmHg e PAD < 90 mmHg, é classificada em Estágio 1, 2 ou 3, de acordo com os valores da PAS nos intervalos indicados.

^cA HA diastólica isolada, caracterizada pela PAS < 140 mmHg e PAD ≥ 90 mmHg, é classificada em Estágio 1, 2 ou 3, de acordo com os valores da PAD nos intervalos indicados.

Source: Adapted from BRANDÃO et al. (2025).

Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Monitoring (HBPM) represent important tools to confirm the diagnosis and identify specific conditions. ABPM records blood pressure values, in an automated way, for 24 hours, allowing the analysis of the circadian profile of blood pressure and the evaluation of prognostic parameters, such as nocturnal blood pressure. HBPM, on the other hand, consists of serial measurement performed by the patient in a home environment, usually for five to seven days, with morning and afternoon measurements under controlled conditions. These methods are essential to detect white-coat hypertension, blood pressure elevation restricted to the clinical environment, and masked hypertension, normal values in the office, but elevated in other situations, preventing diagnostic errors (BRANDÃO et al., 2025; AMORIM et al., 2024; BARROSO et al., 2021).

In addition to blood pressure measurement, the diagnostic evaluation should include detailed anamnesis, complete physical examination, and laboratory and imaging tests. The anamnesis should address cardiovascular risk factors, family history, lifestyle habits (diet, alcohol consumption, smoking, physical activity), use of drugs and presence of comorbidities, such as diabetes mellitus, dyslipidemia and chronic kidney disease. The physical examination should include cardiac and pulmonary auscultation, palpation of peripheral pulses, measurement of weight, height, calculation of body mass index (BMI), measurement of abdominal circumference (WC) and search for signs of target organ

damage or secondary causes of hypertension (BRANDÃO et al., 2025; BARROSO et al., 2021; ALBUQUERQUE, 2024).

The complementary tests aim to confirm the diagnosis, stratify cardiovascular risk and identify subclinical lesions. Fasting blood glucose, lipid profile, serum creatinine, potassium, uric acid, and type I urine test are recommended, in addition to imaging tests, such as electrocardiogram and echocardiogram, useful for the early detection of structural changes, such as left ventricular hypertrophy (BRANDÃO et al., 2025; BARROSO et al., 2021; LEE et al., 2022; WHELTON et al., 2024).

Monitoring SAH, in addition to aiding in diagnosis, is crucial for clinical follow-up and assessment of response to treatment. ABPM and HBPM allow the therapeutic regimen to be adjusted more precisely, to verify the patient's adherence to pharmacological and non-pharmacological measures, and to identify relevant pressure variations. The systematic use of these resources, combined with organized records, favors communication between the patient and the health team, optimizes decision-making, and contributes to the prevention of cardiovascular events (BRANDÃO et al., 2025; BARROSO et al., 2020; ALBUQUERQUE, 2024).

2.1.5 Treatment

The treatment of Systemic Arterial Hypertension (SAH) has as its main objective to reduce and maintain blood pressure levels within parameters considered normal, preventing or delaying the development of target organ damage and significantly reducing the risk of cardiovascular and cerebrovascular events. This therapeutic approach, in addition to reducing the morbidity and mortality associated with the disease, aims to improve the quality of life and life expectancy of patients (BRANDÃO et al., 2025; WHELTON et al., 2024; AMORIM et al., 2024).

Treatment should be based on integrated strategies, combining non-pharmacological and pharmacological measures, whose choice and intensity are determined by the clinical profile, presence of comorbidities, and overall cardiovascular risk. In this context, non-pharmacological measures represent the initial pillar of SAH management and include: smoking cessation; adoption of a healthy dietary pattern, such as the DASH (Dietary Approaches to Stop Hypertension) diet, characterized by high consumption of fruits, vegetables, legumes and low-fat dairy products, associated with a reduction in the intake of sodium and saturated fats; body weight control, with a Body Mass Index (BMI) target between 18.5 and 24.9 kg/m²; moderation of the consumption of alcoholic beverages; regular practice of aerobic physical activity and muscle strengthening; slow breathing techniques

and stress management strategies. Early implementation of these interventions is capable, in many cases, of promoting significant reductions in blood pressure and delaying the need for pharmacological treatment (BRANDÃO et al., 2025; BARROSO et al., 2021).

Pharmacological treatment, on the other hand, is indicated when non-pharmacological measures alone are not sufficient to achieve blood pressure goals or, immediately, in patients with stage 2 hypertension or with high cardiovascular risk. The main classes of antihypertensives, thiazide diuretics (IUDs), calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and beta-blockers (BBs) have demonstrated proven efficacy in reducing blood pressure levels and preventing cardiovascular complications (BRANDÃO et al., 2025; BARROSO et al., 2021; WHELTON et al., 2024). Treatment can be initiated by monotherapy or, preferably, by combination therapy, especially in patients with higher blood pressure values or a higher risk of events. The choice of drug should be individualized, considering pharmacokinetic and pharmacodynamic characteristics, the presence of associated diseases, target organ damage (LOA), and socioeconomic conditions (BRANDÃO et al., 2025; BARROSO et al., 2021).

The clinical management of SAH requires regular follow-up and continuous monitoring, with periodic clinical and laboratory evaluations. In addition to frequent blood pressure measurement, it is essential to control renal function, serum levels of electrolytes, and other biomarkers, allowing early identification of adverse effects and the adequacy of therapy. Patient education plays a crucial role in the process, promoting treatment adherence and the reduction of modifiable risk factors (BRANDÃO et al., 2025; RASMUSSEN et al., 2020; WHELTON et al., 2024).

When properly conducted, the treatment of SAH is able to prevent serious complications, such as acute myocardial infarction, stroke, and chronic renal failure, in addition to contributing to the maintenance of functionality and the improvement of quality of life (BRANDÃO et al., 2025; RASMUSSEN et al., 2020; BARROSO et al., 2021; WHELTON et al., 2024).

2.2 TYPE 2 DIABETES MELLITUS

2.2.1 Etiology

Diabetes Mellitus (DM) is a chronic metabolic syndrome of multifactorial etiology, resulting from the interaction between genetic predisposition, environmental and behavioral factors. The disease has different subtypes, among which type 1 Diabetes Mellitus (DM1) is characterized by the autoimmune destruction of β -pancreatic cells, usually in genetically

predisposed individuals, culminating in absolute insulin deficiency and persistent hyperglycemia. On the other hand, type 2 Diabetes Mellitus (DM2) accounts for more than 90% of cases diagnosed globally and has a complex pathophysiology, marked by ineffective insulin secretion by β cells and resistance of peripheral tissues to its action (ADA, 2024; SBD, 2024; OJO et al., 2023).

T2DM arises from disturbances in the production and utilization of insulin, resulting in persistently high plasma glucose levels. Among the most relevant risk factors, the following stand out: overweight and obesity, chronic hyperglycemia, dyslipidemia, inadequate eating habits, sedentary lifestyle, aging, family history of the disease, as well as psychosocial conditions such as stress, anxiety, and depression (IDF, 2024; COUTO et al., 2024).

Visceral obesity is one of the main determinants of DM2, since the excessive deposition of abdominal fat favors insulin resistance through the release of pro-inflammatory adipokines, compromising peripheral glucose uptake and amplifying the risk of the disease (COUTO et al., 2024). At the same time, physical inactivity increases the prevalence of insulin resistance, while the regular practice of physical exercise plays a protective role, promoting the reduction of abdominal fat, improved glucose tolerance, glycemic control, reduction of oxidative stress, and modulation of inflammatory processes (OLIVEIRA et al., 2023).

In addition, several associated medical conditions, such as systemic arterial hypertension and dyslipidemias, contribute to the pathophysiology of DM2. These comorbidities intensify insulin resistance and significantly increase the risk of cardiovascular complications, such as acute myocardial infarction and stroke (BROWN et al., 2023; IZAR et al., 2021).

Smoking is another aggravating factor, related to an approximately 60% increase in the risk of developing DM2 in smokers of more than 20 cigarettes/day. Nicotine directly affects glucose metabolism, favoring insulin resistance by mechanisms of oxidative stress, systemic inflammation, endothelial dysfunction, and changes in lipid metabolism. In addition, chronic exposure compromises β -pancreatic function, reducing insulin secretion (YANG et al., 2022; OLIVEIRA et al., 2023).

Similarly, excessive alcohol consumption (above 60 g/day) is related to insulin resistance and increased risk of T2DM, promoting hepatic triglyceride accumulation, greater production of reactive oxygen species, and chronic low-grade inflammation (SALAMA et al., 2021).

Finally, aging is highlighted as a non-modifiable and highly relevant factor in the incidence of DM2, as it promotes a physiological increase in insulin resistance, a reduction

in the mass and function of β cells, and a greater predisposition to metabolic complications, especially in elderly populations (ADA, 2024; OLIVEIRA et al., 2023).

2.2.2 Pathogenesis and Clinical Manifestations

The development of type 2 diabetes mellitus (T2DM) is characterized by a complex interaction between peripheral insulin resistance and progressive pancreatic beta cell dysfunction. Insulin resistance initially manifests itself in target tissues, skeletal muscle, liver, and adipose tissue, reducing insulin's ability to promote glucose uptake and utilization. As a compensatory mechanism, beta cells increase insulin secretion; however, over time, functional exhaustion occurs, culminating in a relative deficiency of this hormone (DEFRONZO et al., 2021; ADA, 2023).

Insulin resistance in the liver is responsible for increasing endogenous glucose production, contributing to fasting hyperglycemia, while in skeletal muscle it compromises postprandial glucose uptake, resulting in postprandial hyperglycemia. In addition, adipose tissue has greater lipolysis, promoting excessive release of free fatty acids into the circulation, which interfere with insulin signaling and favor lipotoxicity (DEFRONZO et al., 2021; ADA, 2023;).

Chronic low-grade inflammation and oxidative stress also play a relevant role in the pathogenesis of T2DM. Evidence indicates that pro-inflammatory adipokines, such as TNF- α and IL-6, associated with endothelial dysfunction and increased production of reactive oxygen species, aggravate insulin resistance, establishing a negative feedback loop. The clinical manifestations of DM2 vary according to the stage of the disease and the presence of associated complications. Many patients remain asymptomatic for years, being diagnosed only in routine exams or after the appearance of micro or macrovascular complications (ADA, 2023).

Classic symptoms include polydipsia, polyuria, polyphagia, and unexplained weight loss, which usually become evident only in later stages. Nonspecific symptoms, such as fatigue, blurred vision, recurrent skin infections, and delayed wound healing, may also be present (SDB, 2024).

In addition, chronic complications represent relevant manifestations. Among the microvascular diseases, diabetic retinopathy, nephropathy and peripheral neuropathy stand out. Macrovascular diseases include coronary artery disease, stroke, and peripheral artery disease. These complications are the main cause of morbidity and mortality among individuals with T2DM, highlighting the importance of early diagnosis and appropriate treatment (ADA, 2023).

2.2.3 Pathophysiology

Type 2 diabetes mellitus (DM2) is a complex and multifactorial metabolic disease, whose pathophysiology involves the dynamic interaction between peripheral insulin resistance, progressive β -pancreatic cell dysfunction, and inflammatory and metabolic factors associated with visceral obesity. The end result is the onset of chronic hyperglycemia and the maintenance of a metabolic environment that favors the development of micro and macrovascular complications (GALICIA-GARCIA et al., 2020; OLIVEIRA et al., 2023).

In the early stages of DM2, peripheral tissues, especially skeletal muscle, liver, and adipose tissue, show reduced response to insulin action. This phenomenon compromises glucose uptake by the muscle, increases hepatic glucose production by gluconeogenesis and glycogenolysis, and intensifies lipolysis in adipose tissue. The increased release of free fatty acids into the circulation exerts a lipotoxic effect on different tissues, contributing to the amplification of insulin resistance and, simultaneously, to the elevation of glycemic levels (GALICIA-GARCIA et al., 2020; OLIVEIRA et al., 2023).

To compensate for peripheral resistance, β cells in pancreatic islets increase insulin secretion, leading to a state of compensatory hyperinsulinemia. However, with the advancement of the disease, progressive failure of these cells is observed, characterized by a reduction in pancreatic cell mass, stress of the endoplasmic reticulum, and accumulation of amyloid deposits, which culminate in insufficient insulin secretion. This process represents one of the important milestones in the transition from glucose intolerance to the establishment of DM2 (GALICIA-GARCIA et al., 2020; COUTO et al., 2024).

In addition, excess visceral adipose tissue plays a central role in the pathophysiology of DM2 by behaving as an active endocrine organ. This tissue secretes pro-inflammatory adipokines, such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), which contribute to the establishment of a chronic low-grade inflammatory state. Inflammation, associated with oxidative stress triggered by hyperglycemia and lipotoxicity, compromises insulin sensitivity and accentuates pancreatic dysfunction, creating a pathological feedback loop (OLIVEIRA et al., 2023; COUTO et al., 2024).

In addition, dysfunctions in the gut-pancreas axis play a relevant role in DM2, mainly due to the reduction in the action of incretins, such as glucagon-like peptide type 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These molecules, normally responsible for stimulating postprandial insulin secretion, have a diminished effect in individuals with T2DM, limiting the ability of the pancreas to respond appropriately to glycemic variations after dietary intake (GALICIA-GARCIA et al., 2020).

The interaction between insulin resistance, progressive β cell dysfunction, chronic inflammation, oxidative stress, and reduced incretins effect establishes a vicious cycle. These factors feed back on each other, perpetuating hyperglycemia and accelerating both the progression of the disease and the emergence of its chronic complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular diseases (GALICIA-GARCIA et al., 2020; OLIVEIRA et al., 2023; COUTO et al., 2024).

2.2.4 Diagnosis and Monitoring

The diagnosis of diabetes mellitus (DM) is based on the detection of persistent hyperglycemia by means of standardized laboratory parameters. The Brazilian Diabetes Society (SBD) recommends the use of fasting plasma glucose (FPG), oral glucose tolerance test (OGTT/OTT) and glycated hemoglobin (HbA1c) for diagnostic confirmation. The OGTT consists of measuring blood glucose after one hour (OGTT-1h) or two hours (OGTT-2h) of oral administration of 75 g of glucose (RODACKI et al., 2024).

Laboratory tests should be performed in all individuals with signs or symptoms suggestive of DM, as well as in asymptomatic individuals at increased risk for the disease. The diagnostic criteria are: fasting glucose ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, glucose at OGTT-1h ≥ 209 mg/dL, or glucose at OGTT-2h ≥ 200 mg/dL. If only one of the tests is altered, it should be repeated for confirmation (RODACKI et al., 2024).

During the diagnostic work-up, individuals with mild glycemic alterations who do not meet the criteria for DM may be identified. The *International Diabetes Federation* (IDF) calls this condition intermediate hyperglycemia, which manifests as altered fasting glucose or glucose intolerance after OGTT. The *American Diabetes Association* (ADA) and the SBD, on the other hand, use the term prediabetes, widely accepted in clinical practice due to its clarity in communication, although not all individuals progress to DM (RODACKI et al., 2024).

The OGTT-1h has been increasingly recommended both for the diagnosis of T2DM and for the detection of prediabetes, due to its greater practicality and sensitivity compared to the OGTT-2h. Blood glucose values ≥ 209 mg/dL confirm T2DM, while levels ≥ 155 mg/dL indicate prediabetes. T2D screening is recommended for all individuals aged 35 years and older, as well as for adults who are overweight or obese and have at least one additional risk factor or high or very high FINDRISC (Finnish Diabetes Risk Questionnaire) (RODACKI et al., 2024).

Fasting glucose and/or HbA1c should be considered the first screening tests, and the choice is up to the local availability of HbA1c measurement. In adults already classified as prediabetic by FPG and HbA1c, additional performance of the OGTT-1h is recommended to

identify undiagnosed cases of T2DM (≥ 209 mg/dL) or for future risk stratification (155 - 208 mg/dL) (RODACKI et al., 2024).

At initial screening, if FPG is < 100 mg/dL and HbA1c $< 5.7\%$, in individuals with fewer than three risk factors and low or moderate FINDRISC, there is no need for additional testing. However, in individuals with three or more risk factors or high/very high FINDRISC, it is recommended to perform the OGTT-1h to complement the investigation (RODACKI et al., 2024). After the initial screening for T2DM, it is recommended that a frequency of repeat screening be followed according to the clinical situation presented in the initial investigation, as shown in the table below.

Table 1

Frequency of repeat T2DM screening according to the clinical situation presented in the initial investigation

Clinical Situation	T2D screening frequency
People without symptoms and with only one test meeting criteria for DM	Semester
People with confirmed prediabetes	Annual
People with normal tests and ≥ 3 risk factors	Annual
People with normal tests and high/very high FINDRISC	Annual
People with normal tests and < 3 risk factors	Triennial
People with normal tests and low/moderate FINDRISC	Triennial

Source: Adapted from Rodacki, 2024.

In addition, individuals with comorbidities associated with secondary diabetes (such as endocrinopathies, pancreatic diseases, HIV infection, or metabolic steatotic liver disease - DHEM) should be screened for DM. The SBD recommends screening for EMHD in all patients with T2DM, given the bidirectional relationship between the conditions: EMHD increases the risk of T2DM, and this accelerates the progression of EMHD to more severe forms, such as steatohepatitis, fibrosis, cirrhosis, and hepatocarcinoma (RODACKI et al., 2024). DM screening is also indicated in patients who will start drugs with hyperglycemic potential, such as glucocorticoids and antipsychotics, both before and after the start of treatment. In the case of children and adolescents, it is recommended to start screening from the age of 10 or after the onset of puberty, whenever there is overweight/obesity associated with at least one additional risk factor (RODACKI et al., 2024).

In addition to glycemic control, the follow-up of patients with DM2 should include periodic evaluation of micro and macrovascular complications, as well as associated conditions. Systematic screening of these conditions enables early interventions, reducing morbidity and mortality and improving quality of life. Among the complications monitored are diabetic retinopathy, nephropathy and neuropathy, as well as cardiovascular diseases, such as hypertension and atherosclerosis. Problems such as diabetic foot, obesity and emotional changes also require continuous attention. For this, laboratory and ophthalmological tests, clinical evaluations, and tools such as glycated hemoglobin, capillary glucose, and lipid profile are used, integrating a broad approach to prevention and care (ADA, 2023; SBD, 2024).

Early diagnosis of DM allows for the immediate adoption of glycemic control strategies, lifestyle changes, and interventions that reduce the risk of complications. Because T2DM often has a silent evolution, serious complications can set in before clinical manifestation. Thus, routine exams and regular medical follow-up are essential to monitor glycemic control, adjust therapies, and prevent disease progression (OLIVEIRA et al., 2023).

2.2.5 Treatment

The treatment of type 2 diabetes mellitus (DM2) involves a multifactorial approach, whose central objective is to maintain glycemic control, prevent acute and chronic complications, and promote the improvement of the patient's quality of life. This management is based on three main pillars: lifestyle changes, pharmacological treatment, and continuous monitoring (OLIVEIRA et al., 2023; COUTO et al., 2024).

In the non-pharmacological sphere, health education and the modification of lifestyle habits are indispensable measures. It is recommended that the patient adopt a balanced diet, with individualized nutritional guidance, taking into account both the quality and quantity of calories ingested. This approach aims not only at normalizing blood glucose, but also at reducing cardiovascular risk factors, with emphasis on body weight control. In addition, the regular practice of physical activity plays a fundamental role, since it increases peripheral glucose uptake, contributes to the reduction of insulin resistance, favors weight control, and promotes cardiovascular benefits. In addition, smoking cessation and moderation in alcohol consumption are essential strategies to reduce the risk of complications (OLIVEIRA et al., 2023; COUTO et al., 2024).

It is important to emphasize that such changes should be encouraged from the beginning of treatment, due to their relevance in maintaining a healthy weight and preventing complications. The prescription of physical activity should be carried out in an individualized

and progressive manner, considering the patient's clinical conditions, reinforcing the need for continuous adherence to an active lifestyle as an integral part of the overall therapy of DM2 (OLIVEIRA et al., 2023; COUTO et al., 2024).

When non-pharmacological measures are insufficient to achieve glycemic goals, it becomes necessary to introduce drug treatment. Therapeutic options include oral agents and insulin, selected according to the stage of the disease and the individual characteristics of each patient. Oral drugs, generally used as the first line of treatment, include classes such as biguanides, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide-like receptor agonists type 1 (GLP-1), each of which acts on different mechanisms of the pathophysiology of DM2. This diversity of options allows for a personalized approach, which considers the individual's clinical and metabolic profile (OLIVEIRA et al., 2023; COUTO et al., 2024).

Among the available drugs, metformin, belonging to the biguanide group, is considered the drug of choice due to its proven efficacy in reducing hepatic glucose production, improving insulin sensitivity, and a consolidated safety profile. As the disease progresses or when the initial therapeutic response is not sufficient, other agents can be associated to achieve adequate glycemic control and reduce the risk of complications (OLIVEIRA et al., 2023; COUTO et al., 2024).

In certain cases, insulin therapy becomes necessary, especially in patients with unsatisfactory glycemic control, the presence of advanced complications, or treatment failure due to the progressive reduction in pancreatic insulin secretion, characteristic of DM2. Insulin can be used as monotherapy or in combination with oral agents, and the therapeutic regimen and dosage should be individualized according to the glycemic profile and the specific needs of the patient (OLIVEIRA et al., 2023; COUTO et al., 2024).

Clinical follow-up should be continuous and structured, including periodic assessment of glycated hemoglobin (HbA1c), monitoring of capillary glucose or continuous systems in patients using insulin or at risk of hypoglycemia, in addition to laboratory tests to assess renal function, lipid profile, and liver function. It is also recommended that periodic ophthalmological, neurological and cardiovascular evaluation be carried out, in order to enable early screening of complications. In the long term, the goal of treatment is to prevent complications that compromise the quality of life, productivity, and survival of individuals with DM2 (OLIVEIRA et al., 2023; COUTO et al., 2024; SANTOS et al., 2024).

Finally, it is highlighted that treatment must be individualized, taking into account the patient's age, presence of comorbidities, cardiovascular risk, renal function, and personal preferences. A multidisciplinary approach, involving physicians, nutritionists, nurses, physical

educators, and other health professionals, is essential to favor treatment adherence and optimize long-term results (OLIVEIRA et al., 2023; COUTO et al., 2024; SANTOS et al., 2024).

2.3 HEALTH PROGRAMS FOR DIAGNOSIS AND FOLLOW-UP - HIPERDIA

The HIPERDIA Program (System for the Registration and Monitoring of Hypertensive and Diabetic Patients) was established in 2002 by the Ministry of Health, in the context of the Plan for the Reorganization of Care for Systemic Arterial Hypertension (SAH) and Diabetes Mellitus (DM). Its purpose is to establish goals and guidelines that expand the prevention, diagnosis, treatment, and control actions of these diseases, through the reorganization of the work process in Primary Health Care (PHC) (BACURY et al., 2023).

The process begins with the registration of the patient at the Basic Health Unit (UBS), at which time clinical, socioeconomic and epidemiological information is collected. This registry enables the planning of actions aimed at the prevention, treatment and monitoring of cases, in addition to providing strategic data to support public policies and guide the allocation of resources. Another relevant aspect of HIPERDIA is risk stratification, which allows prioritizing the follow-up of more vulnerable patients, especially those with cardiovascular, neuropathic, or renal complications (BRASIL, 2021; SBD, 2024).

In addition to early diagnosis, the program has regular monitoring as its central axis. Among the follow-up actions are: periodic measurement of capillary glucose and blood pressure, request and analysis of laboratory tests, such as glycated hemoglobin and lipid profile, as well as guidance on lifestyle changes. This continuous follow-up seeks to reduce the risk of acute and chronic complications, such as diabetic ketoacidosis, cardiovascular events, kidney failure, and amputations resulting from the diabetic foot (BRASIL, 2021; SBD, 2024).

Health education is another essential component of HIPERDIA. The program promotes educational activities that involve guidance on healthy eating, regular physical activity, adherence to drug treatment and prevention of risk factors, such as smoking and excessive alcohol consumption. This comprehensive approach contributes to greater adherence to treatment and to improving the quality of life of patients (BRASIL, 2021).

In the scope of management, HIPERDIA provides strategic information to the managers of the Unified Health System (SUS), supporting the organization of care flows and the planning of campaigns aimed at prevention and diagnosis on a large scale. The integration between different professionals, doctors, nurses, nutritionists, pharmacists, and

community health agents, strengthens the multiprofessional character of care, ensuring more efficient care, centered on the patient's needs (SOARES et al., 2024).

Thus, HIPERDIA is configured not only as an instrument for the clinical control of diabetes and hypertension, but also as a strategy capable of reducing the morbidity and mortality associated with these conditions. It represents, therefore, a relevant milestone in the strengthening of public health policies in Brazil (BRASIL, 2021; SBD, 2024; SOARES et al., 2024). The implementation of follow-up programs, such as HIPERDIA, represents an advance in the control of hypertension and diabetes by structuring care flows and promoting adherence to treatment. However, for these programs to fully achieve their objectives, it is essential to integrate the evaluation of clinical and laboratory biomarkers, which provide accurate information on the patient's health status. These indicators allow for early identification of diseases and complications, providing support for more assertive clinical decisions and for reducing the morbidity and mortality associated with these diseases.

3 FINAL CONSIDERATIONS

Systemic arterial hypertension and type 2 diabetes mellitus share etiological determinants, pathophysiological mechanisms, and clinical repercussions that require an integrated and continuous approach. Effective control of these diseases depends on early identification, regular monitoring, and adherence to pharmacological and nonpharmacological treatment. In this context, multidisciplinary action, associated with health education strategies and follow-up programs such as HIPERDIA, is essential to reduce complications, promote self-care, and qualify the care provided to affected individuals.

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CLINICAL AND LABORATORY PARAMETERS AS PROGNOSTIC AND MONITORING BIOMARKERS IN PATIENTS WITH CARDIOVASCULAR AND METABOLIC DISEASES

PARÂMETROS CLÍNICOS E LABORATORIAIS COMO BIOMARCADORES PROGNÓSTICOS E DE MONITORAMENTO EM PACIENTES COM DOENÇAS CARDIOVASCULARES E METABÓLICAS

PARÁMETROS CLÍNICOS Y DE LABORATORIO COMO BIOMARCADORES PRONÓSTICOS Y DE MONITOREO EN PACIENTES CON ENFERMEDADES CARDIOVASCULARES Y METABÓLICAS



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ABSTRACT

Non-communicable chronic diseases represent one of the greatest contemporary challenges to public health due to their high prevalence, impact on morbidity and mortality, and the need for continuous care. In this context, systemic arterial hypertension and type 2 diabetes mellitus play a central role, both because of their frequency in the population and the complexity of their cardiovascular, renal, and metabolic complications. This chapter highlights the importance of using clinical and laboratory biomarkers as tools to support risk stratification, prognosis, and monitoring of these conditions, especially in Primary Health Care. Among the clinical parameters, anthropometric measurements, blood pressure, and cardiovascular assessment stand out, while, in the laboratory field, blood glucose, glycated hemoglobin, lipid profile, renal and hepatic markers, as well as hematological and inflammatory indices derived from complete blood count analyses, gain relevance. The integration of these different parameters makes it possible to increase the sensitivity of clinical assessment, promote the early identification of subclinical alterations, and support individualized management strategies. Thus, the combined use of clinical and laboratory biomarkers constitutes a promising strategy to improve health care quality, especially in resource-limited settings, contributing to the prevention of complications and to better outcomes in patients with chronic diseases.

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Keywords: Non-Communicable Chronic Diseases. Systemic Arterial Hypertension. Type 2 Diabetes Mellitus. Primary Health Care. Clinical Biomarkers. Laboratory Biomarkers.

RESUMO

As doenças crônicas não transmissíveis representam um dos maiores desafios contemporâneos para a saúde pública, em razão de sua elevada prevalência, do impacto na morbimortalidade e da necessidade de cuidado contínuo. Nesse contexto, a hipertensão arterial sistêmica e o diabetes mellitus tipo 2 assumem papel central, tanto pela frequência com que acometem a população quanto pela complexidade de suas complicações cardiovasculares, renais e metabólicas. O capítulo destaca a importância da utilização de biomarcadores clínicos e laboratoriais como instrumentos de apoio à estratificação de risco, ao prognóstico e ao monitoramento desses agravos, especialmente na Atenção Primária à Saúde. Entre os parâmetros clínicos, ressaltam-se medidas antropométricas, pressão arterial e avaliação cardiovascular, enquanto, no campo laboratorial, ganham relevância a glicemia, a hemoglobina glicada, o perfil lipídico, os marcadores renais e hepáticos, além dos índices hematológicos e inflamatórios derivados do hemograma. A integração entre esses diferentes parâmetros permite ampliar a sensibilidade da avaliação clínica, favorecer a identificação precoce de alterações subclínicas e subsidiar condutas individualizadas. Assim, o uso articulado de biomarcadores clínicos e laboratoriais constitui estratégia promissora para qualificar o cuidado em saúde, especialmente em cenários de recursos limitados, contribuindo para a prevenção de complicações e para a melhoria dos desfechos em pacientes com doenças crônicas.

Palavras-chave: Doenças Crônicas Não Transmissíveis. Hipertensão Arterial Sistêmica. Diabetes Mellitus Tipo 2. Atenção Primária à Saúde. Biomarcadores Clínicos. Biomarcadores Laboratoriais.

RESUMEN

Las enfermedades crónicas no transmisibles representan uno de los mayores desafíos contemporáneos para la salud pública, debido a su elevada prevalencia, su impacto en la morbimortalidad y la necesidad de atención continua. En este contexto, la hipertensión arterial sistémica y la diabetes mellitus tipo 2 desempeñan un papel central, tanto por la frecuencia con que afectan a la población como por la complejidad de sus complicaciones cardiovasculares, renales y metabólicas. El capítulo destaca la importancia del uso de biomarcadores clínicos y de laboratorio como herramientas de apoyo para la estratificación del riesgo, el pronóstico y el monitoreo de estas enfermedades, especialmente en la Atención Primaria de Salud. Entre los parámetros clínicos, se destacan las medidas antropométricas, la presión arterial y la evaluación cardiovascular, mientras que, en el ámbito de laboratorio, cobran relevancia la glucemia, la hemoglobina glucosilada, el perfil lipídico, los marcadores renales y hepáticos, además de los índices hematológicos e inflamatorios derivados del hemograma. La integración de estos diferentes parámetros permite ampliar la sensibilidad de la evaluación clínica, favorecer la identificación temprana de alteraciones subclínicas y respaldar conductas individualizadas. Así, el uso articulado de biomarcadores clínicos y de laboratorio constituye una estrategia prometedora para mejorar la calidad de la atención en salud, especialmente en escenarios con recursos limitados, contribuyendo a la prevención de complicaciones y a la mejora de los desenlaces en pacientes con enfermedades crónicas.

Palabras clave: Enfermedades Crónicas No Transmisibles. Hipertensión Arterial Sistémica. Diabetes Mellitus Tipo 2. Atención Primaria de Salud. Biomarcadores Clínicos. Biomarcadores de Laboratorio.

1 INTRODUCTION

Chronic Non-Communicable Diseases (NCDs) are one of the greatest contemporary challenges for public health. According to the World Health Organization (WHO, 2024) and the Ministry of Health (BRASIL, 2021), these diseases are responsible for approximately 74% of deaths in Brazil and more than 70% of deaths worldwide. This group includes conditions of high social, clinical, and economic burden, with emphasis on cardiovascular diseases, neoplasms, chronic respiratory diseases, and diabetes mellitus, which share widely prevalent modifiable risk factors, such as sedentary lifestyle, inadequate diet, smoking, harmful alcohol consumption, and overweight (WHO, 2024).

Data from the National Health Survey (PNS, 2019) indicate that more than half of the Brazilian adult population has already been diagnosed with at least one NCD, evidencing the magnitude and complexity of this problem in the national scenario (IBGE, 2020). Although advances have been observed in recent decades, such as the expansion of epidemiological surveillance and the implementation of national strategic plans, such as the Strategic Action Plan to Combat NCDs 2021–2030, important inequalities persist in access to prevention, timely diagnosis, and continuous treatment. Such inequities affect populations in situations of social vulnerability more intensely, compromising the principles of equity, universality, and integrality of the Unified Health System (SUS) (MALTA et al., 2020).

Among NCDs, cardiovascular diseases (CVDs) stand out as the main single cause of mortality in Brazil and worldwide, in addition to contributing significantly to morbidity and reduced quality of life. This set of diseases encompasses conditions of great clinical relevance, such as acute myocardial infarction (AMI), cerebrovascular accident (CVA), heart failure (HF) and arrhythmias. Although many of these diseases are preventable through health promotion strategies and control of risk factors, their incidence remains high (PAHO, 2025).

At the same time, type 2 Diabetes Mellitus (DM2) is one of the most prevalent and worrisome metabolic diseases today, with increasing incidence projections on a global scale. In Brazil, it is estimated that 16.6 million adults live with diabetes, and approximately 31.9% are unaware of the diagnosis (IDF, 2024). It is a multifactorial condition, associated with aging, obesity, sedentary lifestyle, and inadequate dietary patterns, with a high potential to trigger micro and macrovascular complications, such as retinopathy, nephropathy, neuropathy, amputations, and major cardiovascular events (IDF, 2021; WHO, 2023).

It is also noteworthy that most of the complications associated with systemic arterial hypertension (SAH) and DM2 can be prevented or attenuated through early diagnosis and adequate longitudinal follow-up. However, because these are diseases with an insidious and

often silent course, late diagnoses and interventions in advanced stages are frequent. This scenario reinforces the need for effective mechanisms for tracking, risk stratification, and continuous monitoring, especially within the scope of Primary Health Care (PHC), the main gateway to the SUS and a strategic level for care coordination (IDF, 2021; WHO, 2023).

In this context, the use of clinical and laboratory parameters as biomarkers of risk and prognosis is a fundamental strategy to qualify care and guide early interventions. Among the clinical parameters, body weight, anthropometric measurements, such as body mass index (BMI), abdominal circumference, and hip circumference, as well as pressure assessment using systolic blood pressure (SBP) and diastolic blood pressure (DBP) stand out. Among the low-cost laboratory tests widely available in the public network, fasting glucose, glycated hemoglobin, lipid profile, renal profile, liver profile, and blood count stand out, which allow not only clinical monitoring, but also the early identification of complications and the implementation of individualized therapeutic approaches (PEIXOTO et al., 2021; WHO, 2016).

However, the underuse of these tests as integrated tools to support clinical decision-making, especially in PHC, still constitutes a relevant gap. The isolated analysis of laboratory parameters often does not contemplate the pathophysiological complexity of NCDs, requiring more sensitive and integrative evaluation models (SCHMIDT et al., 2011; BARRETO et al., 2019).

In this sense, the blood count has stood out as a complementary test of great value, as it enables the identification of subclinical inflammation, hematological alterations, and conditions associated with NCDs. Indicators such as hemoglobin, hematocrit, mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MVP), platelet distribution width (PDW), global and absolute leukocyte counts, and cellular relationships derived from the blood count have been associated with outcomes adverse in patients with cardiovascular, renal, and metabolic diseases (ZHANG et al., 2021; LOPES et al., 2022). In addition, immunological biomarkers such as ultrasensitive C-reactive protein (hs-CRP), ferritin, and inflammatory cytokines have been gaining relevance in risk prediction and in the evaluation of low-grade inflammation typical of NCDs (PARK; SHIN, 2021).

The integration between clinical, hematological, and immunological data therefore represents a promising opportunity to improve risk prediction models, qualify prognostic stratification, and personalize the management of NCDs in clinical practice, especially in resource-limited settings. In addition, the use of cell relationships derived from the blood count shows promise in the evaluation of low-grade inflammatory responses, platelet

activation and endothelial dysfunction, constituting an important laboratory parameter for the follow-up and prognosis of hypertensive and/or diabetic patients.

Thus, this chapter aims to describe and analyze the main clinical and laboratory biomarkers applicable to the prognosis, risk stratification and monitoring of people with chronic non-communicable diseases, with emphasis on systemic arterial hypertension and type 2 diabetes mellitus in the context of Primary Health Care. The proposal seeks to contribute to the improvement of care strategies, the prevention of complications and the improvement of the quality of life of affected populations, systematically integrating clinical and laboratory variables as instruments to support decision-making and health care management.

2 CHRONIC NON-COMMUNICABLE DISEASES - NCDs

Chronic Non-Communicable Diseases (NCDs) comprise a group of conditions of prolonged evolution, non-infectious and without transmission between individuals, resulting from the interaction between genetic, physiological, environmental and behavioral factors. They are generally characterized by insidious onset, slow progression, and often absence of signs and symptoms in the early stages (WHO, 2024).

Among the main NCDs, cardiovascular diseases, neoplasms, chronic respiratory diseases, and diabetes mellitus stand out, which, together, represent the highest burden of morbidity and mortality in the global scenario. In addition to their high prevalence, these diseases generate a significant social, economic, and care impact, due to the need for continuous monitoring, prolonged use of medications, and management of acute and chronic complications (MIGOWSKI; COSTA, 2024; WHO, 2024).

The magnitude of this problem is even more evident in low- and middle-income countries, where the highest proportion of premature deaths associated with NCDs occurs. Estimates from the World Health Organization indicate that millions of deaths occur before the age of 70, reflecting inequalities in access to prevention, early diagnosis, and timely treatment (BRASIL, 2021; STOPA et al., 2022; WHO, 2024).

A large part of the burden of NCDs is related to modifiable risk factors, such as inadequate diet, sedentary lifestyle, smoking, harmful alcohol consumption, and overweight. These determinants contribute to metabolic and hemodynamic changes, including arterial hypertension, hyperglycemia, dyslipidemia, and obesity, with a strong association with the development of cardiovascular events and multisystem complications (BRASIL, 2021; VIGITEL, 2023; WHO, 2024).

In this context, systemic arterial hypertension and diabetes mellitus stand out as conditions of high prevalence, high care burden, and important potential for disease prevention. Thus, understanding NCDs and their determinants is essential to guide screening, prevention, and monitoring strategies in Primary Health Care.

2.1 CLINICAL AND LABORATORY BIOMARKERS IN PROGNOSIS AND MONITORING

The follow-up of individuals with systemic arterial hypertension (SAH) and type 2 diabetes mellitus (DM2) requires an integrated approach that includes both clinical and laboratory biomarkers. These indicators play a central role in risk stratification, prognosis assessment, and disease progression monitoring, enabling early detection of complications, optimization of therapeutic interventions, and, consequently, reduction of morbidity and mortality associated with these chronic conditions (MUJADZIC; SKEETE; DIPETTE, 2022; OLIVEIRA et al., 2024).

Clinical biomarkers include parameters obtained during the medical consultation, such as blood pressure, body mass index (BMI), waist circumference, and heart rate, which are indispensable in routine follow-up and identification of additional risk factors. Laboratory biomarkers, on the other hand, include specific tests that allow the evaluation of metabolic control (such as fasting glucose, glycated hemoglobin, and lipid profile) and the early identification of immunohematological, renal, hepatic, and cardiovascular alterations that frequently accompany the course of SAH and DM2 (MUJADZIC; SKEETE; DIPETTE, 2022; OLIVEIRA et al., 2024).

2.1.1 Anthropometry

Anthropometry is a physical assessment method that uses body measurements to analyze the composition and nutritional status of individuals. As it is a non-invasive, low-cost, and easily applicable procedure, it represents a fundamental tool in Primary Health Care, especially in the monitoring of chronic diseases, such as type 2 diabetes mellitus (DM2) and systemic arterial hypertension (SAH) (WHO, 2019; SBD, 2024).

Key anthropometric measurements include body weight, height, waist circumference (WC), hip circumference (HC), body mass index (BMI), and waist-to-hip ratio (WHR). Such parameters allow the identification of both general and central obesity, factors directly associated with insulin resistance, metabolic syndrome, and increased risk of cardiovascular complications (TOMIC; SHAW; MAGLIANO, 2022).

BMI is one of the most used indicators in clinical practice, as it provides an estimate of body weight in relation to height, making it possible to classify it as underweight, normal

weight, overweight and obesity. However, this index has limitations, as it does not differentiate lean mass from fat mass, which can compromise its interpretation in specific groups, such as the elderly and athletes (WHO, 2019). In this sense, waist circumference (WC) has been recommended as a complementary marker, since it reflects visceral fat, whose influence is more significant in the pathophysiology of cardiovascular and metabolic diseases. Elevated WC values are strongly associated with insulin resistance, dyslipidemias, and increased risk of cardiovascular events, regardless of BMI (SBD, 2024).

The waist-to-hip ratio (WHR), obtained by dividing WC by HC, is another robust indicator of cardiometabolic risk, allowing the distinction between central and peripheral obesity. Evidence indicates that visceral fat plays a pro-inflammatory role, stimulating the secretion of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), which contribute to insulin resistance and the progression of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, stroke, and peripheral arterial disease) complications (YOUSEF et al., 2023).

In the context of prognosis and clinical monitoring, anthropometry is a strategic resource for monitoring body changes resulting from therapeutic interventions, such as physical activity programs, dietary modifications, and medication use. In addition, its systematic use contributes to risk stratification and the early identification of individuals susceptible to the development of DM2 and SAH, consolidating itself as an essential tool for health professionals in the context of Primary Care (WHO, 2019; ADA, 2023).

2.1.2 Diastolic and Systolic Blood Pressure

Blood pressure is one of the most relevant clinical biomarkers for the evaluation and follow-up of patients with cardiovascular and metabolic diseases. Its two components, systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as the calculation of mean arterial blood pressure (MAP), provide complementary information on arterial hemodynamics, playing an essential role in risk stratification, prognosis establishment, and monitoring of clinical evolution (BARROSO et al., 2021; WHELTON et al., 2024). In addition to its clinical relevance in diagnosis and monitoring, blood pressure measurement has high applicability in PHC, being a simple, low-cost, and widely available method. In this context, routine assessment of SBP and DBP is one of the main strategies for screening and monitoring cardiovascular and metabolic conditions, especially in scenarios in which laboratory tests or more complex diagnostic methods are less accessible (WHO, 2023; PAHO, 2022).

SBP, which corresponds to the pressure exerted during cardiac systole, is robustly associated with cardiovascular complications in adults and the elderly, and is considered one of the most consistent predictors of events such as stroke, heart failure, and coronary artery disease. On the other hand, DBP, measured during ventricular relaxation (diastole), has greater prognostic relevance in young individuals, in whom the increase in peripheral vascular resistance is more pronounced. Studies indicate that persistently high levels of SBP and DBP are related to the progression of atherosclerosis, cardiac remodeling, and impaired renal function, and are independent prognostic markers (AMORIM et al., 2024; BARROSO et al., 2021).

Regular blood pressure monitoring is essential both to assess the effectiveness of treatment and to identify pressure patterns that may not be detected in specific measurements performed in the office. In this sense, methods such as Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Monitoring (HBPM) have proven to be indispensable tools, allowing the detection of conditions such as masked hypertension and white coat hypertension, in addition to providing more accurate data on blood pressure behavior over 24 hours. This detailed follow-up favors more individualized therapeutic adjustments, with a positive impact on reducing the risk of adverse events (AMORIM et al., 2024; BARROSO et al., 2021).

In addition to the absolute values of SBP and DBP, blood pressure variability (VPA) has emerged as an important prognostic biomarker. APV refers to fluctuations in blood pressure throughout the day, between days, or between months, and elevated levels are associated with a higher risk of cardiovascular events, cognitive decline, progression of chronic kidney disease, and increased mortality. Recent evidence suggests that APC reflects autonomic instability, arterial stiffness, and failures in therapeutic control, constituting a fundamental parameter for risk stratification and longitudinal follow-up. Patients with high variability are more likely to have complications, even when the mean blood pressure is within the reference values, which reinforces the need for an evaluation that goes beyond conventional blood pressure control and considers hemodynamic stability as an indicator of vascular health (LI et al., 2025).

The integration of SBP, DBP, continuous monitoring, and VPA analysis enables a broader understanding of the patient's cardiovascular health. The joint use of these parameters allows for early identification of risk patterns, evaluation of the therapeutic response in a dynamic and personalized way, prediction of cardiovascular and renal complications, and also subsidize Primary Health Care programs, such as HIPERDIA,

optimizing resources and promoting improvements in the management of public health care (PARATI et al., 2023).

In addition, blood pressure should be understood not only as a static indicator, but as a multifaceted biomarker that involves absolute values, circadian patterns, and pressure variability. This integrated approach offers valuable prognostic information, guiding continuous clinical follow-up and therapeutic decision-making more assertively (PEIXOTO et al., 2021; WHO, 2016). Thus, the routine measurement of blood pressure in Primary Health Care assumes a strategic role, as it allows for the early identification of individuals at risk, guide clinical interventions, and subsidize public policies aimed at the control of chronic non-communicable diseases (PARATI et al., 2023).

2.1.3 Cardiovascular Function Assessment

The assessment of cardiovascular function is a central axis in the follow-up of patients with systemic arterial hypertension (SAH) and type 2 diabetes mellitus (DM2), considering that both conditions are closely related to a significant increase in the risk of developing atherosclerotic cardiovascular disease, the main cause of morbidity and mortality in this population group (ADA, 2023; SBD, 2024). Cardiovascular changes resulting from chronic high blood pressure and sustained hyperglycemia can evolve silently, reinforcing the need for clinical and complementary methods that enable the early detection of structural and functional dysfunctions of the cardiovascular system (HERZOG et al., 2025).

The initial clinical evaluation is based on simple, accessible, and non-invasive parameters, such as cardiac auscultation, palpation of peripheral pulses, resting heart rate, and targeted physical examination. These procedures allow the identification of early signs of heart failure, arrhythmias, peripheral arterial disease, and hemodynamic changes. The detection of decreased peripheral pulses, for example, may indicate advanced atherosclerosis, while the presence of peripheral edema suggests possible cardiac or renal dysfunction (BRASIL, 2021; HERZOG et al., 2025).

Among the indirect clinical biomarkers of cardiovascular function, pulse pressure, a marker of arterial stiffness, and the ankle-brachial index (ABI), widely used in the screening of peripheral arterial disease, stand out. Increased arterial stiffness, often observed in hypertensive and diabetic individuals, is associated with a higher risk of adverse events, such as acute myocardial infarction and stroke. Thus, such measures assume relevant prognostic value, allowing not only risk stratification, but also the guidance of preventive conducts (HERZOG et al., 2025).

In the context of longitudinal follow-up, cardiovascular function assessment should be performed periodically and systematically, integrating clinical, laboratory, and imaging data. The combined use of these tools makes it possible to identify subclinical cardiac changes early, allowing the implementation of personalized therapeutic strategies based on the patient's individual risk (ADA, 2023; SBD, 2024).

Thus, the assessment of cardiovascular function transcends the merely diagnostic character and assumes the role of a prognostic biomarker, directly reflecting the impact of metabolic and hypertensive diseases on the integrity of the cardiovascular system. This perspective contributes not only to reducing the occurrence of serious complications, but also to optimizing clinical decision-making and strengthening public health care strategies (ADA, 2023; SBD, 2024).

2.1.4 Regular eye exams

Regular ophthalmologic examinations are an essential strategy in the monitoring of patients with type 2 diabetes mellitus (DM2) and systemic arterial hypertension (SAH), since changes in the retina directly reflect systemic pathological processes. The retina is recognized as a "window to the vascular system", as it allows direct observation of blood microcirculation, making ophthalmological evaluation a non-invasive clinical biomarker, with high diagnostic and prognostic value (CHEN et al., 2024; SBD, 2024).

In the context of DM2, the most relevant ocular complication is diabetic retinopathy (DR), characterized by progressive microvascular changes triggered by chronic hyperglycemia. Among its manifestations are microaneurysms, retinal hemorrhages, hard exudates, and neovascularization, which, when not identified and treated early, can progress to significant visual impairment and even irreversible blindness (ADA, 2023).

In SAH, hypertensive retinopathy stands out, whose alterations include arteriolar narrowing, flame hemorrhages, cotton wool exudates and, in more severe stages, papilla edema. These ophthalmologic signs are directly associated with severity, time of exposure to hypertension, and the extent of systemic vascular involvement, being important markers of disease progression (ALBUQUERQUE, 2024; AMORIM et al., 2024).

Periodic ophthalmologic examinations enable not only the early detection of ocular complications, but also acts as an indicator of systemic vascular health, helping to stratify cardiovascular risk and monitor the efficacy of therapeutic interventions. For this reason, such tests should be incorporated into follow-up routines in Primary Health Care, including national programs such as HIPERDIA, in addition to being part of patients' individualized care plans (BRASIL, 2021; ADA, 2023; SBD, 2024).

Thus, regular ophthalmologic examinations go beyond the dimension of ophthalmologic care alone, configuring themselves as strategic clinical biomarkers in the follow-up of individuals with DM2 and SAH. Its systematic application makes it possible to guide preventive measures, adjust therapies and, above all, reduce the risk of disabling complications, contributing significantly to improving quality of life and reducing morbidity and mortality associated with chronic diseases (CHEN et al., 2024; ADA, 2023).

2.1.5 Biomarkers of the glycemic profile

Glycemic control is a central laboratory parameter in the follow-up of patients with cardiovascular diseases (CVD) and metabolic diseases, especially in Primary Health Care (PHC). From this perspective, laboratory biomarkers of blood glucose have the following purposes: in addition to the diagnosis and monitoring of diabetes mellitus (DM), but can also be evaluated for potential prognosis, contributing to risk stratification and therapeutic decisions that impact clinical outcomes (MUJADZIC; SKEETE; DIPETTE, 2022; OLIVEIRA et al., 2024).

Among the main biomarkers, glycated hemoglobin (HbA1c) is the reference standard for chronic follow-up, reflecting the approximate glycemic mean of the last 2 - 3 months. Persistently high values are associated with a higher risk of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (acute myocardial infarction, stroke) complications, and can be used in addition to monitoring in the prognosis of diabetic patients (COSTA et al., 2020). It is important to consider factors that affect the accuracy of HbA1c (anemia, hemoglobinopathies, chronic kidney disease, erythropoietin use), which reinforces the usefulness of complementary biomarkers in PHC.

Fasting plasma glucose (FPG) is widely used, reflecting baseline glucose concentration after 8 - 12 hours of fasting. High values are used in the diagnosis of T2DM and predict the progression from prediabetes to diabetes. In addition, fasting hyperglycemia is associated with endothelial dysfunction, subclinical atherosclerosis, and increased risk of cardiovascular events. In PHC, FPG is an accessible and cost-effective marker, but it should be interpreted in conjunction with other indicators for better prognostic accuracy (AHMADIZAR et al., 2021; WANG; FANG, 2022).

Glycemic variability (VG), measured by serial capillary glucose (pre- and postprandial) or by continuous glucose monitoring (GCS), which can be applied as a prognostic biomarker. Recent evidence indicates that greater variability, regardless of the glycemic mean, is associated with oxidative stress, vascular inflammation, and atherosclerotic plaque instability, which may explain the increased risk of micro- and macrovascular complications

even with target HbA1c. In PHC, the structuring of capillary monitoring (e.g., 7-point profiles or sampling focused on critical periods) allows the identification of patterns of metabolic instability and guides early and personalized interventions. When available, GCM metrics such as Time on Target (IRR) and Time Over Target (TAR) add prognostic and monitoring value (SOARES; MOTORCYCLE; CORREA, 2025).

The oral glucose tolerance test (OGTT) maintains high sensitivity to detect glucose intolerance and DM, and also offers prognostic value by capturing postload hyperglycemia - expression of dysfunction of the first phase of insulin secretion and peripheral insulin resistance. These alterations are associated with early cardiovascular risk, including in individuals with normal FPG. Thus, the OGTT contributes to identifying high cardiometabolic risk that could be underestimated by FPG alone, reinforcing its strategic usefulness in public health and PHC surveillance programs (CHEN et al., 2021).

The triglyceride-glucose index (TyG), calculated by: $TyG = \log (\text{Triglycerides (mg/dL)} \times \text{Fasting glucose (mg/dL)} / 2)$, has been used as an indirect biomarker of insulin resistance. Population studies have shown that higher TyG values predict a higher risk of T2DM, metabolic syndrome, and subclinical atherosclerosis (TAI et al., 2022), in addition to being associated with cardiovascular events (HUANG; LI; YIN, 2024). Compared to reference methods (e.g., euglycemic clamp), TyG combines simplicity, low cost, and good reproducibility, characteristics that make it especially useful in PHC for monitoring and prognostic stratification. However, the influence of secondary hypertriglyceridemia (alcohol, hypothyroidism, drugs) and the need for contextualized interpretation should be considered (ALOTAIBI et al., 2025; TAO et al., 2022).

In summary, the combined use of these biomarkers becomes very relevant, as the FPG describes the basal state of glycemic homeostasis; glycemic variability captures daily metabolic instability linked to vascular stress; The OGTT detects early glucose intolerance and cardiovascular risk even in fasting normoglycemia and the TyG index is a practical and accessible tool for estimating insulin resistance and cardiometabolic risk. Thus, the integrated evaluation of these markers enables a more comprehensive and prognostically oriented approach to the care of patients with DM2 and CVD, consolidating their role in clinical practice and PHC protocols, with low cost and great applicability (REDDY; VERMA; DUNGAN, 2023; ADA, 2024).

2.1.6 Biomarkers of the lipid profile

Biomarkers of the lipid profile, such as total cholesterol, high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), and triglycerides, are fundamental parameters for the

evaluation of cardiovascular risk and metabolic status in individuals with chronic diseases, particularly diabetes mellitus (DM). Among patients with insulin resistance (diabetics and prediabetics), a characteristic dyslipidemic pattern is frequently observed, characterized by increased triglycerides, reduced HDL-c and predominance of small and dense LDL-c particles, forming the so-called atherogenic lipid profile. This metabolic combination plays a central role in the pathophysiology of cardiovascular diseases (CVD), recognized as the main cause of morbidity and mortality in individuals with diabetes (ADA, 2024; CHAIT et al., 2024).

This atherogenic behavior has been widely documented as an expression of interconnected pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, and endothelial dysfunction. Alterations in lipid metabolism, especially oxidation and glycation of LDL-c particles, accelerate the atherosclerotic process and promote plaque instability. Thus, the monitoring of lipid profile components is not restricted to cardiovascular risk stratification, but also provides relevant indications on the interaction between metabolic and inflammatory pathways associated with DM and the development and progression of other cardiometabolic diseases. Understanding this set of alterations allows us to design more precise therapeutic interventions that are consistent with the metabolic phenotype of each patient (ADA, 2024; CHAIT et al., 2024).

In the prognostic context, elevated LDL-c and triglyceride concentrations, associated with reduced HDL-c levels, are associated with adverse cardiovascular outcomes, even in individuals with adequate glycemic control. In addition, in people with T2DM and SAH, the coexistence of chronic inflammation, oxidative stress, arterial stiffness, and dyslipidemia synergistically amplifies the risk of macrovascular complications, including acute myocardial infarction and stroke. In this sense, the evaluation of lipid biomarkers assumes a strategic role as a predictive tool and as a parameter for evaluating the therapeutic response to primary and secondary CVD prevention strategies (CHAIT et al., 2024).

In view of this scenario, the importance of periodic and systematic monitoring of the lipid profile is reinforced, since it contributes not only to metabolic control, but also to the in-depth understanding of the progression of cardiometabolic diseases. The strengthening of integrated approaches, which include the joint evaluation of lipid, inflammatory, and glycemic biomarkers, has been pointed out as a central guideline in the most recent international recommendations, highlighting the potential of these biomarkers to guide personalized and evidence-based clinical practices (ADA, 2024).

2.1.7 Renal profile biomarkers

The evaluation of the renal profile by means of laboratory biomarkers plays a central role in the prognostic stratification and longitudinal monitoring of patients with cardiovascular and metabolic diseases. The scientific literature shows that even discrete changes in renal function are associated with higher cardiovascular risk, progression of metabolic complications, and increased overall mortality, highlighting that renal function should be understood as a systemic marker of health and not just as an isolated indicator of renal disease. In this context, widely available biomarkers, such as serum urea and creatinine, qualitative urine testing, albuminuria, and glomerular filtration rate (eGFR) estimation, are indispensable tools for the early detection of kidney lesions and for the integrated management of these patients (KHAN et al., 2026; HASSAN et al., 2025).

Serum urea and creatinine remain among the most commonly used biomarkers for assessing renal function. Creatinine, a product of muscle metabolism, is filtered by the glomeruli, and its elevation indicates a reduction in the glomerular filtration rate. Although influenced by age, sex, race, and muscle mass, serum creatinine remains a key marker, especially when interpreted in conjunction with eGFR equations, as recommended by the KDIGO guidelines (2024). Urea, although less specific, provides complementary information on metabolic and hemodynamic status, reflecting influences such as protein intake, hydration, and catabolism. In Primary Health Care (PHC), the integrated interpretation of these parameters contributes to the early detection of renal alterations in individuals with arterial hypertension, diabetes mellitus, and other cardiometabolic conditions (GUPTA et al., 2024; KDIGO, 2024).

Considering the limitations of the isolated use of urea and creatinine, its joint use is highlighted, which expands the diagnostic capacity of the laboratory evaluation of renal function. In this context, the analysis of the urea/creatinine ratio emerges as an important complementary tool for the differentiation of pathophysiological mechanisms involved in changes in renal function. In addition, the relationship is an auxiliary parameter often used in clinical practice to improve the interpretation of traditional markers of kidney function (LIU et al., 2022).

The urea/creatinine ratio can provide relevant information about the patient's hemodynamic and metabolic status, contributing to the differentiation between prerenal, intrinsic renal, and postrenal causes of renal dysfunction. In prerenal conditions, such as dehydration, hypovolemia, or reduced renal blood flow, there is a disproportionate increase in urea relative to creatinine, resulting in an elevation of the urea-to-creatinine ratio, usually greater than 20:1. On the other hand, in intrinsic renal lesions, such as acute tubular

necrosis, the elevation of these biomarkers tends to occur more proportionally, keeping the relationship within values close to normal. Thus, the evaluation of this ratio, associated with other laboratory biomarkers and the patient's clinical context, contributes to a more accurate interpretation of changes in renal function and helps in clinical decision-making, especially in scenarios of initial evaluation and monitoring of patients with cardiovascular and metabolic diseases (DOSSETOR, 1966; OSTERMANN et al., 2020; KDIGO, 2024).

Among the available biomarkers, eGFR is considered the main indicator of global renal function, being essential for the staging of Chronic Kidney Disease (CKD) and for the assessment of associated cardiovascular risk. Evidence shows that progressive reductions in GFR, even when discrete, are associated with cardiovascular events, recurrent hospitalizations, and increased mortality, reinforcing its clinical relevance. In the context of PHC, eGFR guides therapeutic decisions, drug adjustments, and timely referrals, functioning as a robust prognostic marker in populations with cardiovascular and metabolic diseases (KILLEEN; HOROWITZ, 2022; GUPTA et al., 2024; KDIGO, 2024).

Qualitative urine testing, in turn, stands out as a low-cost, widely accessible tool, and has great clinical sensitivity. Alterations such as proteinuria, hematuria, leukocyturia, or cylindruria allow early identification of kidney lesions even before significant changes in serum creatinine. In patients with metabolic conditions, this test also helps to identify associated complications, such as urinary tract infections, which are often underdiagnosed and can accelerate the progression of renal dysfunction. Thus, the urine test is a complementary biomarker of great value in the global assessment of renal and systemic health (GUTPA et al., 2024; KDIGO, 2024).

Albuminuria stands out as one of the main prognostic biomarkers of kidney injury and cardiovascular risk. Its presence indicates increased glomerular permeability and endothelial dysfunction, and is strongly associated with the progression of CKD and increased cardiovascular events. Recent research has shown that even slightly elevated urinary albumin levels are already correlated with a worse prognosis, regardless of eGFR, reinforcing its role in early risk stratification. Recent guidelines recommend its routine evaluation, especially in patients with diabetes mellitus, hypertension, and metabolic syndrome, as a way to monitor the therapeutic response and the impact of pharmacological and non-pharmacological interventions on PHC (PERILLO et al., 2025; GUPTA et al., 2024; KDIGO, 2024).

The integrated evaluation of these biomarkers enables a more comprehensive, sensitive, and early view of renal function, contributing not only to the diagnosis and staging of CKD, but also to the stratification of cardiovascular and metabolic risk. This approach,

widely recommended by international guidelines, has high applicability in PHC due to its low cost, high availability, and significant clinical impact on the follow-up of vulnerable populations (KDIGO, 2024).

2.1.8 Liver profile biomarkers

Hepatic alterations of metabolic etiology, especially nonalcoholic fatty liver disease (NASH), are a condition of high global prevalence and often underdiagnosed in clinical practice. In the context of cardiometabolic diseases, the monitoring of liver function by means of laboratory biomarkers plays a strategic role in the identification of initial dysfunctions, for risk stratification, and for the longitudinal follow-up of patients. Liver enzymes, bilirubins, and derived indices offer valuable information on hepatocellular, cholestatic, and metabolic alterations, allowing a broad and integrated approach within the scope of Primary Health Care (PHC) (RINELLA et al., 2023; MIN et al., 2024; COUTINHO et al., 2025).

Liver enzymes, including TGO/AST, TGP/ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH), constitute the classic set of biomarkers used to assess hepatocellular integrity and metabolic function of the liver. AST is considered the most specific marker of hepatocellular injury, while ALT, because it is present in other tissues such as skeletal muscle and myocardium, reflects both hepatic alterations and systemic disorders that often coexist in individuals with high cardiovascular risk. Persistent elevation of transaminases has been strongly associated with NASH and cardiometabolic risk, even in the absence of advanced liver disease, reinforcing its potential as an early marker of underlying metabolic changes (GORCZYCA-GŁOWACKA et al., 2023; RINELLA et al., 2023; COUTINHO et al., 2025).

GGT stands out as a sensitive biomarker of both liver injury and cholestasis, showing a robust association with insulin resistance, low-grade systemic inflammation, and oxidative stress, central components in the pathophysiology of metabolic diseases. Recent studies reinforce that GGT is an independent prognostic marker for cardiovascular events and mortality, which gives it expanded clinical relevance in cardiometabolic populations (WANG et al., 2024; AL-SUHAIMI; AL-RUBAISH, 2024). ALP, traditionally associated with cholestatic conditions, has also been related to higher cardiovascular risk when persistently elevated, suggesting interactions between hepatic metabolism, bone remodeling, and systemic inflammation (ADAMIDIS et al., 2024). LDH, on the other hand, although less specific, reflects tissue damage and anaerobic metabolism, configuring a complementary marker in complex inflammatory and metabolic states (PABIN et al., 2025).

Total bilirubin and fractions (direct and indirect) represent essential biomarkers for the evaluation of hepatobiliary function and hemoglobin metabolism. In addition to its role in detecting cholestasis and hepatocellular dysfunction, bilirubin has significant antioxidant properties. Reduced levels were associated with higher oxidative stress and cardiovascular risk, while moderately high concentrations seem to have a protective effect against inflammation and endothelial dysfunction. Thus, its measurement contributes both to liver diagnosis and to the evaluation of redox balance and systemic inflammation in cardiometabolic patients treated in PHC (RINELLA et al., 2023; COUTINHO et al., 2025; AL-SUHAIMI; AL-RUBAISH, 2024).

The TGP/TGO (ALT/AST) ratio is a widely used index for the evaluation of metabolic liver diseases. High values of this relationship suggest the presence of NASH and are particularly observed in individuals with obesity, diabetes mellitus and metabolic syndrome, conditions that make up the cardiometabolic risk spectrum. In addition, it is a useful marker to identify subclinical hepatocellular changes and to monitor therapeutic response to clinical interventions or lifestyle changes (KOUVARI et al., 2023; RINELLA et al., 2023).

In this scenario, recent literature has highlighted the use of derived laboratory indices that integrate liver enzymes and hematological parameters, especially platelet count, expanding the capacity for early identification of hepatic structural alterations and cardiometabolic risk. Among these indices, the ratio between platelets and GO (PLT/TGO) stands out as screening tools for liver fibrosis, especially in metabolic conditions. The reduction in platelet count associated with elevated AST may reflect hepatic structural changes and impaired portal flow, indicating greater disease severity. In this sense, indices such as PLT/TGO have significant applicability in PHC, as they use simple and low-cost laboratory parameters, helping to recognize individuals at increased risk of liver disease progression and cardiometabolic complications (KOUVARI et al., 2023; CASTELLI et al., 2025).

In addition to the isolated use of indices such as PLT/TGO for the evaluation of liver fibrosis, recent evidence suggests that the interaction between liver enzymes and hematological parameters, especially platelet count, reflects complex pathophysiological processes that connect the liver to systemic cardiometabolic risk. Transaminase changes often coexist with chronic low-grade inflammatory states and endothelial dysfunction, conditions that also influence platelet dynamics and inflammatory thrombus activation. In this context, the combination of elevated liver enzymes and platelet changes has been associated with a higher risk of metabolic syndrome, atherosclerotic cardiovascular disease, and progression of metabolic liver disease. Population studies indicate that these

parameters, when evaluated in an integrated manner, can act as indirect markers of systemic inflammation, insulin resistance, and vascular remodeling, reinforcing their usefulness as accessible biomarkers for risk stratification in populations served in Primary Health Care (KOUVARI et al., 2023; LIAO; ZHU; CHANG, 2024; HUANG et al., 2023; LEE et al., 2020; YU et al., 2021).

Among the most commonly used laboratory indices for noninvasive evaluation of liver fibrosis are the APRI (*AST to Platelet Ratio Index*) and the FIB-4 (*Fibrosis-4 Index*), both of which are widely used in clinical practice and in epidemiological studies. APRI is based on the relationship between AST levels and platelet count, whereas FIB-4 incorporates age, GOT, TGP, and platelet count in its calculation. These indices have demonstrated good accuracy in identifying moderate and advanced degrees of liver fibrosis, especially in individuals with hepatic steatosis associated with metabolic dysfunction. In addition to their usefulness in the evaluation of liver, recent evidence indicates that high values of these scores are also associated with a higher risk of cardiovascular events, mortality, and progression of metabolic diseases, reinforcing the interconnection between liver dysfunction, systemic inflammation, and cardiometabolic risk. Because they use widely available and low-cost laboratory parameters, the APRI and FIB-4 represent relevant tools for screening and risk stratification in Primary Health Care (KOUVARI et al., 2023; RINELLA et al., 2023).

The integrated analysis of liver biomarkers, including enzymes, bilirubins, and derived indices, contributes to a broad assessment of the metabolic, inflammatory, and functional status of patients, favoring prognostic stratification and monitoring of clinical evolution in individuals with cardiovascular and metabolic diseases. This multidimensional approach reinforces the importance of the liver as a central organ in systemic metabolism and highlights the relevance of liver biomarkers in PHC (COUTINHO et al., 2025).

2.1.9 Hematologic Biomarkers

Hematological biomarkers, obtained through blood count, are instruments widely used in clinical practice and have significant relevance as prognostic markers in the follow-up of individuals with cardiovascular and metabolic diseases. Because they simultaneously reflect hematological, inflammatory, and immunological changes, these parameters allow for an integrated assessment of the physiological and functional status of patients, contributing to the early detection of diseases and to the monitoring of clinical evolution (LIU et al., 2023).

- Erythrocyte Parameters

Erythrocyte parameters, including erythrocyte count, hemoglobin, hematocrit, and hematimetric indices (VCM, HCM, CHCM), provide essential information about the patient's

oxygen-carrying capacity, nutritional status, and metabolic profile. Alterations in these indices allow the morphological characterization of anemias and help in the identification of nutritional deficiencies, chronic inflammation, and metabolic disorders often associated with cardiovascular diseases. Anemia, as well as variations in hematimetric indices, has been associated with a worse cardiovascular prognosis, a higher risk of hospitalizations, and increased mortality, reinforcing the relevance of erythrocyte parameters as complementary markers in the clinical and prognostic evaluation of PHC (SENAPATI et al., 2025; LULE et al., 2026; RESENDE et al., 2026).

The Red Cell Distribution Width (RDW), expressed by RDW-CV and RDW-SD measurements, reflects the variability of erythrocyte size and has emerged as an important prognostic biomarker in different cardiometabolic conditions. High RDW values are associated with systemic inflammation, oxidative stress, nutritional dysfunction, and worse clinical outcome in patients with cardiovascular diseases, regardless of the presence of anemia. Recent evidence shows that RDW has a consistent association with cardiovascular mortality and adverse events, configuring itself as a simple and low-cost marker with high applicability (ARKEW et al., 2022; SENAPATI et al., 2025).

- *Leukocyte Parameters*

The evaluation of the leukocyte profile, by means of the global leukocyte count and the differential count, is a relevant tool for the analysis of the inflammatory and immunological status in patients with cardiovascular and metabolic diseases. The total leukocyte count reflects the activation of the immune system and has been associated with chronic low-grade inflammatory processes, characteristic of conditions such as obesity, T2DM, and metabolic syndrome. Persistently elevated values, even within the upper limits of normality, have been linked to increased cardiovascular risk, progression of atherosclerosis, and worse clinical outcomes (AJOOLABADY et al., 2024; MENSAH et al., 2026).

The differential leukocyte count provides additional and more specific information about the different components of the immune response. Neutrophils play a central role in innate immunity and inflammatory response, and their elevation is often associated with systemic inflammatory activation, oxidative stress, and endothelial dysfunction. In patients with cardiometabolic diseases, neutrophilia has been related to greater instability of atherosclerotic plaques and an increased risk of cardiovascular events (LIBBY et al., 2018; LIAN et al., 2025).

Lymphocytes are predominantly involved in adaptive immunity and modulation of chronic inflammation. Relative lymphopenia has been observed in settings of persistent inflammation and is associated with poorer cardiovascular prognosis and increased mortality.

Changes in lymphocyte count reflect immunological imbalances related to chronic metabolic conditions, reinforcing their prognostic value when analyzed in an integrated manner with other hematological parameters (LIBBY et al., 2018; ZAFRIR et al., 2022; MADJID et al., 2004; SOEHNLEIN; LIBBY, 2021).

Monocytes actively participate in chronic inflammation and atherogenesis, as they migrate to the vascular wall and differentiate into macrophages, contributing to the formation and progression of atherosclerotic plaques. Monocytosis has been associated with a higher inflammatory burden, cardiovascular disease progression, and worse clinical outcome, especially in individuals with diabetes mellitus and dyslipidemias (KOZLOV et al., 2025; MADJID et al., 2004; SOEHNLEIN; LIBBY, 2021).

Eosinophils and basophils, although less frequently altered in cardiometabolic diseases, provide complementary information about the patient's immunological profile. Changes in subpopulations may be related to concomitant inflammatory, allergic, or infectious processes, which influence systemic inflammatory status and should be considered in the global interpretation of cardiometabolic risk (XU et al., 2025; MADJID et al., 2004; SOEHNLEIN; LIBBY, 2021).

- *Platelet Parameters*

The evaluation of the platelet profile, by means of total platelet count and indices related to platelet size and heterogeneity, is an important component in the analysis of cardiovascular risk and systemic inflammatory status in patients with cardiovascular and metabolic diseases. Platelets play a central role not only in hemostasis, but also in the inflammatory response, interaction with the vascular endothelium, and progression of atherogenesis (ZVETKOVA et al., 2024; HAMO et al., 2025).

Total platelet count provides information on hemostatic balance and may reflect underlying inflammatory and metabolic changes. Both thrombocytosis and thrombocytopenia have been associated with chronic inflammatory states, endothelial dysfunction, and increased cardiovascular risk. In patients with metabolic diseases, variations in platelet count may be related to persistent inflammatory activation, liver changes, or impaired platelet production and consumption (SHARMA et al., 2025; HAMO et al., 2025).

Mean platelet volume (MPV) is an indicator of platelet activity and reactivity, since larger platelets are metabolically more active and prothrombotic. Elevated MPV values have been associated with systemic inflammation, platelet activation, and increased cardiovascular risk, including thrombotic events. In individuals with diabetes mellitus and metabolic syndrome, MV has been shown to be a relevant marker of worse prognosis

(DAHAN et al., 2025; CHEN et al., 2025; BRAHMBHATT et al., 2022; BARROS; CARVALHO, 2024).

Platelet distribution width (PDW) reflects platelet size variability and is related to the heterogeneity of the circulating platelet population. Increased PDW indicates higher platelet anisocytosis and has been associated with platelet activation and chronic inflammatory processes. Evidence shows an association between elevated PWD and higher cardiovascular risk, especially when evaluated in conjunction with MV and platelet count (POGORZELSKA et al., 2020; ZHOU et al., 2026).

In addition to reflecting changes in platelet activation, platelet parameters have been progressively investigated as indirect indicators of chronic low-grade inflammation associated with insulin resistance. This systemic inflammatory state is considered one of the main pathophysiological mechanisms involved in the development of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases. Insulin resistance promotes metabolic changes that favor the production of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, in addition to increasing oxidative stress and endothelial dysfunction. These processes contribute to platelet activation and morphological modifications of circulating platelets, reflected by changes in indices such as MPV and PDW (DAHAN et al., 2025; CHEN et al., 2025; BRAHMBHATT et al., 2022; POGORZELSKA et al., 2020; ZHOU et al., 2026).

In this context, individuals with obesity, metabolic syndrome, type 2 diabetes mellitus, and hypertension often have increased platelet reactivity, characterized by increased MV and greater heterogeneity in platelet size. Larger platelets have higher granule content, greater capacity to release inflammatory mediators, and greater thrombogenic potential, contributing to the progression of atherosclerosis and increased risk of cardiovascular events. Thus, the integrated evaluation of platelet count and platelet indices derived from the blood count has been proposed as a complementary strategy for the identification of chronic inflammatory states and insulin resistance, especially in populations with cardiometabolic diseases followed up in Primary Health Care (SHARMA et al., 2025; DAHAN et al., 2025).

- *Relationships Derived from Blood Count*

Blood count-derived relationships have gained increasing relevance as indirect biomarkers of systemic inflammation, metabolic stress, and cardiometabolic risk. These indices combine different components of the immune and hematological response, allowing the identification of inflammatory and immunological alterations that are often not detected by the parameters isolated from the blood count. The integration of these relationships has been shown to be useful for prognostic stratification and monitoring of individuals with

chronic metabolic diseases, given its wide availability, low cost, and immediate clinical applicability (SEO; LEE, 2022; NASCIMENTO et al., 2024).

The neutrophil-lymphocyte ratio (NLR) has been validated as an indirect marker of systemic inflammation and immune imbalance. Its usefulness stems from the fact that it integrates the activity of innate immunity, represented by neutrophils, and adaptive immunity, represented by lymphocytes. High values reflect greater neutrophil-mediated inflammatory activation and relative suppression of adaptive immunity, a phenomenon observed in states of chronic low-grade inflammation, such as those that characterize obesity, type 2 diabetes mellitus, metabolic syndrome, and subclinical atherosclerosis. Several evidences demonstrate that NLR is associated with increased cardiovascular risk, progression of atherosclerosis, instability of atherosclerotic plaques, and worse clinical outcomes, configuring a biomarker of high prognostic robustness, simple, reproducible, and with strong applicability in clinical practice (PADILHA et al., 2025; NASCIMENTO et al., 2024).

The platelet-to-lymphocyte ratio (RPL) incorporates elements of platelet activation and adaptive immune response. Platelets participate not only in hemostasis, but also in inflammatory processes, synthesis of prothrombotic mediators, endothelial activation, and progression of atherogenesis. Thus, elevated RPL values reflect a prothrombotic state associated with systemic inflammation and endothelial dysfunction. In populations with cardiometabolic diseases, increased LPR has been associated with a higher probability of cardiovascular events, progression of atherosclerosis, and worse clinical outcome. When integrated with other inflammatory and hematological biomarkers, LPR expands the predictive potential of blood count and contributes to monitoring and risk stratification strategies in Primary Health Care (PADILHA et al., 2025; ZHAI et al., 2021; NASCIMENTO et al., 2024).

The monocyte-lymphocyte ratio (RML) represents another index of increasing relevance, especially in the context of chronic metabolic diseases. The increase in monocytes, associated with the proportional reduction of lymphocytes, indicates activation of innate immunity and reduction of the immunoregulatory mechanisms of adaptive immunity. Monocytes play a critical role in atherogenesis by migrating to the endothelium and differentiating into macrophages, cells that accumulate lipids and contribute to the formation of fatty streaks and the progression of atherosclerotic plaques. Evidence associates high RML values with higher cardiovascular risk, worse clinical outcome, and increased mortality, especially in individuals with diabetes mellitus, dyslipidemias, and other metabolic conditions. Thus, RML is established as a relevant complementary biomarker in the

longitudinal monitoring and prognostic stratification of these patients (NASCIMENTO et al., 2024; VAKHSHOORI et al., 2023).

In addition to the relationships involving leukocytes, indices derived from the platelet profile have also been investigated as markers of systemic inflammation and thrombotic risk. The relationship between mean platelet volume and platelet distribution width (MPV/PDW) provides an integrated assessment of the reactivity and heterogeneity of circulating platelets. VPM reflects the degree of platelet activation, since larger platelets are more metabolically active, while PDW expresses platelet size variability, related to platelet renewal and activation in inflammatory conditions. Thus, changes in this index indicate increased thrombogenic and inflammatory activity, with a consistent association with cardiovascular risk, especially in individuals with chronic metabolic diseases. It is an accessible biomarker of great clinical utility, based on routinely evaluated parameters of the blood count, which facilitates its implementation and interpretation in care practice (KORNILUK et al., 2019; PEREZ et al., 2024; CAKIR; TAYMAN, 2025).

In recent years, in addition to the classic indices, composite inflammatory indices derived from the blood count have been proposed with the objective of integrating multiple components of the immune response and increasing the capacity to detect systemic inflammation, which are widely used in acute inflammatory conditions, but can also be used in chronic inflammatory processes. Among these indices, the *Systemic Immune-Inflammation Index* (SII) and the *Aggregate Index of Systemic Inflammation* (AISi) stand out, calculated from the combination of leukocyte and platelet parameters obtained from the blood count. IBS is generally defined by the formula $\text{platelets} \times \text{neutrophils} / \text{lymphocytes}$, while AISi additionally incorporates monocytes ($\text{neutrophils} \times \text{monocytes} \times \text{platelets} / \text{lymphocytes}$), more comprehensively reflecting the interaction between innate immunity, inflammatory response, and thrombotic activation. Recent evidence indicates that these indices are associated with systemic inflammatory processes, cardiovascular risk, insulin resistance, and progression of chronic metabolic diseases. Although they are still considered emerging markers, studies have shown that high IBS and SIA values may reflect states of chronic low-grade inflammation, characteristic of conditions such as obesity, type 2 diabetes mellitus, metabolic syndrome, and metabolic liver disease, expanding the analytical potential of the blood count as a tool for inflammatory assessment in clinical practice and in epidemiological studies (ZHAO et al., 2023; BO et al., 2025; XIU et al., 2025).

In general, the relationships derived from the blood count substantially increase the prognostic value of the traditional blood count, allowing the identification of subclinical inflammatory patterns and contributing to a more accurate approach to cardiometabolic risk.

The growing robustness of the available evidence positions these indices as promising tools for clinical practice and for monitoring at-risk populations in Primary Health Care.

2.1.10 Biomarkers of the Inflammatory Profile

Low-grade systemic inflammation plays a central role in the pathophysiology of cardiovascular and metabolic diseases, constituting an important link between insulin resistance, endothelial dysfunction, vascular remodeling, oxidative stress, and progression of atherogenesis. This chronic inflammatory state is underpinned by persistent activation of innate and adaptive immune pathways, mediated by pro-inflammatory cytokines, adipokines, and intracellular metabolic changes that reinforce a continuous cycle of tissue damage. In this context, the use of inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) becomes strategic for the evaluation of systemic inflammation, providing valuable information on inflammatory activity and overall cardiometabolic risk (AJOOLABADY et al., 2024; OU et al., 2024).

Erythrocyte sedimentation rate is a traditional marker of inflammation, widely used in clinical practice due to its technical simplicity, low cost, tracking capability, and wide availability. The increase in ESR is mainly due to the increase in acute phase proteins, such as fibrinogen and immunoglobulins, which alter the electrostatic repulsion between red blood cells, promoting their aggregation and increasing the sedimentation rate. Despite its non-specificity, ESR has relevant clinical utility, especially because it reflects underlying inflammatory processes of slow and prolonged evolution. In individuals with metabolic and cardiovascular diseases, persistently high ESR values indicate a higher systemic inflammatory burden, being associated with the progression of atherosclerotic complications and a worse prognosis, especially when interpreted in conjunction with more specific inflammatory markers (TISHKOWSKI; ZUBAIR, 2025; BROWN et al., 2025).

C-reactive protein is one of the most sensitive and widely validated inflammatory biomarkers in the literature. Produced predominantly by the liver in response to interleukin-6 and other pro-inflammatory cytokines, CRP has a strong ability to detect acute and chronic inflammatory processes, including those associated with cardiometabolic diseases. High CRP values, even at levels considered moderate, have been consistently associated with increased cardiovascular risk, evidencing its relevance as an independent marker of adverse events, including mortality, acute myocardial infarction, and stroke. In addition, CRP integrates the communication axis between inflammation, metabolism, and endothelial function, reflecting the degree of systemic immune activation and contributing to the stratification of metabolic risk in different populations. Contemporary studies reinforce that

high-sensitivity CRP (HSCR-CRP) further enhances the predictive capacity of this biomarker, allowing the identification of subclinical inflammation associated with the early onset of atherosclerotic processes (BROWN et al., 2025; MOISSL et al., 2025).

The combined interpretation of ESR and CRP allows for a more comprehensive assessment of the systemic inflammatory response. While ESR captures sustained and longer-lasting inflammatory phenomena, CRP responds more quickly and sensitively to acute and chronic inflammatory stimuli, reflecting different stages and dynamics of inflammation. This analytical complementarity favors the use of both parameters in clinical practice, especially in Primary Health Care, where low-cost, widely available, and fast-performing tests are essential for risk stratification and longitudinal follow-up. The integration of these biomarkers into the set of clinical and laboratory information contributes to the early detection of relevant inflammatory processes, aiding in decision-making and appropriate management of populations at increased cardiometabolic risk (BROWN et al., 2025).

In addition, the use of inflammatory biomarkers in the metabolic context allows a better understanding of the interaction between chronic inflammation, energy metabolism, and endothelial function. Both ESR and CRP reflect changes in immunometabolic communication, a fundamental characteristic of cardiometabolic diseases, in which changes in adipose tissue, activation of intracellular inflammatory pathways, and immune system dysfunction play determining roles (BROWN et al., 2025). Thus, these biomarkers have not only diagnostic and prognostic utility, but also potential to guide therapeutic interventions and monitor their effectiveness over time.

3 FINAL CONSIDERATIONS

Chronic Noncommunicable Diseases remain among the greatest challenges for public health, due to their high prevalence, multifactorial character and impact on morbidity and mortality. In this scenario, the use of clinical and laboratory biomarkers is essential to qualify risk assessment, support early diagnosis, guide therapeutic conducts, and monitor the clinical evolution of patients.

The integration of parameters such as anthropometry, blood pressure, glycemic, lipid, renal, hepatic, hematological, and inflammatory profiles allows for a broader and more sensitive analysis of health status, favoring safer and more individualized clinical decisions. In addition, the incorporation of these markers into the routine of Primary Health Care strengthens longitudinal care, expands tracking capacity, and contributes to the prevention of cardiovascular and metabolic complications.

Thus, the adoption of low-cost, accessible, and clinically relevant biomarkers may represent a promising strategy to improve care, especially in scenarios with greater social vulnerability and less availability of diagnostic resources. Therefore, the judicious use of these indicators, associated with multiprofessional action and continuous follow-up, is essential for the qualification of care and for the improvement of health outcomes.

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USE OF CANNABIDIOL IN THE PREVENTION OF POSTOPERATIVE COMPLICATIONS AFTER THIRD MOLAR EXTRACTIONS

USO DO CANABIDIOL NA PREVENÇÃO DE COMPLICAÇÕES PÓS-OPERATÓRIAS EM EXODONTIAS DE TERCEIROS MOLARES

USO DE CANNABIDIOL EN LA PREVENCIÓN DE COMPLICACIONES POSTOPERATORIAS EN EXTRACCIONES DE TERCEROS MOLARES



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ABSTRACT

Third molar extraction is among the most frequently performed procedures in Oral and Maxillofacial Surgery and is commonly associated with postoperative complications such as pain, edema, trismus, and functional limitation. In this context, cannabidiol (CBD) has attracted growing scientific interest due to its analgesic, anti-inflammatory, and endocannabinoid system-modulating properties, emerging as a potential therapeutic alternative for postoperative management in oral surgery. This study aimed to analyze, through an integrative literature review, the current scientific evidence regarding the use of cannabidiol in the prevention and control of postoperative complications associated with third molar extractions. The methodological framework was based on the stages proposed by

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Whittemore and Knafl (2005). The bibliographic search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, and SciELO databases, considering studies published between 2015 and 2025 in English, Portuguese, and Spanish. Clinical trials, systematic reviews, observational studies, and experimental research related to the use of CBD in orofacial pain, inflammation, and oral surgery were included. The findings demonstrated that cannabidiol presents relevant analgesic and anti-inflammatory potential by modulating nociception and inflammatory responses through mechanisms associated with CB1 and CB2 receptors, in addition to reducing pro-inflammatory cytokines and nociceptive sensitization. Clinical studies reported reduction of postoperative pain, functional improvement, and possible reduction in the need for conventional analgesics. However, important methodological limitations remain, including heterogeneity among therapeutic protocols, differences in dosage and routes of administration, small sample sizes, and lack of clinical standardization. It is concluded that cannabidiol demonstrates promising therapeutic potential in the prevention and control of postoperative complications following third molar extractions, although further robust and standardized clinical studies are still required to consolidate its applicability in contemporary dental practice.

Keywords: Cannabidiol. Tooth Extraction. Third Molar. Postoperative Pain. Inflammation.

RESUMO

A exodontia de terceiros molares está entre os procedimentos mais realizados na Cirurgia e Traumatologia Bucomaxilofacial, sendo frequentemente associada a complicações pós-operatórias como dor, edema, trismo e limitação funcional. Nesse contexto, o canabidiol (CBD) tem despertado crescente interesse científico devido às suas propriedades analgésicas, anti-inflamatórias e moduladoras do sistema endocanabinoide, configurando-se como potencial alternativa terapêutica no manejo pós-operatório em odontologia cirúrgica. O presente estudo teve como objetivo analisar, por meio de uma revisão integrativa da literatura, as evidências científicas atuais acerca da utilização do canabidiol na prevenção e no controle das complicações pós-operatórias associadas às exodontias de terceiros molares. A construção metodológica foi fundamentada nas etapas propostas por Whittemore e Knafl (2005). A busca bibliográfica foi realizada nas bases PubMed/MEDLINE, Scopus, Web of Science e SciELO, considerando estudos publicados entre 2015 e 2025, nos idiomas inglês, português e espanhol. Foram incluídos ensaios clínicos, revisões sistemáticas, estudos observacionais e pesquisas experimentais relacionados ao uso do CBD em dor orofacial, inflamação e cirurgia oral. Os achados demonstraram que o canabidiol apresenta potencial analgésico e anti-inflamatório relevante, atuando na modulação da nocicepção e da resposta inflamatória por meio de mecanismos associados aos receptores CB1 e CB2, além da redução de citocinas pró-inflamatórias e da sensibilização nociceptiva. Estudos clínicos indicaram redução da dor pós-operatória, melhora funcional e possível diminuição da necessidade de analgésicos convencionais. Entretanto, persistem limitações metodológicas importantes, incluindo heterogeneidade entre protocolos terapêuticos, diferenças de dose, vias de administração, tamanho amostral reduzido e ausência de padronização clínica. Conclui-se que o canabidiol apresenta potencial terapêutico promissor na prevenção e no controle das complicações pós-operatórias em exodontias de terceiros molares, embora ainda sejam necessários estudos clínicos mais robustos e padronizados para consolidação de sua aplicabilidade na prática odontológica contemporânea.

Palavras-chave: Canabidiol. Exodontia. Terceiro Molar. Dor Pós-Operatória. Inflamação.

RESUMEN

La extracción de terceros molares es uno de los procedimientos más frecuentes en Cirugía Oral y Maxilofacial y Traumatología, y suele asociarse a complicaciones postoperatorias

como dolor, edema, trismo y limitación funcional. En este contexto, el cannabidiol (CBD) ha despertado un creciente interés científico debido a sus propiedades analgésicas, antiinflamatorias y moduladoras del sistema endocannabinoide, posicionándose como una potencial alternativa terapéutica en el manejo postoperatorio de la cirugía dental. Este estudio tuvo como objetivo analizar, mediante una revisión integradora de la literatura, la evidencia científica actual sobre el uso de cannabidiol en la prevención y el control de las complicaciones postoperatorias asociadas a las extracciones de terceros molares. La metodología se basó en los pasos propuestos por Whittemore y Knafl (2005). La búsqueda bibliográfica se realizó en las bases de datos PubMed/MEDLINE, Scopus, Web of Science y SciELO, considerando estudios publicados entre 2015 y 2025, en inglés, portugués y español. Se incluyeron ensayos clínicos, revisiones sistemáticas, estudios observacionales e investigaciones experimentales relacionadas con el uso de CBD en el dolor orofacial, la inflamación y la cirugía oral. Los hallazgos demostraron que el cannabidiol posee un potencial analgésico y antiinflamatorio relevante, actuando sobre la modulación de la nocicepción y la respuesta inflamatoria a través de mecanismos asociados a los receptores CB1 y CB2, además de reducir las citocinas proinflamatorias y la sensibilización nociceptiva. Los estudios clínicos indicaron una reducción del dolor postoperatorio, una mejoría funcional y una posible disminución de la necesidad de analgésicos convencionales. Sin embargo, persisten importantes limitaciones metodológicas, como la heterogeneidad entre los protocolos terapéuticos, las diferencias en la dosificación, las vías de administración, el tamaño reducido de la muestra y la falta de estandarización clínica. Se concluye que el cannabidiol presenta un potencial terapéutico prometedor en la prevención y el control de las complicaciones postoperatorias en las extracciones de terceros molares, aunque aún se necesitan estudios clínicos más sólidos y estandarizados para consolidar su aplicabilidad en la práctica odontológica actual.

Palabras clave: Cannabidiol. Exodoncia. Tercer Molar. Dolor Postoperatorio. Inflamación.

1 INTRODUCTION

Third molar extraction surgery represents one of the most performed procedures in Oral and Maxillofacial Surgery and Traumatology, and is often indicated in cases of dental impaction, pericoronitis, caries, root resorptions, periodontal alterations and prevention of future complications. Although widely performed and considered safe, it is a procedure associated with a significant postoperative inflammatory response, often accompanied by pain, facial edema, trismus, and functional limitation, factors that directly impact clinical recovery and quality of life of patients. The intensity of these complications may vary according to the surgical complexity, operative time, tissue trauma, and individual systemic characteristics of the patient (FERREIRA; RIBEIRO; MANDARINO, 2022).

In view of this scenario, different pharmacological strategies have been used with the aim of minimizing the inflammatory and painful repercussions resulting from extractions of third molars. Among the conventional approaches, nonsteroidal anti-inflammatory drugs and corticosteroids, especially dexamethasone and betamethasone, which are widely used in the prevention of postoperative edema, pain, and trismus, stand out. Recent studies have shown that the preemptive administration of these drugs presents satisfactory results in reducing inflammatory complications, especially when associated with multimodal analgesic protocols. However, adverse effects, clinical contraindications, and therapeutic limitations related to the prolonged or indiscriminate use of these drugs stimulate the search for safer and more effective therapeutic alternatives (GOMES JÚNIOR et al., 2025).

In this context, cannabidiol (CBD), a non-psychoactive compound derived from *Cannabis sativa*, has aroused growing scientific interest due to its analgesic, anti-inflammatory, anxiolytic and endocannabinoid system modulating properties. The endocannabinoid system plays an important role in modulating nociception, inflammatory response, and immune activity, acting through CB1 and CB2 receptors distributed in neural and peripheral structures related to pain control. Recent evidence suggests that CBD can reduce nociceptive sensitization, modulate pro-inflammatory cytokines, and contribute to the control of orofacial pain and inflammatory processes associated with the oral cavity, configuring itself as a potential therapeutic alternative in contemporary dentistry (TANGANELI et al., 2023).

In recent years, clinical studies and systematic reviews have begun to investigate the use of CBD in acute painful conditions related to dentistry, including spontaneous odontogenic pain and postoperative pain after tooth extractions. Randomized controlled trials have demonstrated significant pain reduction in patients undergoing oral use of CBD, as well as functional improvement related to bite force and possible decrease in the need for

conventional analgesics. In addition, recent reviews indicate that cannabinoids may exert favorable effects on oral inflammation, tissue edema, and bone healing, although the results still show methodological heterogeneity and limitations related to sample size, therapeutic standardization, and methodological quality of the available studies (CHREPA et al., 2024; CAMPANA et al., 2025).

Despite the advancement of research involving the therapeutic use of cannabidiol in dentistry, the scientific evidence currently available still remains limited, especially in the specific context of postoperative complications resulting from extractions of third molars. Although recent studies have demonstrated analgesic, anti-inflammatory, and nociceptive response modulating potential associated with CBD, the available results still show important methodological heterogeneity, including differences related to the formulations used, doses administered, routes of administration, therapeutic protocols, clinical outcomes evaluated, and patient follow-up time. In addition, there are still relevant gaps regarding the safety profile, therapeutic standardization, comparative clinical efficacy, and applicability of CBD compared to conventional pharmacological protocols employed in postoperative management in oral surgery.

In this context, the present study aims to analyze, through an integrative literature review, the current scientific evidence on the use of CBD in the prevention and control of postoperative complications associated with third molar tooth extractions, focusing on outcomes related to pain, edema, trismus, inflammation and functional recovery, seeking to contribute to the consolidation of more effective therapeutic approaches, safe and grounded in contemporary scientific evidence (WALCZYŃSKA-DRAGON et al., 2025; CARRASCOSA et al., 2024).

2 METHODOLOGY

This is an integrative literature review, developed with the objective of gathering, analyzing and critically synthesizing the available scientific evidence on the use of cannabidiol in the prevention and control of postoperative complications associated with extractions of third molars. The methodological construction of the study was based on the steps proposed by Whittemore and Knafl (2005), widely used in integrative reviews in the health area, contemplating the identification of the problem, definition of the search strategy, establishment of eligibility criteria, selection of studies, data extraction, critical analysis of the evidence and synthesis of the knowledge produced.

The main bibliographic search was performed in the PubMed/MEDLINE, Scopus, Web of Science and SciELO databases. Articles published between 2015 and 2025, in

English, Portuguese, and Spanish, were considered. Descriptors indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) were used, including the terms "Cannabidiol", "CBD", "Third Molar", "Tooth Extraction", "Oral Surgery", "Postoperative Pain", "Edema", "Trismus", "Inflammation" and "Orofacial Pain", combined using the Boolean operators AND and OR. The search strategy was adapted according to the specificities of each database, seeking to increase the sensitivity of the identification of studies related to pain management, inflammation, and postoperative recovery in surgical dentistry.

Randomized clinical trials, systematic reviews, observational studies, review studies, and experimental research that addressed the use of cannabidiol or other cannabinoids in the management of pain, edema, inflammation, trismus, bone healing, and other postoperative complications related to surgical dentistry, especially in third molar extractions, were included. Studies focused on the endocannabinoid system and its participation in the pathophysiological mechanisms of orofacial pain were also considered, due to the relevance of these findings for understanding the possible therapeutic effects of CBD. Duplicate articles, studies without full text available, publications with insufficiently described methodology, studies without a direct relationship with the proposed theme, and studies directed exclusively to medical conditions unrelated to the dental context were excluded.

The selection of studies occurred in two stages. Initially, the titles and abstracts were read to identify potentially eligible works. Subsequently, the selected articles were submitted to full reading and critical analysis regarding thematic relevance, methodological consistency, and adequacy to the objectives of the review. During the evaluation of the studies, important limitations were observed related to the methodological heterogeneity of research involving CBD in dentistry, including differences between doses administered, routes of administration, pharmaceutical formulations, therapeutic protocols, and clinical outcomes analyzed, factors that hinder direct comparisons and limit the standardization of currently available evidence.

The data extracted from the included studies included information regarding the authors, year of publication, methodological design, study population, characteristics of the CBD intervention, route of administration, main outcomes evaluated, and results found. Subsequently, the findings were organized descriptively and submitted to critical qualitative analysis, allowing the construction of an integrative synthesis of scientific evidence related to the therapeutic potential of CBD in the prevention and control of postoperative complications in third molar tooth extractions, with emphasis on the effects on pain, edema, inflammation, trismus, and postoperative functional recovery.

3 RESULTS AND DISCUSSION

The studies included in this integrative review showed a progressive growth in scientific interest in the therapeutic application of cannabidiol (CBD) in the management of orofacial pain and postoperative complications associated with extractions of third molars. There was a predominance of systematic reviews, randomized clinical trials, experimental studies, and investigations related to the endocannabinoid system, with a main focus on pain modulation, inflammatory response, and postoperative functional recovery. Although a significant part of the literature is still composed of heterogeneous studies and small samples, current findings suggest relevant clinical potential of CBD as an adjuvant agent in the control of pain and inflammation in surgical dentistry (CAMPANA et al., 2025; WALCZYŃSKA-DRAGON et al., 2025).

Postoperative pain resulting from third molar tooth extractions is a direct consequence of surgical tissue injury, activation of peripheral nociceptors, and release of inflammatory mediators, including prostaglandins, bradykinin, substance P, and proinflammatory cytokines. In this context, the pharmacological mechanisms associated with CBD have shown a potentially favorable relationship with the modulation of these pathophysiological processes. The endocannabinoid system actively participates in nociceptive regulation through action on CB1 and CB2 receptors, distributed in central neuronal structures, peripheral nerve endings, and immune system cells. The indirect activation of these receptors by CBD seems to contribute to the reduction of nociceptive sensitization and modulation of pain transmission, in addition to influencing serotonergic receptors and TRPV1 channels involved in the perception of inflammatory and neuropathic pain (TANGANELI et al., 2023; CARRASCOSA et al., 2024).

From a clinical point of view, the findings related to postoperative analgesia were particularly promising. The clinical trial conducted by Chrepa et al. (2024) identified a significant reduction in acute odontogenic pain in patients undergoing oral use of CBD, with progressive improvement in pain intensity and functional increase related to bite force. Similar results were observed in a recent pilot study involving post-tooth extraction pain, in which higher concentrations of CBD showed an analgesic trajectory qualitatively comparable to conventional therapy based on ibuprofen and acetaminophen, suggesting a possible sparing effect of traditional analgesics in certain clinical contexts (ABIDI; KASSAN; DEREFINKO, 2025).

In addition to nociceptive modulation, the results suggest an important role of CBD in the control of the post-surgical inflammatory response. Activation of the endocannabinoid system appears to reduce the production of pro-inflammatory cytokines, such as TNF- α , IL-

1 β , and IL-6, as well as modulate inflammatory cell migration and oxidative stress associated with surgical trauma. These mechanisms are directly related to the pathophysiology of edema and trismus observed after extractions of third molars. Recent reviews have indicated that CBD can exert relevant anti-inflammatory effects on oral tissues and masticatory muscle structures, contributing to less functional limitation and improved postoperative recovery (CAMPANA et al., 2025; WALCZYŃSKA-DRAGON et al., 2025).

Although the literature specifically related to post-tooth extraction trismus still remains limited, studies involving orofacial pain, temporomandibular disorders, and muscle inflammation suggest that CBD may exert a favorable effect on muscle spasm and mandibular functional limitation. This effect is probably due to the reduction of peripheral inflammatory activity associated with the modulation of neuronal and muscular excitability. In clinical terms, this possible action becomes particularly relevant in surgeries of impacted third molars, in which muscle edema, surgical trauma, and limitation of mouth opening represent important factors of postoperative morbidity.

Another aspect discussed in the literature refers to the potential impact of CBD on healing and tissue repair. Experimental studies have shown that CB2 receptors can influence mechanisms related to bone remodeling, osteoblastic activity, and control of inflammatory bone resorption. Additionally, the antioxidant and immunomodulatory effects attributed to CBD seem to contribute to the reduction of local oxidative damage and modulation of the persistent inflammatory response. Although such mechanisms still lack robust clinical validation in surgical dentistry, current findings suggest a possible contribution of the endocannabinoid system to alveolar repair and post-tooth extraction tissue recovery (CAMPANA et al., 2025).

From a comparative perspective, CBD has potentially interesting pharmacological characteristics in relation to non-steroidal anti-inflammatory drugs and corticosteroids traditionally used in the postoperative period of tooth extractions. Although dexamethasone, betamethasone, and NSAIDs remain largely effective in reducing edema, pain, and trismus, their gastrointestinal, cardiovascular, metabolic, and renal adverse effects limit long-term use in certain patient groups. In this scenario, CBD emerges as a promising alternative within contemporary multimodal analgesia, especially due to the possibility of simultaneous action on pain, perioperative anxiety, and inflammation, without the typical psychoactive effects associated with tetrahydrocannabinol (THC). However, current evidence does not yet allow us to affirm therapeutic superiority over conventional pharmacological protocols, mainly due to the absence of robust and standardized comparative clinical trials.

Regarding therapeutic safety, the studies analyzed demonstrated a relatively favorable tolerability profile, with a predominance of mild and self-limiting adverse effects, including somnolence, mild gastrointestinal discomfort, xerostomia, and mild changes in taste. No serious complications related to the use of CBD were identified in the clinical studies evaluated. Even so, the literature highlights the need for caution regarding the pharmacokinetic variability of commercial formulations, differences in oral bioavailability, and possible drug interactions involving cytochrome P450-dependent hepatic metabolism (CARRASCOSA et al., 2024).

Despite the promising results, this review highlighted important methodological limitations in the currently available research. There was high heterogeneity among the studies regarding the doses administered, routes of administration, duration of use, pharmaceutical formulations, and clinical outcomes evaluated. In addition, many studies have shown small sample sizes, short follow-up periods, and lack of therapeutic standardization, factors that hinder more consistent clinical extrapolations. A significant part of the evidence still derives from experimental studies, narrative reviews, or investigations focused on general orofacial pain, not specifically directed at postoperative complications in extractions of third molars. Thus, although CBD demonstrates relevant therapeutic potential in modulating pain and postoperative inflammatory response, randomized clinical trials with greater methodological robustness are still needed, capable of establishing standardized therapeutic protocols, safe doses, and more reliable clinical parameters for routine application in surgical dentistry.

4 CONCLUSION

The use of cannabidiol in the context of third molar tooth extractions represents an emerging and potentially promising therapeutic approach for the management of postoperative complications associated with oral surgery. The evidence analyzed in this integrative review suggests that CBD may exert favorable effects on pain, inflammation, edema, and functional recovery, mainly due to its modulatory action on the endocannabinoid system, peripheral nociceptive mechanisms, and postoperative inflammatory response. In addition, their analgesic, anti-inflammatory, and anxiolytic properties reinforce the growing interest in the incorporation of cannabinoids into contemporary strategies of multimodal analgesia in dentistry.

The available findings also indicate that CBD has a relatively safe tolerability profile, with a low incidence of serious adverse effects in currently published clinical studies. However, despite the promising results, the evidence remains insufficient to consolidate

standardized clinical protocols for routine use in extractions of third molars. The literature shows important methodological heterogeneity, including differences related to the doses administered, routes of administration, pharmaceutical formulations, follow-up time, and clinical outcomes evaluated, in addition to the limitation due to small samples and scarcity of randomized clinical trials with greater methodological robustness.

Thus, it is concluded that cannabidiol emerges as a potential adjuvant alternative in the control of postoperative complications in third molar surgery, especially in the management of pain and inflammatory response. However, larger, standardized, and methodologically consistent clinical studies are still needed to better define its clinical efficacy, therapeutic safety, ideal dosage, and applicability in contemporary dental practice.

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IMPACT OF POLYPHARMACY ON THE HEALTH OF THE ELDERLY PERSON: NURSING STRATEGIES

IMPACTO DA POLIFARMÁCIA NA SAÚDE DA PESSOA IDOSA: ESTRATÉGIAS DE ENFERMAGEM

IMPACTO DE LA POLIFARMACIA EN LA SALUD DE LA PERSONA MAYOR: ESTRATEGIAS DE ENFERMERÍA



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ABSTRACT

Objective: To analyze the impacts of polypharmacy on the health of elderly people and the nursing strategies for the prevention of adverse events.

Methodology: This is an integrative literature review, conducted in the Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), SciELO, and Google Scholar databases, considering publications from 2020 to 2025. Controlled descriptors from DeCS were used, combined by Boolean operators: Elderly (Aged) AND Polypharmacy (Polypharmacy) AND Nursing Care (Nursing Care).

Results: A total of 225 studies were identified in the databases. After applying the inclusion and exclusion criteria and reading titles and abstracts, 33 articles remained. After removing duplicates, 27 studies were selected for full-text reading, resulting in a final sample of 12 articles that met the research objective.

Conclusion: Polypharmacy constitutes an important challenge for the health of the elderly population, being a multifactorial phenomenon associated with the presence of chronic

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diseases, physiological aging, and vulnerabilities in healthcare. The fundamental role of nursing in preventing adverse events is highlighted, through strategies such as nursing consultations based on the Nursing Process, health education, and the Systematization of Nursing Care, contributing to safer care and the improvement of the elderly person's quality of life.

Keywords: Polypharmacy. Elderly. Nursing. Public Health.

RESUMO

Objetivo: Analisar os impactos da polifarmácia na saúde da pessoa idosa e as estratégias de enfermagem para a prevenção de eventos adversos.

Metodologia: Trata-se de uma revisão integrativa da literatura, realizada nas bases de dados Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), SciELO e Google Acadêmico, considerando publicações no período de 2020 a 2025. Foram utilizados descritores controlados do DeCS combinados por operadores booleanos: Idosos (Aged) AND Polifarmácia (Polypharmacy) AND Cuidados de Enfermagem (Nursing Care).

Resultados: Foram identificados 225 estudos nas bases de dados. Após a aplicação dos critérios de inclusão e exclusão e leitura de títulos e resumos, restaram 33 artigos. Após a remoção de duplicidades, 27 estudos foram selecionados para leitura na íntegra, resultando em uma amostra final de 12 artigos que atenderam ao objetivo da pesquisa.

Conclusão: A polifarmácia configura-se como um importante desafio para a saúde da população idosa, sendo um fenômeno multifatorial associado à presença de doenças crônicas, ao envelhecimento fisiológico e às fragilidades no cuidado em saúde. Evidencia-se o papel fundamental da enfermagem na prevenção de eventos adversos, por meio de estratégias como a consulta de enfermagem pautada no Processo de Enfermagem, a educação em saúde e a Sistematização da Assistência de Enfermagem, contribuindo para um cuidado mais seguro e para a melhoria da qualidade de vida da pessoa idosa.

Palavras-chave: Polifarmácia. Idoso. Enfermagem. Saúde Pública.

RESUMEN

Objetivo: Analizar los impactos de la polifarmacia en la salud de la persona mayor y las estrategias de enfermería para la prevención de eventos adversos.

Metodología: Se trata de una revisión integrativa de la literatura, realizada en las bases de datos Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), SciELO y Google Académico, considerando publicaciones en el período de 2020 a 2025. Se utilizaron descriptores controlados del DeCS combinados mediante operadores booleanos: Ancianos (Aged) AND Polifarmacia (Polypharmacy) AND Cuidados de Enfermería (Nursing Care).

Resultados: Se identificaron 225 estudios en las bases de datos. Tras la aplicación de los criterios de inclusión y exclusión y la lectura de títulos y resúmenes, quedaron 33 artículos. Tras la eliminación de duplicados, 27 estudios fueron seleccionados para lectura completa, resultando en una muestra final de 12 artículos que cumplieron con el objetivo de la investigación.

Conclusión: La polifarmacia se configura como un importante desafío para la salud de la población anciana, siendo un fenómeno multifactorial asociado a la presencia de enfermedades crónicas, al envejecimiento fisiológico y a las fragilidades en la atención en

salud. Se evidencia el papel fundamental de la enfermería en la prevención de eventos adversos, mediante estrategias como la consulta de enfermería basada en el Proceso de Enfermería, la educación en salud y la Sistematización de la Asistencia de Enfermería, contribuyendo a un cuidado más seguro y a la mejora de la calidad de vida de la persona anciana.

Palabras clave: Polifarmacia. Anciano. Enfermería. Salud Pública.

1 INTRODUCTION

The process of population aging is growing all over the world. According to the World Health Organization (WHO), the elderly person is one who belongs to the age group of 65 years older in developed countries and 60 years older in developing countries, as is the case of Brazil. According to the last demographic census, carried out in 2022 by the Institute of Geography and Statistics (IBGE), the country has approximately 32 million elderly people, which corresponds to 15.8% of the total population (Brasil, 2023).

Population aging is associated with several factors, such as the reduction in the fertility rate and the increase in life expectancy and the growth of chronic non-communicable diseases, which contributes to the growing use of health services and multiple medications of continuous use by the same individual, a condition known as polypharmacy (Oliveira; Brito; Siqueira, 2020).

Polypharmacy is defined as the concomitant use of four or more simultaneous medications by the same individual, and is a common practice among elderly people. Although it can bring therapeutic benefits, its inappropriate use is associated with significant risks, such as adverse reactions, drug interactions, and increased morbidity and mortality (Macêdo et al., 2023). According to Oliveira; Brito; Siqueira (2020) approximately 93% of the elderly over 65 years of age in Brazil use at least one drug and about 18% use five or more drugs simultaneously.

In this context, the role of nursing in the care of the elderly is highlighted, especially with regard to the safe use of medications. The changes inherent to aging interfere with pharmacokinetics and pharmacodynamics, increasing vulnerability to adverse events. Thus, it is essential that nurses consider the specificities of each individual, such as clinical, functional, and sociodemographic aspects, in order to plan and implement safe and effective care (Cavalcante et al., 2022).

In view of the above, this study aims to describe the impact of polypharmacy on the health of the elderly and to analyze nursing approaches aimed at preventing adverse events.

2 METHODOLOGY

It is an integrative literature review, a method that enables the synthesis of available evidence on the chosen topic, contributing to evidence-based practice and identification of gaps in knowledge (Macêdo et al., 2023).

This study was conducted in six stages: (1) identification of the theme and formulation of the guiding question; (2) definition of inclusion and exclusion criteria; (3) literature search; (4) selection of studies; (5) analysis and interpretation of the results; (6) Submission of the

review.

The guiding question was: How does polypharmacy impact the health of the elderly and what nursing approaches can be adopted to prevent adverse events related to the concomitant use of multiple medications?

The search was carried out in the MEDLINE/PubMed, SciELO and Google Scholar databases, considering publications in the period from 2020 to 2025. Health Sciences Descriptors (DeCS) were used, combined by operators: Elderly (Aged) AND Polypharmacy AND Nursing Care (NursingCare).

The inclusion criteria were: articles published between 2020 and 2025, available in full, in Portuguese and English, and that directly addressed the topic. Theses, dissertations, monographs, opinion articles and duplicate studies were excluded.

The selection of studies occurred through the reading of titles, abstracts and full texts. Initially, 225 studies were identified, of which 33 met the inclusion criteria. After excluding duplicates, 27 studies remained for full reading, resulting in a final sample of 12 articles.

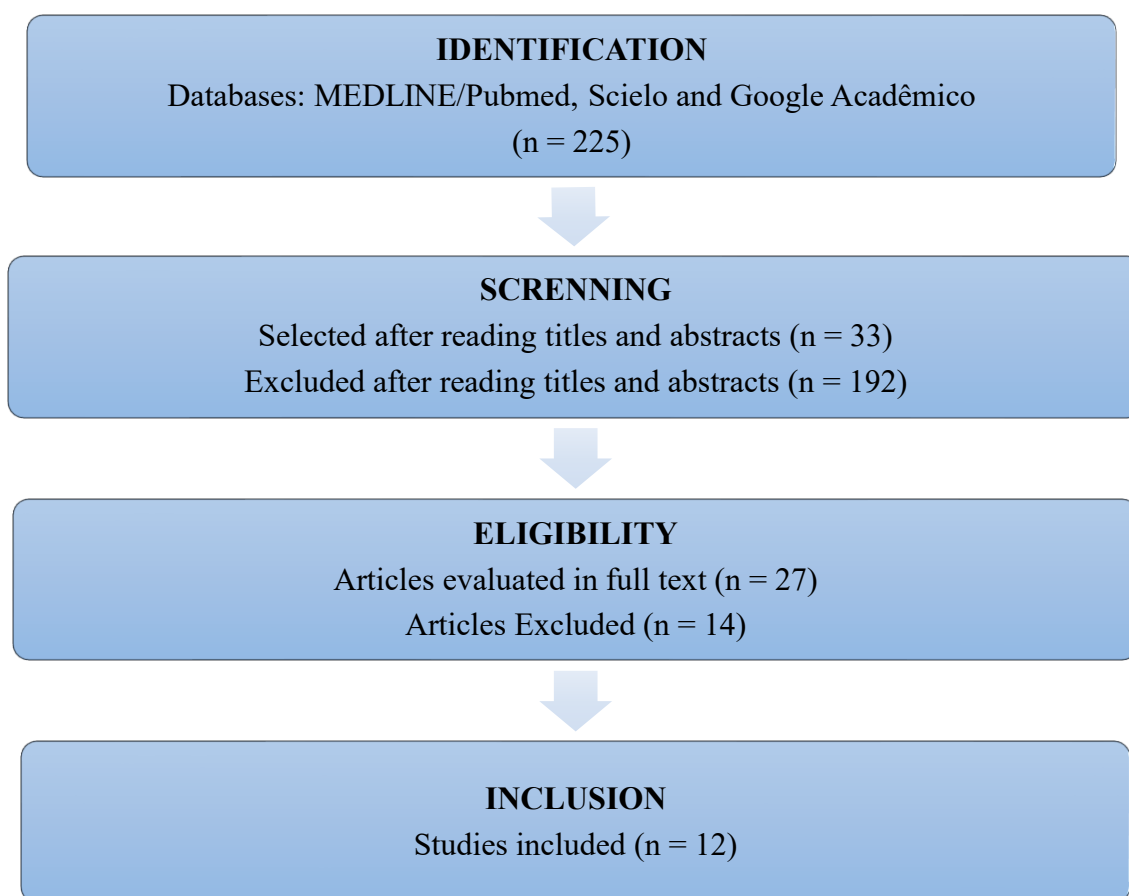
The results were presented based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), adapted for integrative review. The study did not require approval by the Research Ethics Committee, as it used secondary data available in databases in the public domain, respecting the ethical principles established by Resolution No. 466/12 of the National Health Council.

3 RESULTS

The articles selected for this study were described following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), as shown in the flowTable (Figure 1).

Figure 1

PRISMA flowTable of the article selection process



Source: Authors, 2026

After the completion of the article selection process, as shown in the PRISMA flowTable, the articles were systematized and organized according to year of publication, authorship, methodology, objective and results found, as shown in Table 1.

The analysis allowed the organization of the findings into two thematic categories: impacts of polypharmacy on the health of the elderly and nursing strategies for the prevention of adverse events.

Table 1

Selected articles on polypharmacy in the elderly and nursing approaches, 2020 to 2025

Author Year	Title	Methodology	Objective	Result
Leal, R. C. et al. 2020	Polypharmacy in the elderly: the role of nursing in the prevention of iatrogenic diseases	Descriptive study	To identify the use of medication by the elderly in a Basic Family Health Unit from the perspective of care in the prevention of iatrogenic diseases	Polypharmacy with the use of drugs to lower blood pressure and hypoglycemic drugs by the elderly, inferring the educational importance of health professionals, especially nurses, in helping the elderly to minimize possible

				iatrogenic events that polypharmacy can cause.
Oliveira, RP et al. 2020	Systematization of nursing care in the prevention of drug interactions among elderly people in polypharmacy.	Integrative literature review	To describe the Systematization of Nursing Care (NCS) in the prevention of drug interactions (DI) among elderly people in polypharmacy.	The use of NCS as a strategy for caring for the elderly in polypharmacy in the context of DI prevention is essential, and the Nursing Process should be applied to these individuals as a form of disease prevention.
Rodrigues, DS et al. 2021	Impacts caused by polypharmacy in the elderly: an integrative review.	Descriptive review	To identify the impacts caused by polypharmacy in the elderly.	The use of several medications, combined or not with other forms of supplementary health care, is a common practice in the elderly and is frequently described in the literature as a current difficulty due to complications and their impacts on health care costs.
Cavalcante, AS et al. 2022	Nursing care based on Virginia Henderson's theory for the elderly using polypharmacy.	Theoretical-reflective study	To list the main nursing diagnoses, outcomes and interventions according to Virginia Henderson's theory for the elderly who use polypharmacy	The diagnoses raised were ineffective self-management of health, risk of falling, risk of dysfunctional gastrointestinal motility, risk of impaired liver function, and risk of electrolyte imbalance.
Canteri, VA et al. 2023	Nursing care for the elderly using polypharmacy.	Literature review	To review the scientific publications on nursing care for the elderly using polypharmacy, and to highlight the importance of nursing in the face of the problem presented.	Nurses are indispensable for promoting the quality of life of the elderly, therefore, the need for qualification of these professionals is evident.
Macedo, VMF et al. 2023	Nursing care in primary care with elderly people undergoing polypharmacy treatment.	Integrative review	To identify in the scientific literature which care strategies are used by nurses with elderly people undergoing polypharmacy treatment in primary care.	The main strategies found were: motivational interviewing; integrated intervention; educational intervention; integrated review of medications; guided care; periodic nursing consultation.
Souza, AES et al. 2023	Nursing role in reducing risks associated with the use of polypharmacy in the elderly.	Scoping Review	To investigate the role of Nursing in reducing risks in the use of polypharmacy in the elderly.	The performance of the nursing professional is essential to minimize the damage caused by the simultaneous use of several medications, as well as, in the administration, adequate scheduling, monitoring and planning of the

				medication routine, seeking to reduce polypharmacy and promoting a lifestyle favorable to active aging.
France, JMM; Felicio, LR 2024	Polypharmacy in the elderly: impacts and prevention from the nurse's perspective.	Literature review	To analyze the impact of polypharmacy on population aging and to identify prevention strategies from the perspective of nurses.	There is a need for a more active role of nurses in geriatric polypharmacy, being a key player in the identification, prevention and minimization of risks.
Arruda, M.A. et al. 2025	Prevention of Polypharmacy in the Elderly in Primary Health Care: a literature review.	Integrative literature review	To identify in the scientific literature the strategies used by nurses with the elderly to prevent polypharmacy in Primary Health Care.	The nurse can reduce the appearance of adverse reactions and drug interactions, providing safer and more effective care to the elderly.
Jesus, JC et al. 2025	Polypharmacy: strategies used by nurses to reduce the impacts on the health of the elderly	Literature review	To identify the strategies used by nurses during nursing consultations, in order to reduce the specific effects of polypharmacy on the health of the elderly.	Among the main goals, we highlight the guidance on the dangers linked to the excessive use of medications, the identification of actions to minimize these problems, in addition to the creation of educational practices aimed at the elderly and their caregivers.
Lago, P.A. et al. 2025	Impacts of Polypharmacy on the Quality of Life of Elderly People: an integrative literature review.	Integrative literature review	To analyze what has been published scientifically about the interference of the use of polypharmacy in the quality of life of elderly people living in the community	A total of 7 articles were found that showed a decrease in the quality of life of elderly people using polypharmacy, enhanced by the lack of adequate follow-up. Communication between health professionals and patient is essential to minimize the risks of polypharmacy.
Melo, ALFM et al. 2025	The impact of polypharmacy on the health of the elderly: nursing approaches.	Literature search	To analyze, based on the scientific literature, the effects of polypharmacy on the health of the elderly population, as well as to identify strategies for the promotion of the rational use of medicines and the reduction of therapeutic risks	Polypharmacy is highly prevalent among the elderly and represents an important public health problem.

Source: Authors, 2026

4 DISCUSSIONS

When analyzing the studies, it was found that polypharmacy in the elderly is multifactorial, closely linked to the aging of the population, the presence of chronic diseases and fractionation of the care offered in primary care. Rodrigues *et al.*, (2021); Lago *et al.*, (2025) and Melo *et al.*, (2025) agree that the use of several drugs significantly increases the risk of adverse reactions, drug interactions, decreased quality of life, and increased hospitalizations.

Arruda *et al.*, (2025) and França; Felício (2024) agree that the prevention of polypharmacy should be planned through strategies carried out and developed in primary care, always with the concern of periodically reviewing prescriptions and continuous monitoring of the elderly. In this sense, Jesus *et al.*, (2025) and Souza *et al.*, (2023) highlight that the nurse's performance is essential in this process, especially through health education and continuous monitoring of the correct use of drugs, evidencing an alignment between studies and the role of nursing.

Regarding systematized care, Canteri *et al.* (2023), Macêdo *et al.* (2023) and Oliveira *et al.* (2020) agree that the Systematization of Nursing Care (NCS) and the Nursing Process are fundamental tools for identifying risks related to polypharmacy. In addition, they argue that its application enables a comprehensive assessment of the elderly, favoring the implementation of safer and more individualized interventions.

Cavalcante *et al.* (2022) expand this discussion by basing care on Virginia Henderson's theory, highlighting the importance of meeting basic human needs and contributing to a more patient-centered and humanized approach. This approach reinforces the importance of nursing care that considers the biopsychosocial dimensions of the elderly using polypharmacy, aligning with the need for comprehensive care.

Although there is consensus regarding the negative impacts of polypharmacy, authors such as Leal *et al.*, (2020) and Rodrigues *et al.*, (2021) point out important gaps, such as lack of standardized protocols and lack of integration between the multiprofessional health team, which can negatively affect the safety of the elderly.

In the field of public policies, Informative Note No. 5/2023 reinforces the right to comprehensive care for the elderly, which is in line with the principles of the National Health Policy for the Elderly (PNSPI), which establishes the promotion of healthy and active aging. However, it was found in the studies analyzed that there are still challenges in the implementation of these guidelines, especially with regard to the organization of services and training of professionals for the correct management of elderly people who use polypharmacy.

In view of this, the implications for nursing practice are visible, and the nursing consultation becomes a strategic moment aimed at identifying problems related to the use of drugs, which allows the implementation of educational actions and strengthening of self-care. In addition, the nursing process contributes to safer clinical decision-making, encouraging the reduction of diseases, in addition to improving the quality of life of the elderly.

Thus, it was evident that although there have been advances in the understanding of polypharmacy and its impacts, it is still necessary to strengthen care practices, expand research and invest in continuing education aimed at health professionals, with the objective of ensuring more comprehensive, safe and effective care for the elderly population.

5 CONCLUSION

Polypharmacy is an important challenge for the health of the elderly population, being associated with an increased risk of adverse events, hospitalizations, drug interactions, and compromised quality of life. It was evidenced that this is a multifactorial phenomenon, mainly related to the presence of chronic diseases, physiological aging and weaknesses in health care.

In this context, the relevance of nursing approaches in the prevention of these diseases is highlighted, highlighting the essential role of nurses in the early identification of risks, in the promotion of the rational use of medications and in the continuous monitoring of the elderly, especially in the context of Primary Health Care. Strategies such as nursing consultations based on the Nursing Process and health education actions are important tools for reducing iatrogenic events and strengthening self-care.

In addition, the nurse plays a central role in the articulation of care, contributing to a humanized, integral and safe approach, aligned with the guidelines of public policies aimed at the health of the elderly. Thus, this study synthesizes relevant evidence for the field of nursing, by reinforcing the importance of professional qualification, the organization of health services and the expansion of care strategies aimed at the safe use of drugs.

Finally, the need to strengthen care practices and investment in continuing education is highlighted, as well as the expansion of scientific production on the subject, in order to support more effective interventions that reduce the impacts of polypharmacy and promote the improvement of the quality of life of the elderly population.

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HYDROLOGICAL DISASTERS AND HUMAN HEALTH: SCOPING REVIEW

DESASTRES HIDROLÓGICOS E SAÚDE HUMANA: UMA REVISÃO DE ESCOPO

DESASTRES HIDROLÓGICOS Y SALUD HUMANA: UNA REVISIÓN DEL ALCANCE



<https://doi.org/10.56238/sevened2026.020-049>

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ABSTRACT

The objective of this scoping review is to evaluate literature between 2013 and 2023 focused on human health and hydrological disasters. The research databases were: Lilacs, Medline via PubMed, Scopus, Web of Science, ScienceDirect. Eligibility was determined using inclusion and exclusion criteria, and the search strategy included: (Health) AND (Hydrologic Disaster), (Health Risk) AND (Hydrologic Disaster). Initially, 58 articles were selected, but after systematic screening, only 12 were relevant to the topic. The results indicated that the prevalence of post-disaster infectious diseases is a recurring and relevant theme in the literature. In short, scientific collaboration highlighted the need for more comprehensive and multidisciplinary work, with the potential to act in the formulation of public policies and international partnerships, preparation of health managers and professionals, development of plans, research and interventions in the relationship between health and hydrological disasters.

Keywords: Flooding. Health. Infectious Diseases. Stormwater Drainage and Healthcare Professionals.

RESUMO

O objetivo desta revisão de escopo é avaliar literatura entre 2013 e 2023 relacionada objetivamente à saúde humana e desastres hidrológicos. As bases de pesquisa foram: Lilacs, Medline via PubMed, Scopus, Web of Science, ScienceDirect. Para elegibilidade utilizou-se critérios de inclusão e exclusão, e estratégia de busca: (Health) AND (Hydrologic

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Disaster), (Health Risk) AND (Hydrologic Disaster). Inicialmente, foram selecionados 58 artigos, porém após a seleção sistematizada apenas 12 estavam aptos à temática sugerida. Os resultados indicaram que a prevalência de doenças infecciosas pós desastre é um tema recorrente e relevante na literatura. Em suma, a colaboração científica foi capaz de indicar a necessidade de trabalhos mais abrangentes e multidisciplinares, com potencial para atuar na formulação de políticas públicas e parcerias internacionais, preparação de gestores e profissionais de saúde, elaboração de planos, pesquisas e intervenções na relação saúde e desastres hidrológicos.

Palavras-chave: Inundação. Saúde. Doenças Infecciosas. Drenagem Pluvial e Profissionais de Saúde.

RESUMEN

El objetivo de esta revisión de alcance es evaluar la literatura entre 2013 y 2023 relacionada objetivamente con la salud humana y los desastres hidrológicos. Las bases de datos de investigación fueron: Lilacs, Medline vía PubMed, Scopus, Web of Science, ScienceDirect. Para la elegibilidad, se utilizaron los criterios de inclusión y exclusión y la estrategia de búsqueda: (Salud) Y (Desastre Hidrológico), (Riesgo de Salud) Y (Desastre Hidrológico). Inicialmente se seleccionaron 58 artículos, pero luego de la selección sistemática solo 12 fueron adecuados para el tema sugerido. Los resultados indicaron que la prevalencia de enfermedades infecciosas después de los desastres es un tema recurrente y relevante en la literatura. En síntesis, la colaboración científica pudo indicar la necesidad de un trabajo más amplio y multidisciplinario, con potencial para actuar en la formulación de políticas públicas y alianzas internacionales, preparación de gestores y profesionales de salud, elaboración de planes, investigaciones e intervenciones en la relación entre salud y desastres hidrológicos.

Palabras clave: Inundaciones. Salud. Enfermedades Infecciosas. Drenaje Pluvial y Profesionales de la Salud.

1 INTRODUCTION

Natural disasters — such as extreme storms, floods, tropical cyclones, wildfires, windstorms, landslides, and droughts — have claimed millions of lives in recent decades and adversely affected the lives of millions more around the world, causing extensive material damage. From 1970 to 2012, 1.94 million deaths and US\$2.4 trillion in economic losses were reported globally as a result of 8,335 disasters directly linked to meteorological and hydrological conditions (Patz; Grabow; Limaye, 2014).

The findings of many empirical studies indicate that people's preparedness for disasters and the associated factors are closely related to individual and family socioeconomic characteristics, as well as personal experiences with disasters (Xu et al., 2018). Disproportionate flooding in socially vulnerable communities leads to unequal environmental and public health impacts. Substantial research on natural hazards has demonstrated that individuals living in poverty, the elderly, minority groups, and those without access to transportation are at greater risk of adverse health outcomes associated with disasters (Newman et al., 2022). The health impacts of floods may include drowning, injuries, animal bites, and communicable diseases, as well as chronic illnesses and long-term mental health effects (Zhong et al., 2018; Du et al., 2010).

Studies on the health impacts of natural disasters highlight that such events affect populations unequally and in different ways, both directly and indirectly, with short- to long-term effects depending on the characteristics of the event and the socio-environmental vulnerability of the affected area (Alderman; Turner; Tong, 2012). The World Health Organization acknowledges that the mental health consequences of flooding have not been fully addressed by those involved in disaster preparedness or service provision, although it is widely accepted that natural disasters such as earthquakes, floods, and hurricanes take a significant toll on the mental health of affected individuals — most of whom live in developing countries where the capacity to address such problems is extremely limited (WHO, 2001). Floods have increasingly become serious public health issues, especially in developing countries such as Brazil, where legal advancements have not been matched by effective enforcement and still require the establishment of participatory mechanisms and educational actions as complementary measures (Freitas; Ximenes, 2012).

While natural disasters such as earthquakes, hurricanes, and tsunamis have been the most extensively studied in the health field, other types of disasters — such as floods and droughts — remain under-researched. Moreover, studies on post-disaster diseases and health effects require more scientific evidence on the topic (Sweileh, 2019).

The study by Charnley et al. (2021) identified ten different types of disasters and thirty-nine diseases across six continents, offering a broad, global perspective on post-disaster impacts. The study highlighted the need for a specific scoping review focused on hydrological disasters and their relationship with health, in order to address scientific gaps.

In this context, the objective of this scoping review is to quantify and evaluate the literature on human health and hydrological disasters. This study seeks to answer the question: What does the literature report about Human Health and Hydrological Disasters?

2 METHODOLOGY

This study is a scoping review. The research employs exploratory and descriptive approaches to the data, using both quantitative and qualitative analyses. The scoping review aimed to analyze publications related to human health and hydrological natural disasters.

A scoping review is characterized by specific steps, including the definition of eligibility criteria, database selection, search strategy, screening process, study selection, data extraction, and synthesis of results (Munn et al., 2018). This scoping review was conducted systematically, following the PRISMA-ScR guidelines (Tricco et al., 2018).

The first step was defining the research question using the PCC strategy — Population, Concept, and Context — which is used to structure research questions and enhance the relevance of scoping reviews (Peters, 2016). Based on the research question, the search terms were identified through the Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH) databases. The search strategy included English-language terms drawn from these sources (DeCS, 2024; MeSH, 2023).

The systematic search for studies was carried out up to April 14, 2024, by two researchers independently using the following databases: Lilacs, Medline via PubMed, Scopus, Web of Science, and ScienceDirect. The aim was to find evidence that met the established eligibility criteria. The eligibility of the articles included in the study was based on two main criteria: (1) inclusion criteria and (2) exclusion criteria. The inclusion criteria were: open-access scientific articles available in full; systematic review studies; publications from 2013 to 2023; and written in English. The exclusion criteria included: gray literature (not peer-reviewed or publicly available); studies outside the scope of the research topic; papers that did not contribute to answering the research question; and studies with incomplete or superficially detailed methodology.

Following PRISMA-ScR recommendations, the scoping review protocol was registered on the Open Science Framework (OSF) through the link: <https://doi.org/10.17605/OSF.IO/ZTXQ9>, a public platform for registering scoping review

protocols (Van den Akker et al., 2023). Full-text reading of the selected articles was conducted by two blinded reviewers. The data extracted from the full texts included: author, year, country, participants, keywords, titles, study type, measured outcomes, and findings. The resulting themes from the articles were then categorized. To remove duplicate records, the Rayyan platform—designed to support the scoping review process—was used (Ouzzani et al., 2016).

3 RESULTS AND DISCUSSION

The database search retrieved a total of 4,199 articles, as shown in Table 1. To eliminate duplicates, the Rayyan platform was used. Rayyan identified 2,036 duplicate records, resulting in 2,105 articles to be analyzed according to the research topic and guiding question.

Table 1

Scoping review search strategy by database, for the period from 2013 to 2023

Database	Search Strategy	Total Articles
Lilacs via BVS Regional Portal	(health) AND (natural disasters)	36
	(health risk) AND (natural disasters) AND (fulltext:("1" OR "1")	11
	(Health) AND (Hydrologic Disaster)	0
	(Health Risk) AND (Hydrologic Disaster)	0
MEDLINE via PubMed	(Health) AND (Natural Disasters)	517
	(Health Risk) AND (Natural Disasters)	204
	(Health) AND (Hydrologic Disaster)	06
	(Health Risk) AND (Hydrologic Disaster)	04
Scopus	TITLE-ABS-KEY (health AND " Natural Disasters ")	1.195
	TITLE-ABS-KEY ("Health Risk" AND "Natural Disasters")	89
	TITLE-ABS-KEY (health AND "Hydrologic Disaster")	01
	"Health Risk" AND "Hydrologic Disaster"	0
Web of Science	(Health) AND (Natural Disasters)	539
	(Health Risk) AND (Natural Disasters)	297
	(Health) AND (Hydrologic Disaster)	16
	(Health Risk) AND (Hydrologic Disaster)	11
ScienceDirect	Health AND (Natural Disasters)	779
	"Health Risk" AND "Natural Disasters"	474
	Health AND "Hydrologic Disaster"	17
	"Health Risk" AND "Hydrologic Disaster"	03
Total		4.199

Source: prepared by the authors.

In a preliminary analysis of the retrieved studies, it was observed that some articles addressed various types of natural disasters such as hurricanes, tsunamis, and wildfires, which, however, were not the focus of this study. This led to a refinement of the search strategy to better align the selected articles with the study's objective. The strategy (Health) AND (Hydrologic Disaster) and Health Risk AND Hydrologic Disaster was implemented as a solution. The results of this refined search are presented in Table 2.

Table 2

Refined search strategy for studies addressing the relationship between human health and hydrologic disasters

Database	Search Strategy	Total Articles
Lilacs	(Health) AND (Hydrologic Disaster)	0
	(Health Risk) AND (Hydrologic Disaster)	0
Medline via PubMed	(Health) AND (Hydrologic Disaster)	06
	(Health Risk) AND (Hydrologic Disaster)	04
Scopus	TITLE-ABS-KEY (health AND "Hydrologic Disaster")	01
	"Health Risk" AND "Hydrologic Disaster"	0
Web of Science	(Health) AND (Hydrologic Disaster)	16
	(Health Risk) AND (Hydrologic Disaster)	11
ScienceDirect	Health AND "Hydrologic Disaster"	17
	"Health Risk" AND "Hydrologic Disaster"	03
Total		58

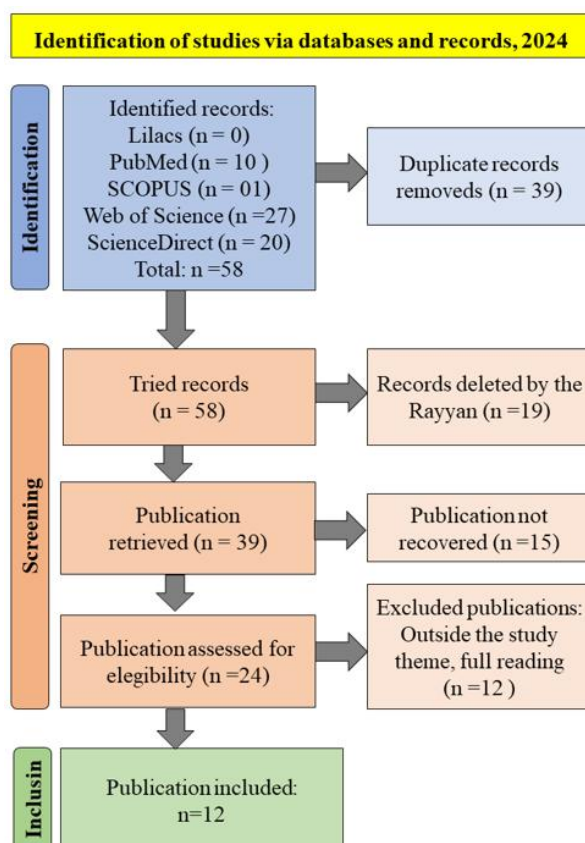
Source: prepared by the authors.

According to the theme of this study — the relationship between human health and hydrologic disasters — a targeted search for articles was conducted. Table 2 presents the corresponding databases, descriptors, and the number of documents retrieved from each platform.

The 58 selected articles were screened using the Rayyan application, which identified 39 duplicates. Consequently, 19 articles were excluded due to overlap among databases. After screening titles and abstracts based on the search strategy and the study theme, 15 articles were excluded for being outside the scope, resulting in 24 articles for full-text reading.

Among the 24 eligible publications, following the full-text analysis, 12 articles were excluded for not aligning with the study topic, leaving 12 articles for inclusion and data analysis (Figure 1).

From the full-text reading of the 12 included articles, data were extracted, and the main themes emerging from these articles were identified (Table 3).

Figure 1*Flowchart of the selected studies, 2024*

Source: prepared by the authors.

Table 3**Summaries of the twelve included studies**

AUTHOR/ YEAR	COUNTRY	PARTICIPANTS	KEYWORDS	TITLE	STUDY TYPE	DATABASE	OUTCOME MEASURES	MAIN FINDINGS
LIU <i>et al.</i> (2019)	China	All countries and territories worldwide that reported flood-related natural disasters from 1990 to 2019.	Flood disasters; Infectious diseases; Disease burden; Trend; Global	Association of natural flood disasters with infectious diseases in 168 countries and territories from 1990 to 2019: A worldwide observational study	Observational Study	ScienceDirect	From 1990 to 2019, flood-related natural disasters occurred over a cumulative 47,368 days in 168 countries and territories, resulting in a total of 242,516 deaths.	This was the first study to estimate the association between flood-related natural disasters and new cases and deaths from various infectious diseases across 168 countries worldwide from 1990 to 2019.
THERON <i>et al.</i> (2022)	South Africa	Six articles included in the final analysis. Data derived from four countries: Uganda, Ghana, Tanzania, and Nigeria.	Climate change; Disaster preparedness; Climate change adaptation; Climate change resilience; Emergency medicine	Climate change and emergency care in Africa: A scoping review	Scoping Review	ScienceDirect	The five studies focused on communicable diseases. Specific illnesses contributed to human mobility and outbreaks of infectious diseases.	The findings align with other studies highlighting the urgent need to prepare healthcare systems and professionals to address the health impacts of climate change.
LIANG; MESSENGER (2018)	USA	Emergency physicians and first responders.	Flood; Hurricane; Tsunami; Infectious diseases; Soft tissue infections; Respiratory infections; Gastrointestinal infections; Vector-borne diseases	Infectious diseases after hydrologic disasters	Literature review	ScienceDirect	Most communicable infections emerged among displaced populations in settings characterized by inadequate shelter, overcrowding, poor sanitation, and lack of access to safe food and drinking water.	Infectious diseases have been linked to hydrological events and their consequences. Most communicable infections emerge among displaced populations in settings characterized by inadequate shelter, overcrowding, poor sanitation, and lack of access to safe food and drinking water.
CHARNLEY <i>et al.</i> (2021)	UK	A total of 132 studies were selected.	Climate-change impacts; Climate-change mitigation; Natural hazards; Infectious diseases; Risk factors	Traits and risk factors of post-disaster infectious disease outbreaks: a systematic review	Systematic review	PubMed	The studies covered the period from 1940 to 2019 and included ten different types of disasters and 39 different diseases across six continents.	Reported outbreaks were often disaster-specific; therefore, diseases associated with hydrological events and conflicts were frequently documented.
PAITZ; GRABOW; LIMAYE (2014)	USA	Health consequences of climate change; study conducted on the relationship between health and post-disaster events.	Extreme weather events; global climate change; greenhouse gas emissions; health; vulnerable populations	When It Rains, It Pours: Future Climate Extremes and Health	Literature review	ScienceDirect	Geographic location played a significant role in the potential for adverse health effects associated with climate change	Mental health disorders, such as post-traumatic stress disorder (PTSD), can substantially affect the well-being of populations following natural disasters.
NEWMAN <i>et al.</i> (2022)	USA	Neighborhoods in the city of Houston, United States.	Landscape performance: green infrastructure; stormwater; resilience; equity	A Framework for Evaluating the Effects of Green Infrastructure in Mitigating Pollutant Transfer and Flood Events in Sunnyside, Houston, TX	Experimental study	Web of Science	Impact of the master plan on flood reduction and contamination control.	Improvements in urban stormwater management and water quality were observed. The master plan incorporated green roofs and rain gardens.
SALVATI <i>et al.</i> (2021)	Italy	Buildings assessed through active participation of citizens, municipal technicians, civil protection volunteers, and researchers.	Vulnerability indicators; Digital survey-forms; Urban context; Geo-hydrological hazard; Landslide susceptibility; Risk awareness	Acquiring vulnerability indicators to geo-hydrological hazards: An example of mobile phone-based data collection	Experimental study	ScienceDirect	A total of 1,375 building survey forms were compiled using building-specific assessment instruments.	The physical vulnerability of buildings at risk and their surroundings was identified and varied according to hazard type. Most buildings were located in the flat coastal area of the historic city, exposed to pluvial and fluvial flooding.
DÍAZ-DELGADO; GAYTÁN-INESTRA (2014)	Mexico	Mexican emergency plans and hydrometeorological warning systems.	Flood early warning system; humanitarian logistics; flood risk assessment; evacuation plan	Flood Risk Assessment in Humanitarian Logistics Process Design	Observational study	ScienceDirect	Analysis of early flood warning systems and performance measurement of relief operations.	Creation of a necessary database for flood forecasting and to strengthen multidisciplinary and multisectoral teamwork.
SALVATI <i>et al.</i> (2018)	Italy	Data on 1,292 landslides and 771 flood-related deaths that occurred in Italy over a 50-year period (1965–2014).	Deaths; Loss of life; Flood and landslide fatalities; Flood and landslide mortality; Statistical approach; Gender and age analysis; Geo-hydrological disasters	Gender, age and circumstances analysis of flood and landslide fatalities in Italy	Observational study	ScienceDirect	Summarized data from 35 catalogs reporting fatalities caused by geo-hydrological events, including 20 catalogs with information on flood and flash flood-related deaths.	Floods and landslides causing human fatalities in Italy demonstrated mortality dependence on gender and age. Landslides in Italy resulted in significantly more deaths (1,292) than floods (771) during the investigated period.
TIN <i>et al.</i> (2024)	USA	Retrospective analysis of natural disasters recorded in the Emergency Events Database from 1995 to 2022.	Natural disasters; Earthquakes; Floods; Mitigation; Response	Natural disasters: a comprehensive study using EMDAT database 1995-2022	Observational study	ScienceDirect	Emergency Events Database (EM-DAT) used to assess all natural disasters occurring between January 1, 1995, and December 31, 2022.	Between 1995 and 2022, 11,360 natural disasters occurred, averaging 398 per year. Asia recorded the highest number of disasters (4,390) and the greatest number of casualties (918,198). Hydrological disasters were the most common subgroup (4,969).
LAMBERTI; CASTRONO; VO <i>et al.</i> (2022)	Italy	A total of 145 studies and medical records were selected.	Primary healthcare; Disaster preparedness; H-EDRM; Framework; Health system strengthening	Primary health care disaster preparedness: A review of the literature and the proposal of a new framework	Systematic review	ScienceDirect	As of March 2022, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.	Development of a set of guidelines for primary healthcare systems to assess and enhance their disaster preparedness.
MANANDHAR <i>et al.</i> (2023)	China	Urban floods in South Asian countries; 105 publications were selected for analysis.	Climate change; early warning system; flood; hydrological model; land use land cover change; urbanization	Urban Flood Hazard Assessment and Management Practices in South Asia: A Review	Literature review	Web of Science	Evaluation of hydraulic and hydrological modeling approaches.	The main causes of increased flood risk in Asia are climate change and uncontrolled urbanization. Flood impacts can be mitigated through risk mapping.

Source: prepared by the authors.

The twelve studies included in this review presented a diverse range of geographic origins regarding scientific production, encompassing countries such as China, South Africa, the United States, the United Kingdom, Italy and Mexico. This diversity highlights the global interest in investigating the impacts of natural disasters and their consequences for public health.

The analyzed articles were classified into five main thematic areas. The first addresses infectious diseases following floods, highlighting the work of Liu et al. (2019), Theron et al. (2022), Liang and Messenger (2018), Charnley et al. (2021), and Patz, Grabow, and Limaye (2014), who explore how these events can facilitate the spread of diseases. Indirectly, these studies also discuss the premises of global warming as a driver of natural disasters and the socio-environmental and economic vulnerability of affected populations as a critical weak point. The operational challenges faced by public health systems in the wake of natural disasters also receive considerable attention.

The second thematic area focuses on flood risk mitigation, with studies such as Newman et al. (2022), Salvati et al. (2021), Díaz-Delgado and Gaytán-Iniestra (2014), and Manandhar et al. (2023), which discuss strategies to reduce flood-related damages. These studies propose the application of models such as landscape performance associated with other models (Newman et al., 2022), the use of mobile technology for precipitation data collection (Salvati et al., 2021), flood risk assessment through adaptation of hydrological models (Díaz-Delgado and Gaytán-Iniestra, 2014), and the adoption of nature-based solutions integrated into urban planning (Manandhar et al., 2023). What they share in common is a set of palliative responses through inclusive technologies amid the inefficiency of emergency managers due to various factors.

The third category addresses data on deaths caused by floods and landslides, represented by the study of Salvati et al. (2018), which analyzes statistics and patterns related to fatalities by age and gender variables over a 50-year period. Although there is low consistency by age group, male mortality appears to have been predominant for both floods and landslides.

The fourth thematic area covers the types of natural disasters, with emphasis on the study by Tin et al. (2024), which classifies and describes different types of environmental disasters. According to their findings, the most common subgroup of disasters was hydrological (4,969, 43.7%), but geophysical disasters caused the highest number of deaths (770,644, 45.8%), while biological disasters caused the greatest number of injuries (2,544,177, 33.5%), occurring most frequently in Africa (771, 32.2% of total disasters in Africa). The authors suggest that recognizing the historical impacts of the various subtypes

of natural disasters can help different regions better analyze and mitigate specific risks associated with such events.

Finally, the fifth focus area examines the preparedness of primary healthcare professionals to face disasters, addressed in the work of Lamberti-Castronuovo et al. (2022), which discusses training strategies and effective response in critical scenarios. In summary, the authors present the foundations of a disaster-prepared primary healthcare system. They argue that primary healthcare has the potential to help reduce the health effects of disasters by acting in all phases of the disaster management cycle.

According to Liu et al. (2019), their study was the first to evaluate the association between flood disasters and infectious disease mortality cases across 168 countries worldwide, covering the years 1990 to 2019. The study revealed that infectious diseases most frequently reported in the aftermath of floods were diarrhea, cholera, dengue, malaria, and acute respiratory infections. Theron et al. (2022) reported outbreaks of infectious diseases in three disasters over the five years prior to publication, involving healthcare units. These results align with other studies (Silva et al., 2021; Fernandes et al., 2019) suggesting urgent attention to prepare health systems and professionals to deal with the health effects of climate change.

An important finding from post-hydrological disaster studies is that most transmissible infections arise among displaced populations living in inadequate shelters, overcrowded conditions, poor sanitation, and lack of access to food and potable water (Charnley et al., 2021; Liang and Messenger, 2018). Another public health issue highlighted by Patz, Grabow, and Limaye (2014) is mental health disorders, such as post-traumatic stress, which can substantially affect the well-being of populations displaced or affected by climate change.

Flood disasters can increase exposure to groundwater and overflow of sewage treatment systems in certain regions. The study by Newman et al. (2022) emphasizes the need to improve urban stormwater management and water quality through green infrastructure. Additionally, the authors highlight the importance of implementing green roofs and rain gardens in urban master plans to reduce risks and post-disaster impacts. Díaz-Delgado and Gaytán-Iniestra (2014) suggest establishing a database for flood forecasting and strengthening multidisciplinary, multisectoral teams responsible for finding practical solutions to flood disasters.

Tin et al. (2024) conducted a comprehensive study using an emergency events database covering all natural disasters from 1995 to 2022, totaling 11,360 natural disasters with an average of 398 per year. Asia recorded the highest number of disasters (4,390) and the highest number of victims (918,198). Hydrological disasters were the most common

subgroup (4,969). The main causes of increased flood risk in Asia are related to climate change and uncontrolled urbanization, and their impact can be reduced by risk mapping to accurately predict potential areas (Manandhar et al., 2023).

Lamberti-Castronuovo et al. (2022) claim to have conducted the first systematic review proposing a framework for disaster preparedness in Primary Health Care (PHC). The research lays the foundation for practical recommendations to assess and improve PHC disaster preparedness. Preparedness characteristics cited include policy planning, unified disaster management strategy, continuity of care, integration of routine services with emergency services, community-level disaster preparedness strategies, and vulnerability assessment during the preparation phase. According to the authors, each PHC facility should adopt a disaster response plan, with multidisciplinary collaboration fundamental to building optimal preparedness strategies, along with appropriate medical and laboratory equipment and supplies.

Despite the limited number of studies associating health with hydrological natural disasters, it was possible to outline an overview of publications on the topic. With climate change driven by increasing anthropogenic impacts each year, studies relating environmental health are increasingly necessary. Therefore, future research on this subject should be encouraged, especially focusing on the preparedness of health systems and professionals in planning, managing, and responding to natural disasters, which will become more frequent worldwide.

4 CONCLUSION

In the search for a relationship between hydrological disasters and health, it was found that the prevalence of infectious diseases following such disasters is a recurrent and relevant theme in the literature. Disasters can act as facilitators for a range of diseases that are of major concern in public health.

The impacts of flood disasters and the mitigation of risks to affected populations were the second most recurrent theme in the literature. This highlights the need for strategic measures to reduce the damage caused by floods. Fatalities (mortality) as a consequence of floods were also addressed, along with the classification and occurrence of different types of disasters.

The preparedness of primary healthcare professionals to face disasters was also discussed, presenting strategies for training and effective response in critical scenarios.

In summary, it is possible to observe that the review gathered, although in an isolated manner, causes, consequences, and potential solutions for mitigating the impact of

hydrological disasters. This reinforces the urgent need to integrate and compile this relevant information for various sectors that have been experiencing considerable losses due to hydrological disasters. There is also a need for comprehensive frameworks that can encompass all these themes to produce more technical outcomes that can serve as a basis for public managers' actions.

However, the review results indicated that international scientific collaboration has succeeded in highlighting the necessity for broader and multidisciplinary efforts capable of contributing to the formulation of public policies and more effective international partnerships, the preparation of managers and health professionals, and the development of plans, research, and interventions related to health and hydrological disasters.

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THERAPEUTIC ALTERNATIVES IN HYPERTENSIVE PATIENTS INTOLERANT TO ACE INHIBITORS/ARBs: A LITERATURE REVIEW

ALTERNATIVAS TERAPÊUTICAS EM PACIENTES HIPERTENSOS COM INTOLERÂNCIA À IECA/BRA: UMA REVISÃO DA LITERATURA

ALTERNATIVAS TERAPÉUTICAS EN PACIENTES HIPERTENSOS INTOLERANTES A LOS INHIBIDORES DE LA ECA/ARA II: UNA REVISIÓN DE LA LITERATURA



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ABSTRACT

Systemic arterial hypertension (SAH) is a chronic multifactorial condition clinically defined by elevated blood pressure levels (SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg). SAH is classified into stage 1 (SBP 130-139 mmHg and/or DBP 80-89 mmHg) and stage 2 (SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg). Treatment of SAH is multifactorial and includes both pharmacological and non-pharmacological therapy.^{1,2} The main drug classes include thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs). Some patients develop adverse drug reactions and require alternative therapies.⁴ Intolerance to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) can be defined as the occurrence of clinically relevant adverse effects that prevent the safe and continuous maintenance of these therapies, requiring their definitive discontinuation. In the case of ACE inhibitors, the events most frequently associated with intolerance include persistent dry cough and angioedema, both largely related to bradykinin accumulation resulting from angiotensin-converting enzyme inhibition. Other manifestations, such as significant hyperkalemia and deterioration of renal function, may also limit the use of this class, especially in patients with associated comorbidities. Although ARBs have a lower incidence of these adverse effects because they do not interfere with bradykinin degradation, cases of intolerance, including angioedema, have been described, suggesting the possibility,

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albeit rare, of cross-reactivity between these pharmacological classes. Therefore, identifying intolerance requires careful clinical evaluation, since its presence directly influences the choice of therapy and the appropriate management of systemic arterial hypertension.

Keywords: Intolerance. Therapeutic Alternatives. Angiotensin-Converting Enzyme Inhibitors. Angiotensin II Receptor Blockers.

RESUMO

A hipertensão arterial sistêmica (HAS) é uma condição crônica multifatorial definida clinicamente por níveis pressóricos elevados (PAS $\geq$ 130 mmHg e/ou PAD $\geq$ 80 mmHg). A HAS é classificada em estágio 1 (PAS 130-139 mmHg e/ou PAD 80-89 mmHg) e estágio 2 (PAS $\geq$ 140 mmHg e/ou PAD $\geq$ 90 mmHg). O tratamento da HAS é multifatorial e inclui terapia medicamentosa e não medicamentosa.^{1,2} As principais classes medicamentosas incluem diuréticos tiazídicos, inibidores da enzima conversora de angiotensina II (IECAs), bloqueadores dos receptores da angiotensina II (BRAs) e bloqueadores dos canais de cálcio (BCCs). Alguns pacientes desenvolvem reações adversas aos medicamentos e precisam de alternativas terapêuticas.⁴ A intolerância aos inibidores da enzima conversora de angiotensina (IECA) e aos bloqueadores dos receptores da angiotensina II (BRA) pode ser definida como a ocorrência de efeitos adversos clinicamente relevantes que impedem a manutenção segura e contínua dessas terapias, exigindo sua suspensão definitiva. No caso dos IECA, os eventos mais frequentemente associados à intolerância incluem tosse seca persistente e angioedema, ambos relacionados, em grande parte, ao acúmulo de bradicinina decorrente da inibição da enzima conversora de angiotensina. Outras manifestações, como hipercalemia significativa e deterioração da função renal, também podem limitar o uso dessa classe, especialmente em pacientes com comorbidades associadas. Embora os BRA apresentem menor incidência desses efeitos adversos por não interferirem na degradação da bradicinina, casos de intolerância, incluindo angioedema, foram descritos, sugerindo a possibilidade, ainda que rara, de reação cruzada entre essas classes farmacológicas. Dessa forma, a identificação da intolerância requer avaliação clínica criteriosa, uma vez que sua presença influencia diretamente a escolha terapêutica e o manejo adequado da hipertensão arterial sistêmica.

Palavras-chave: Intolerância. Alternativas Terapêuticas. Inibidores da Enzima Conversora de Angiotensina. Bloqueadores dos Receptores de Angiotensina II.

RESUMEN

La hipertensión arterial sistémica (HAS) es una afección crónica multifactorial definida clínicamente por niveles elevados de presión arterial (PAS $\geq$ 130 mmHg y/o PAD $\geq$ 80 mmHg). La HAS se clasifica en estadio 1 (PAS 130-139 mmHg y/o PAD 80-89 mmHg) y estadio 2 (PAS $\geq$ 140 mmHg y/o PAD $\geq$ 90 mmHg). El tratamiento de la HAS es multifactorial e incluye terapia farmacológica y no farmacológica.^{1,2} Las principales clases de fármacos incluyen diuréticos tiazídicos, inhibidores de la enzima convertidora de angiotensina (IECA), bloqueadores de los receptores de angiotensina II (ARA II) y bloqueadores de los canales de calcio (BCC). Algunos pacientes desarrollan reacciones adversas a los medicamentos y requieren terapias alternativas.⁴ La intolerancia a los inhibidores de la enzima convertidora de angiotensina (IECA) y a los bloqueadores de los receptores de angiotensina II (ARA II) se define como la aparición de efectos adversos clínicamente relevantes que impiden el mantenimiento seguro y continuo de estas terapias, lo que requiere su interrupción definitiva. En el caso de los IECA, los eventos más frecuentemente asociados con la intolerancia incluyen tos seca persistente y angioedema, ambos relacionados en gran medida con la acumulación de bradicinina resultante de la inhibición de la enzima convertidora de angiotensina. Otras manifestaciones, como hiperpotasemia significativa y deterioro de la función renal, también pueden limitar el

uso de esta clase, especialmente en pacientes con comorbilidades asociadas. Aunque los ARA II tienen una menor incidencia de estos efectos adversos porque no interfieren con la degradación de la bradisinina, se han descrito casos de intolerancia, incluido el angioedema, lo que sugiere la posibilidad, aunque rara, de reactividad cruzada entre estas clases farmacológicas. Por lo tanto, la identificación de la intolerancia requiere una evaluación clínica cuidadosa, ya que su presencia influye directamente en la elección del tratamiento y en el manejo adecuado de la hipertensión arterial sistémica.

Palabras clave: Intolerancia. Alternativas Terapéuticas. Inhibidores de la Enzima Convertidora de Angiotensina. Bloqueadores de los Receptores de Angiotensina II.

1 INTRODUCTION

Systemic arterial hypertension (SAH) is a chronic condition, characterized by elevated systolic blood pressure (SBP ≥ 130 mmHg) and/or diastolic blood pressure (DBP ≥ 80 mmHg). The European Society of Hypertension defined high blood pressure as SBP ≥ 120 -129 mmHg and PAD < 80 mmHg, while SAH would have two stages; stage 1: SBP from 130 mmHg with a maximum value of 139 mmHg and DBP from 80 mmHg and a maximum value of 89 mmHg; stage 2: SBP equal to or greater than 140 mmHg and DBP equal to or greater than 90 mmHg.^{1,3}

SAH is a multifactorial condition, which depends on genetic/epigenetic, environmental, and social factors, and is the main modifiable risk factor with independent, linear, and continuous association for cardiovascular diseases (CVD), chronic kidney disease (CKD), and premature death.^{1,2}

SAH presents as risk factors for its development the use of cigarettes, obesity or overweight, DM2 and chronic kidney disease. Its main long-term complications are: coronary heart disease, atherosclerosis, peripheral vascular disease, renal dysfunction, ischemic and hemorrhagic stroke, dementia and cognitive deficit.³

To confirm the diagnosis of hypertension, it is necessary to collect a complete clinical history, physical examination, laboratory tests such as blood count, serum electrolytes, serum creatinine, lipid profile, glucose or hemoglobin A1c [HbA1c], thyroid-stimulating hormone, urinalysis, albumin/creatinine ratio in the urine, and diagnostic procedures such as 12-lead ECG. This approach aims to exclude secondary causes of SAH and identify potential end-organ damage.³

The treatment of SAH is multifactorial and includes non-pharmacological and pharmacological treatment. The first consists of weight loss for overweight and obese patients, physical activity, implementation of the DASH diet, reduction of sodium intake, potassium replacement, except for patients with CKD or patients who use potassium-sparing medications, reduction of alcohol consumption, meditation to reduce stress.²

Pharmacological treatment is recommended from stage 2 onwards (SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg) in order to reduce cardiovascular risk and mortality. Other indications include patients with SAH, regardless of stage, and with cardiovascular disease should start medications to reduce blood pressure levels. The objective of this therapy is to reduce morbidity and mortality by reducing BP followed by reducing cardiovascular outcomes such as AMI, STROKE, CAD, and CKD.⁸

Major drug classes include thiazide diuretics, angiotensin-converting enzyme II inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and calcium channel

blockers (CCBs). The use of beta-blockers is reserved for clinical conditions such as coronary syndromes (post-AMI and angina), with a history of AF, heart failure with reduced ejection fraction (HFrEF), and in women who wish to become pregnant.^{4,8}

Studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are fundamental pillars in the treatment of systemic arterial hypertension, not only for the effective control of blood pressure levels, but also for the proven reduction of cardiovascular and renal morbidity and mortality. These pharmacological classes are associated with a decrease in the incidence of major cardiovascular events, such as acute myocardial infarction, stroke, progression of chronic kidney disease, and mortality from cardiovascular causes, which justifies their recommendation as first-line therapies in national and international guidelines.^{6,8}

Angiotensin-converting enzyme II inhibitors act on the renin-angiotensin system. Juxtaglomerular cells present in afferent arterioles produce and secrete renin in response to decreased blood pressure identified by baroreceptors. Renin, in turn, acts on the liver by stimulating the production of angiotensin I. Angiotensin-converting enzyme (ACE) is essential for this system, as it converts angiotensin I into angiotensin II, which exerts multiple physiological effects, leading to an increase in systemic blood pressure. ACE inhibitors inhibit ACE and, therefore, block the conversion of angiotensin I into angiotensin II, preventing the hypertensive effects of angiotensin II.⁸

Similar to angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs) play a central role in the treatment of systemic arterial hypertension. These drugs act by selectively blocking AT1 receptors of angiotensin II, preventing its vasoconstrictive, pro-inflammatory, and hydrosaline retention effects, which results in reduced peripheral vascular resistance, decreased aldosterone secretion, and favorable effects on cardiovascular and renal remodeling.⁸

Intolerance to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) can be defined as the occurrence of clinically relevant adverse effects that prevent the safe and continuous maintenance of these therapies, requiring their definitive discontinuation.⁶

ACE inhibitors have some adverse effects that can be classified as physiological and non-physiological. Among the physiological aspects, hypotension, reduced glomerular filtration rate (GFR), hyperkalemia, and contraindication during pregnancy due to the risk of fetal ischemia due to decreased fetoplacental blood flow stand out.

Non-physiological side effects include cough, angioedema, and anemia. The cough is dry and is due to the increase in bradykinin and other vasoactive peptides such as Substance

P, which can play a role as a second messenger in triggering the cough reflex and to be sure that the symptom is caused by the medication one should discontinue the medication and reassess the patient after a few weeks.⁶

Angioedema is potentially life-threatening and may initially present with nonspecific oral, lingual, and lip symptoms that are often attributed to concomitant food or other medications. Angioedema can be explained because ACE, also known as kininase II, is additionally responsible for the degradation of bradykinin. Bradykinin is generated from the high molecular weight kininogen by kallikrein. Through bradykinin 2 receptors, bradykinin affects vascular permeability and stimulates the release of substance P, a peptide that causes vasodilation and extravasation of fluids into the tissues. Therefore, blockade of bradykinin degradation is a likely explanation for ACE inhibitor-induced angioedema. Angioedema can be effectively controlled in the long term with simple discontinuation of the offending ACE inhibitor.¹

Anemia caused by the use of ACE inhibitors is due to the suppression of erythropoietin in a dose-dependent manner, related to the accumulation of N-acetyl-seryl-aspartyl-lysyl-proline, a substance acting as a potent natural inhibitor of hematopoietic stem cell proliferation, as well as an antifibrotic moiety, which is degraded mainly by ACE.⁹

Physiological side effects with an ACE inhibitor may be correctable and often allow medication to be restarted in more controlled and assisted circumstances. Non-physiological side effects are unpredictable in their occurrence and may go unnoticed; however, when recognized, the decision to discontinue an ACE inhibitor should be considered.⁹

Several studies have shown that ARBs have efficacy similar to that of ACE inhibitors in reducing blood pressure levels and preventing adverse cardiovascular and renal outcomes, including acute myocardial infarction, stroke, and progression of chronic kidney disease. Because of these benefits, this class is widely recommended as first-line therapy in national and international guidelines, especially in patients with diabetes mellitus, diabetic nephropathy, heart failure, or ACE inhibitor intolerance.⁸

A relevant characteristic of ARBs is the fact that they do not interfere with the degradation of bradykinin, unlike ACE inhibitors, which explains the lower incidence of adverse effects such as dry cough and angioedema. This pharmacological difference makes ARBs a particularly important therapeutic alternative in patients who develop persistent cough associated with ACE inhibitors. However, although uncommon, there are reports of cross-intolerance, especially in patients with a history of ACE inhibitor-induced angioedema, in which case the prescription of ARBs should be performed with caution and adequate clinical monitoring (BAS et al., 2015; KOSTIS et al., 2018).

However, the use of ACE inhibitors and ARBs may be limited by the occurrence of adverse effects that constitute intolerance to treatment. Intolerance is characterized by the inability to maintain continuous use of the drug due to clinically relevant adverse reactions, such as persistent cough, angioedema, significant hyperkalemia, or deterioration of renal function, which make it necessary to permanently suspend the medication (KOSTIS et al., 2018; BAS et al., 2015). Although ARBs have a lower incidence of bradykinin-related adverse effects when compared to ACE inhibitors, the possibility of cross-intolerance, especially in the context of angioedema, should be considered (BROWN et al., 2017).

The presence of intolerance to ACE inhibitors and/or ARBs represents a significant challenge in the management of hypertension, particularly in patients with resistant hypertension or with multiple cardiovascular and renal comorbidities. The impossibility of using these classes can compromise adequate blood pressure control and limit access to therapies with proven prognostic benefit, resulting in a higher risk of adverse cardiovascular events and progression of target organ damage.^{6,8}

In view of this scenario, it is essential to identify and understand effective and safe therapeutic alternatives for hypertensive patients who do not tolerate ACE inhibitors or ARBs. The choice of substitute pharmacologic strategies should consider not only the efficacy in lowering blood pressure, but also the safety profile, associated comorbidities, and the potential impact on cardiovascular and renal outcomes.⁴

Thus, the objective of this study is to analyze the main therapeutic alternatives available for the treatment of systemic arterial hypertension in patients with intolerance to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, emphasizing their clinical applicability, efficacy and limitations, in the light of current scientific evidence.

2 METHODOLOGY

The present study is a literature review, in which 15 articles published between January 2010 and September 2025 were selected. The materials used for the preparation of the article were found using the descriptors: "ACE inhibitors" OR "ARB") AND ("intolerance" OR "adverse effects") AND ("therapy alternatives" OR "antihypertensive") with the Boolean operator "and". The databases consulted included PubMed, SciELO, LILACS, Cochrane, and Cochrane, which are recognized for their relevance and comprehensiveness in the scientific literature. The inclusion criteria defined for this review were: articles, systematic reviews, and clinical trials published in the period between 2010 and 2025; guidelines published in the last 5 years. The exclusion criteria were: studies that were not available in English, Portuguese and Spanish; articles, systematic reviews and clinical trials published

more than 15 years ago; guidelines published more than 5 years ago; non-systematic reviews or personal opinions that did not present substantial empirical data.

3 RESULTS

In hypertensive patients with intolerance to ACE inhibitors, especially those with persistent cough or angioedema, angiotensin II receptor blockers (ARBs) represent the main therapeutic alternative, since they maintain the blockade of the renin-angiotensin-aldosterone system (RAAS) and have a lower risk of bradykinin-related adverse effects.^{1,2} However, in cases of previous severe angioedema, caution is recommended in the use of ARBs due to the possibility of cross-reaction.³

When ARBs are not sufficient to achieve the blood pressure goal or are contraindicated, other antihypertensive classes can be employed. Calcium channel blockers (CCBs), such as amlodipine, promote arterial vasodilation by inhibiting L-type calcium channels in smooth muscle cells, reducing afterload and blood pressure. They are particularly effective in isolated systolic hypertension and in the elderly, with a mean reduction of 8–15 mmHg in systolic pressure and 5–10 mmHg in diastolic pressure, and are well tolerated, although dose-dependent peripheral edema and headache may occur.^{4,11,12} Non-dihydropyridine CCBs, such as diltiazem, may be useful when an additional effect on heart rate is desired.

Beta-blockers, such as carvedilol, bisoprolol, and metoprolol, block cardiac β_1 and vascular β_2 receptors, reducing heart rate, contractility, and plasma renin activity. They are indicated preferentially in patients with coronary heart disease, heart failure, or arrhythmias, presenting modest reduction in blood pressure and potential worsening of insulin resistance, fatigue, and bradycardia as adverse effects.^{5,14} For this reason, they are not considered first-line in isolation in essential hypertension.

Diuretics, especially thiazides such as hydrochlorothiazide, chlorthalidone, and indapamide, increase renal excretion of sodium and water, decreasing intravascular volume and blood pressure, with an average reduction of 10/5 mmHg, in addition to preventing cardiovascular events. Spironolactone, a mineralocorticoid antagonist, has been shown to be effective in resistant hypertension, but requires monitoring of potassium and renal function due to the risk of hyperkalemia and gynecomastia^{6,7}. Alpha-blockers, such as doxazosin and prazosin, promote arteriolar and venous vasodilation by blocking α_1 adrenergic receptors, and are useful especially when there is associated prostatic hyperplasia, but they present a risk of postural hypotension and are not recommended as first-line monotherapy⁸.

Among the emerging therapies, the direct renin inhibitor aliskiren has shown efficacy in reducing blood pressure, but studies such as ALTITUDE have shown an increase in renal and cardiovascular events in high-risk diabetic patients when combined with ACE inhibitors or ARBs, limiting its clinical use and availability⁹. Sacubitril/valsartan (ARNI) combines AT1 receptor blockade with neprilysin inhibition, promoting vasodilation and natriuresis, and has demonstrated significant reduction in mortality and hospitalizations in patients with heart failure with reduced ejection fraction. Its use in isolated hypertension is limited, and a washout period of at least 36 hours after ACE inhibitors should be respected due to the risk of angioedema.¹⁰ The combination of hydralazine associated with nitrate, although little used in primary hypertension, has a benefit in black patients with symptomatic heart failure, reducing mortality and improving functional capacity, but its use is limited by headache, hypotension, and the need for multiple daily doses.¹¹

In addition to pharmacologic therapies, nonpharmacologic interventions remain essential in the management of hypertension. Reducing salt intake to less than 5 g/day is associated with a significant drop in blood pressure, especially in sodium-sensitive individuals.¹² Even modest weight loss (5–10% of body weight) can reduce systolic pressure by approximately 5 mmHg.¹² Regular physical activity, combining aerobic exercise (150–300 minutes per week) and twice-weekly resistance training, improves blood pressure, insulin sensitivity, and lipid profile.¹³ Diets proven to be cardioprotective, such as DASH and Mediterranean, also contribute to further blood pressure reduction and favorable metabolic effects.¹⁴ Finally, strict control of comorbidities, including diabetes mellitus and dyslipidemia, is crucial for the prevention of cardiovascular events and progression of end-organ damage.¹⁵

The management of hypertension in patients with ACE inhibitor intolerance should be individualized, considering the severity of the adverse reaction, associated comorbidities, availability and cost of medications, as well as adherence to nonpharmacological interventions. The integration of these strategies allows optimizing blood pressure control, reducing cardiovascular events, and improving the patient's overall prognosis.

4 DISCUSSION

Intolerance to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers has a great impact on the management of hypertension, especially in patients with resistant hypertension, chronic kidney disease, and high cardiovascular risk. These classes are the main ones used for the treatment of arterial hypertension because they are highly effective in reducing blood pressure, they are considered nephroprotective and

cardioprotective. The outcome of adverse effects limits the use of such classes and requires the implementation of alternative therapeutic strategies.

Regarding ACE inhibitor intolerance, especially patients with persistent dry cough, angiotensin II receptor blockers (ARBs) are the main alternative therapeutic drug class, as they have a lower risk of adverse effects related to bradykinin.^{1,2} However, for patients who have had previous cases of severe angioedema, the use of ARBs should be reconsidered due to the possibility of cross-reaction.

Intolerance to ACE inhibitors or ARBs may be temporary, especially in cases of cough associated with the use of ACE inhibitors, which may regress after prolonged suspension. Recent guidelines highlight the importance of periodic clinical reassessment of drug tolerability, allowing, in selected situations, the cautious reintroduction of ARBs or the optimization of the therapeutic regimen. This dynamic approach avoids the definitive exclusion of classes with proven prognostic benefit and contributes to a more flexible and rational management of hypertension over time (HU et al., 2023; BRUNSTRÖM et al., 2023).

Other drug classes become essential when there are cases of adverse events and when blood pressure targets are not being achieved through the use of ACE inhibitors and ARBs. Calcium channel blockers, especially dihydropyridines such as amlodipine, have demonstrated high efficacy in lowering blood pressure, with particular benefit in the elderly and in patients with isolated systolic hypertension. However, the main adverse effect related to this class is dose-dependent peripheral edema. During this clinic, another antihypertensive class can be chosen. Non-dihydropyridine blockers, such as diltiazem, may be useful in situations that require additional heart rate control.

Thiazide diuretics are an essential class for the management of hypertension and should be used mainly for patients with a history of cardiovascular events, such as acute myocardial infarction (AMI) due to reduced cardiovascular events and morbidity and mortality.

In addition, this class has additional benefits in the prevention of heart failure and is recommended as first-line therapy by international guidelines, especially in the elderly, black patients, and individuals with salt-sensitive hypertension^{2,4}. Chlorthalidone stands out for its greater potency and duration of action compared to hydrochlorothiazide, being associated with better cardiovascular outcomes in comparative analyses³. Despite the potential metabolic adverse effects, such as electrolyte disturbances, hyperuricemia, and glucose intolerance, the use in low to moderate doses, combined with adequate clinical monitoring, maintains thiazide diuretics as a safe, effective, and cost-effective option in the treatment of

arterial hypertension, especially in scenarios of intolerance to blockers of the renin-angiotensin-aldosterone system ^{4,5}.

Another relevant aspect is the differential impact of antihypertensive classes on cardiac and vascular remodeling. Evidence from studies with echocardiography and cardiac magnetic resonance imaging indicates that some therapies have a greater effect on the regression of left ventricular hypertrophy and the improvement of arterial compliance. Thiazide diuretics and renin-angiotensin antagonists demonstrate significant structural benefits, while older generation beta-blockers appear less effective in this regard. Regression of left ventricular hypertrophy is strongly associated with a reduction in cardiovascular mortality, regardless of the absolute reduction in blood pressure (Thais et al., 2025; PÓVOA, Fernando Focaccia, 2019).

Mineralocorticoid antagonists, the main example being spironolactone, stand out in the treatment of resistant hypertension. Spironolactone binds to aldosterone receptors in the renal tubules promoting greater elimination of water and sodium by the kidneys. However, it prevents potassium loss, being a potassium sparing. Its use requires close monitoring of renal function and serum potassium levels due to the risk of hyperkalaemia. Mineralocorticoid antagonists may be an alternative for the treatment of hypertension, especially in hypertensive patients with significant edema, congestive heart failure, and ascites.^{1,4}

Beta-blockers block adrenaline and noradrenaline receptors. They reduce heart rate, cardiac output and blood pressure. They can be non-selective, selective, and third-generation. Non-selective receptors, also called first generation, block beta-1 and beta-2 receptors, the main example being propranolol. The selective, second-generation ones have a greater affinity for beta-1, and atenolol and metoprolol belong to this division. Third-generation drugs have greater vasodilator action, with carvedilol and nebivolol being the main drugs. This class is an alternative for patients with ACEI/ARB intolerance, and is mainly indicated for hypertensive patients with arrhythmia, coronary artery disease, heart failure, and post-AMI. They are not recommended as first-line monotherapy in essential hypertension, but they play an important role in hypertensive patients with coronary artery disease, heart failure, or arrhythmias, especially when associated with other pharmacological classes.⁵

Among the less conventional therapies is aliskiren, a direct renin inhibitor. It acts by blocking the onset of the Renin-Angiotensin-Aldosterone System (RAAS), consequently reducing the formation of angiotensin I and II, vasoconstrictor substances. It has a vasodilator action and provides a decrease in blood pressure. It can be used in

monothematic or in combination with other classes. Studies have shown no additional benefit in cardiovascular outcomes and an increase in renal adverse events when associated with ACE inhibitors or ARBs in high-risk patients, restricting their use.² The combination with hydralazine and nitrates has proven benefit in black patients with heart failure, with reduced mortality and functional improvement, but its use in primary hypertension is limited by lower tolerability and the need for multiple daily administrations.¹

Sacubitril/valsartan, an angiotensin-neprisin receptor inhibitor, works by promoting vasodilation and reducing fluid retention. It has a significant impact on reducing mortality and hospitalizations in patients with heart failure with reduced ejection fraction. However, its treatment as monotherapy for hypertensive patients is still limited. In addition, it has an intense drug interaction with ACE inhibitors because it aggravates cough and angioedema, causes hypotension and hyperkalemia, and the washout period after the use of ACE inhibitors should be respected.⁴

Additionally, recent evidence indicates that emerging cardiometabolic therapies, such as sodium-glucose cotransporter ² (SGLT2) inhibitors, block the reabsorption of sodium and glucose by the kidneys. The urine becomes more concentrated and, consequently, there is greater loss of fluids through the urine, which is favorable for hypertensive patients due to volume depletion. These are drugs that exert favorable effects on blood pressure, in addition to promoting cardiovascular and renal protection in patients with type 2 diabetes mellitus. Although they are not indicated as primary antihypertensive agents, these drugs can contribute to blood pressure control and the reduction of overall cardiovascular risk in specific populations, such as hypertensive and diabetic patients, especially when there is a limitation to the use of ACE inhibitors or ARBs.^{7,14}

Non-pharmacological interventions remain fundamental in the management of hypertension, with a significant impact on BP reduction and the prevention of cardiovascular events. Measures such as sodium consumption restriction, weight loss, regular physical activity, and strict control of metabolic comorbidities enhance the effects of pharmacological treatment and can reduce the need for multiple antihypertensive drugs.⁴

Shared decision-making has been recognized as a central element in the contemporary management of hypertension, especially in patients with drug intolerance and multiple comorbidities. Recent guidelines highlight that the therapeutic choice should consider not only the efficacy in reducing blood pressure, but also the profile of adverse effects, patient preferences, impact on quality of life, and adherence to treatment.^{3,8} Evidence indicates that patient-centered approaches are associated with greater therapeutic persistence and better blood pressure control, reducing clinical inertia and treatment

abandonment (MARTELL CLAROS, N., 2023). Thus, shared decision-making is a fundamental strategy to optimize clinical outcomes and the effectiveness of antihypertensive treatment.

Thus, the management of arterial hypertension in patients with intolerance to ACE inhibitors and/or ARBs should be individualized, considering the clinical profile, associated comorbidities, cardiovascular risk, and therapeutic availability. The rational choice of pharmacological alternatives, associated with non-pharmacological measures and, when indicated, the use of adjuvant cardiometabolic therapies, allows optimizing blood pressure control and reducing adverse cardiovascular and renal outcomes.

5 CONCLUSION

The findings discussed throughout this study demonstrate that the management of arterial hypertension in patients with intolerance to angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers requires an expanded, dynamic, and individualized therapeutic approach, since these classes play a central role in cardiovascular and renal protection. In these situations, it is essential to carefully select alternative therapies that ensure adequate blood pressure control without compromising patient safety.

The choice of therapeutic regimen should be individualized, considering associated comorbidities, overall cardiovascular risk, adverse effect profile, and impact on treatment adherence. Periodic reassessment of drug tolerability, associated with shared decision-making, contributes to greater therapeutic persistence, better blood pressure control, and reduction of adverse cardiovascular outcomes.

Despite the limitations of the available evidence for populations intolerant to blockade of the renin-angiotensin-aldosterone system, integration between pharmacological and non-pharmacological strategies remains critical. This approach allows optimizing the management of hypertension in a safe, effective, and sustainable way, in line with contemporary recommendations and patient-centered clinical practice.

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CHILD FOOD EDUCATION: ASSESSMENT OF DIETARY PROFILE AND PLAYFUL STRATEGIES FOR THE PROMOTION OF HEALTHY HABITS WITH CHILDREN FROM COMMUNITIES IN RECIFE

EDUCAÇÃO ALIMENTAR INFANTIL: AVALIAÇÃO DO PERFIL ALIMENTAR E ESTRATÉGIAS LÚDICAS PARA A PROMOÇÃO DE HÁBITOS SAUDÁVEIS COM CRIANÇAS DE COMUNIDADES DO RECIFE

EDUCACIÓN ALIMENTARIA INFANTIL: EVALUACIÓN DEL PERFIL ALIMENTARIO Y ESTRATEGIAS LÚDICAS PARA LA PROMOCIÓN DE HÁBITOS SALUDABLES CON NIÑOS DE COMUNIDADES DE RECIFE



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ABSTRACT

The increase in childhood obesity in Brazil has raised concerns, especially in vulnerable communities, where factors such as low educational levels, limited access to healthy foods, and cultural habits hinder the promotion of nutritional health. In this context, playful educational activities have proven effective in engaging children in learning about healthy eating from an early age. This project aimed to evaluate the knowledge of children aged 7 to 12 years regarding healthy eating habits and to promote awareness through interactive workshops. The activity was carried out in December 2024 with 23 children from communities near the Federal Rural University of Pernambuco, conducted by Nursing students from UNINASSAU Recife Caxangá. Diagnostic questionnaires, thematic presentations, games ("true or false" and "food memory"), sensory dynamics, a final quiz, and the distribution of educational materials were applied. The questionnaire results showed that the children have a high consumption of ultra-processed foods and a low intake of fruits and vegetables. The playful strategies promoted greater engagement and understanding among the children regarding healthy eating, especially in the correct identification of natural and processed foods. The experience also contributed to the training of the extension students and reinforced the role of the university as an agent of social transformation.

Keywords: Food Education. University Extension. Childhood Obesity. Health Promotion. Healthy Eating.

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RESUMO

O aumento da obesidade infantil no Brasil tem gerado preocupação, especialmente em comunidades vulneráveis, onde fatores como baixa escolaridade, acesso limitado a alimentos saudáveis e hábitos culturais dificultam a promoção da saúde nutricional. Nesse contexto, ações educativas lúdicas mostram-se eficazes para envolver crianças no aprendizado sobre alimentação saudável desde os primeiros anos. Este projeto teve como objetivo avaliar o conhecimento de crianças de 7 a 12 anos sobre hábitos alimentares saudáveis e promover a conscientização por meio de oficinas interativas. A atividade foi realizada em dezembro de 2024 com 23 crianças de comunidades próximas à Universidade Federal Rural de Pernambuco, conduzida por alunos do curso de Enfermagem da UNINASSAU Recife Caxangá. Foram aplicados questionários diagnósticos, apresentação da temática, jogos (“verdadeiro ou falso” e “memória alimentar”), dinâmicas sensoriais, quiz final e distribuição de material educativo. Os resultados do questionário mostraram que as crianças têm alto consumo de alimentos ultraprocessados e baixa ingestão de frutas e vegetais. As estratégias lúdicas promoveram maior engajamento e entendimento das crianças sobre alimentação saudável, com destaque para a identificação correta de alimentos naturais e industrializados. A experiência também contribuiu para a formação dos extensionistas e reforçou o papel da universidade como agente de transformação social.

Palavras-chave: Educação Alimentar. Extensão Universitária. Obesidade Infantil. Promoção da Saúde. Alimentação Saudável.

RESUMEN

El aumento de la obesidad infantil en Brasil ha generado preocupación, especialmente en comunidades vulnerables, donde factores como el bajo nivel educativo, el acceso limitado a alimentos saludables y los hábitos culturales dificultan la promoción de la salud nutricional. En este contexto, las acciones educativas lúdicas se muestran eficaces para involucrar a los niños en el aprendizaje sobre alimentación saludable desde los primeros años. Este proyecto tuvo como objetivo evaluar el conocimiento de niños de 7 a 12 años sobre hábitos alimentarios saludables y promover la concientización mediante talleres interactivos. La actividad se realizó en diciembre de 2024 con 23 niños de comunidades cercanas a la Universidade Federal Rural de Pernambuco, llevada a cabo por estudiantes del curso de Enfermería de UNINASSAU Recife Caxangá. Se aplicaron cuestionarios diagnósticos, presentación de la temática, juegos (“verdadero o falso” y “memoria alimentaria”), dinámicas sensoriales, un cuestionario final y distribución de material educativo. Los resultados del cuestionario mostraron que los niños tienen un alto consumo de alimentos ultraprocesados y una baja ingesta de frutas y vegetales. Las estrategias lúdicas promovieron un mayor compromiso y comprensión de los niños sobre la alimentación saludable, destacándose la correcta identificación de alimentos naturales e industrializados. La experiencia también contribuyó a la formación de los extensionistas y reforzó el papel de la universidad como agente de transformación social.

Palabras clave: Educación Alimentaria. Extensión Universitaria. Obesidad Infantil. Promoción de la Salud. Alimentación Saludable.

1 INTRODUCTION

According to the study carried out by the Observatory of Childhood Health, data released at the end of 2023 showed that Brazil has almost 3 times more overweight children (such as overweight and obesity), compared to the global average. Thus, it is notorious that diseases that were previously more common in adults, such as diabetes, had an aggravating increase in children during the COVID-19 pandemic period, between 2019 and 2021.

Healthy eating in childhood is essential to ensure the proper growth and development of children, in addition to contributing to the prevention of chronic diseases throughout life. Understanding the concept of healthy eating in this period is essential to guide balanced eating practices from the first years of life. A diet rich in fruits, vegetables, grains and quality proteins contributes to physical and mental development, strengthening the daily disposition. However, for a large part of the population in poverty, this dietary pattern is still a privilege. According to Müller et al. (2025), the difficulty in accessing healthy foods compromises the construction of adequate eating habits, especially in childhood, which can perpetuate inequalities throughout life. Complementing this panorama, a study by Fiocruz revealed that factors such as low education, precarious housing conditions, and consolidated cultural habits hinder the adoption of healthy eating practices in primary care services, increasing the challenges of health promotion in vulnerable communities (Silva et al., 2016).

In this context, public health promotion policies play a decisive role. Programs such as the National School Feeding Program (PNAE), the Unified Health System (SUS) and the Family Health Strategy act directly to guarantee the right to adequate food and nutritional education for families, especially in the most vulnerable communities.

In addition, according to scientific studies by the Pan American Health Organization (PAHO) on the role of nursing in Primary Care and in the Family Health Strategy (FHS), professionals in the area have made a difference in the promotion of child health, through constructive dialogical attitudes that prepare parents and families to have skills in the comprehensive care of children. Therefore, this care model aims to ensure health education on a continuous basis, through community actions to help prevent diseases and injuries, such as hypertension and diabetes, which are treated by nurses.

The application of playful methodologies in early childhood education has proven to be an effective tool to involve children in the learning process about healthy habits. Through games, stories and interactive activities, it is possible to raise awareness and educate the little ones about the importance of a nutritious and balanced diet. Activities such as children's culinary workshops, where students participate in the preparation of healthy snacks, allow direct contact with food and arouse interest in new flavors. Educational games such as "food

bingo", "food memory" and "food wheel" help to fix knowledge in a fun way. Other strategies include storytelling with characters that encourage healthy choices, puppet theaters that address the importance of fruits and vegetables, and the use of themed drawings and music. These methodologies favor not only learning, but also the change in eating behavior from childhood.

Given this, it is of fundamental relevance to take care of one's health from childhood to have a healthy growth. It is worth mentioning that university extension activities are important, as they show that the learning obtained in the nursing undergraduate course goes far beyond patient care in the hospital environment, as this training can also be used as a tool for social transformation, which can help promote the quality of life of society by providing health guidance. Therefore, it can be seen that the performance of socio-educational actions can make children's eating habits healthier. Finally, the justification for the project is based on the urgent need to promote educational actions that strengthen knowledge about healthy eating from childhood, preventing future health problems, such as cases of obesity, diabetes, hypertension, and other chronic diseases among children, as evidenced by Soares et al. (2023), who point to a direct relationship between the increase in the prevalence of Chronic Non-Communicable Diseases (NCDs), and contributing to the formation of a more conscious and healthy generation. In view of the above, this article aims to assess the level of knowledge of children between 7 and 12 years old about healthy eating habits and to promote awareness through educational workshops.

2 MATERIAL AND METHODS

The action was developed at the Department of Consumer Sciences of the Federal Rural University of Pernambuco (UFRPE), carried out in December 2024, with 23 children (between 7 and 12 years old) from communities surrounding the academic community of UFRPE, through playful workshops with games and presentations. The action was taught by students from the health courses of UNINASSAU Recife Caxangá.

The present extension report was developed with participating children, whose legal guardians previously signed the Term of Authorization for Participation and Use of Image, ensuring agreement and awareness of the activities carried out. The project was conducted in accordance with the General Law for the Protection of Personal Data (Law No. 13,709/2018), ensuring the protection and confidentiality of the information collected, as well as the restricted use of the images for academic and scientific purposes. It is noteworthy that this is an extension project of an educational nature, without the involvement of additional risks to health, without collection of sensitive data or to the physical integrity of the

participants. Strict ethical principles were observed, in order to respect the dignity, privacy and rights of the children involved, in line with national regulations and the principles of ethics in research with human beings.

Initially, a bibliographic survey was carried out for the construction of the workshops, in a monographic bank, internet research, scientific journals and books, in addition to the search for materials for the elaboration of the dynamics. The topics addressed in the action, through a presentation with contextualized slides, were: healthy eating, food functions, healthy habits, quality of life and promotion of children's health.

To assess and promote children's knowledge about healthy eating, several educational strategies were adopted. Initially, a questionnaire (Figure 1) was applied with open and closed questions to identify the participants' previous knowledge.

Figure 1

Application of a questionnaire to the children to assess previous knowledge and eating habits



Source: Authors (2025).

At the beginning of the action, this questionnaire was applied with the objective of evaluating the children's eating habits. The questions address aspects such as: what they usually eat for breakfast, if they have the habit of consuming natural juice, vegetables and fruits, what is their favorite fruit and if they prefer fried foods or healthy foods. From the answers, it was possible to observe that most of the children had an inadequate eating pattern, with high consumption of processed foods, such as filled cookies and artificial juices.

Then, interactive presentations were made, with accessible language and attractive visual resources, followed by practical activities, a game of the senses (Figure 2), in which the blindfolded children tried to guess what the foods were through touch and smell, true or

false about eating habits, memory game of healthy habits (Figure 3) and finally, an evaluative quiz to verify the knowledge acquired. The children also received educational material in book format on the importance of fruit consumption (Figure 3), which reinforced the concepts worked on during the activities. All actions were planned to stimulate learning in a playful, participatory and reflective way.

Figure 2

Playful activity (game of the senses) developed with the children



Source: Authors (2025).

Figures 3

Playful activity (memory game about vitamins) and reading a textbook about healthy eating



Source: Authors (2025).

3 RESULTS AND DISCUSSION

The analysis of children's eating habits revealed that most opt for ultra-processed foods for breakfast, a pattern that has also been identified in other studies on children's eating behavior (Monteiro et al., 2019; Costa et al., 2021). However, after carrying out the educational activities, there was greater engagement and understanding of the importance of healthier food choices, which reinforces the relevance of extension actions as tools for social transformation (Silva et al., 2020).

Figure 4 shows that most children reported drinking water throughout the day, 10 children reported drinking water constantly and 11 reported drinking water a few times a day. This result is a positive indicator, since adequate water intake is essential for maintaining hydration and for the proper functioning of the body (Pearson et al., 2009; Popkin, D'Anci & Rosenberg, 2010). However, two children reported not consuming water regularly, signaling the need for continuous educational strategies to encourage this habit, either through school campaigns or through greater family involvement (Vargas et al., 2018).

Figure 4

Do you usually drink water during the day?



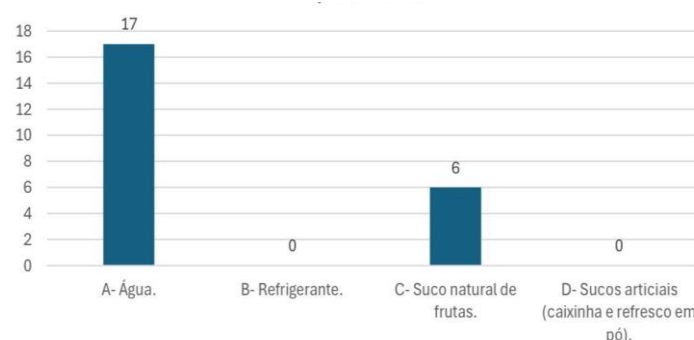
Figure 5 reinforces the positive trend, indicating that 17 children declared a preference for water as their main drink. This data is relevant for health promotion, since the consumption of water to the detriment of sugary drinks contributes to the prevention of obesity and chronic non-communicable diseases (Malik et al., 2010; WHO, 2020). None of the children indicated soda as their preferred drink, an unusual result, which may be associated with a process of awareness already present in the school or family environment. In addition, six children showed a preference for natural juice, as long as it does not add sugar, which is also considered a healthy habit. It is also noteworthy that industrialized juices

(boxed) were not mentioned, which is positive, since they generally have high levels of sugars, additives, and dyes (Monteiro et al., 2018; Pearson et al., 2009).

Together, these findings highlight the role of educational actions in promoting healthier food choices among children, especially in school environments, corroborating studies that defend the importance of food and nutrition education as a health prevention tool (Triches & Giugliani, 2005; Jaime & Lock, 2009).

Figure 5

What would you rather drink?



The analysis of Figure 6 shows that most children (n=18) declared a preference for salty foods. Although this choice is not, in itself, negative, it may reflect a trend towards the consumption of ultra-processed foods, such as snacks, filled cookies, and fast foods, which generally have a high content of sodium, fats, and additives (Monteiro et al., 2019; Louzada et al., 2015). This scenario deserves attention, since frequent consumption of these products is associated with future risks of obesity and chronic non-communicable diseases (Costa et al., 2021).

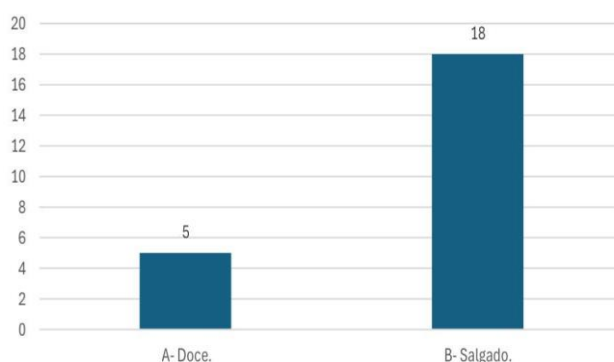
On the other hand, five children reported a preference for sweet foods, which may also represent greater exposure to industrialized sweets, rich in simple sugars and additives. Frequent consumption of this type of food can negatively impact oral and metabolic health, in addition to reinforcing unhealthy eating patterns from childhood (Malik et al., 2010; WHO, 2020).

These results may be related to the fact that children's palate is naturally inclined to sweet and salty flavors, as already demonstrated in studies of eating behavior (Mennella, 2014; Ventura & Mennella, 2011). Early and repeated exposure to these stimuli can intensify preferences for foods with high energy density and low nutritional value, making it difficult to accept healthier foods, such as fruits, vegetables, and legumes (Nicklaus, 2009).

Therefore, the findings highlight the importance of early intervention through food and nutrition education strategies in school environments, as well as the involvement of the family in the provision of more nutritious foods, in order to positively shape food preferences in childhood (Triches & Giugliani, 2005; Jaime & Lock, 2009).

Figure 6

Do you consume more sweet or salty food?



When asked if children like fruits (Figure 4), 21 children stated that they like fruits, which shows good acceptance of these foods. This data is important to support interventions that increase the frequency of consumption. It also demonstrates that home environments rich in fruits and vegetables increase the acceptance of these foods among children (Pearson et al. 2009).

Figure 7

Do you like fruit?

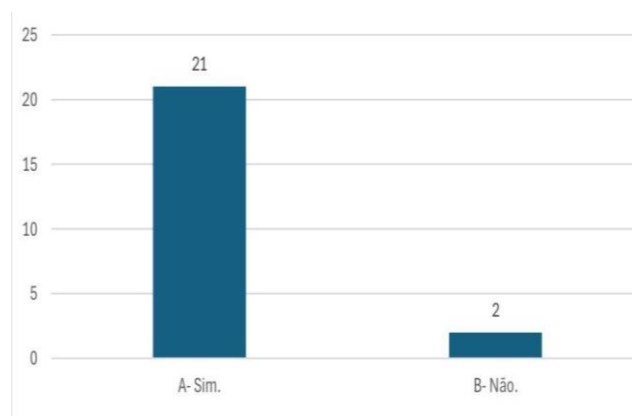


Figure 7 showed that 21 children said they liked fruit, but when asked how often they consumed fruit (Figure 8), only 7 reported consuming it every day. This shows a contrast

between taste and practice, indicating that even if they like it, fruits may not be being offered frequently at home or at school (Patton et al. 2009).

Figure 9

How Often Do You Eat Fruit?

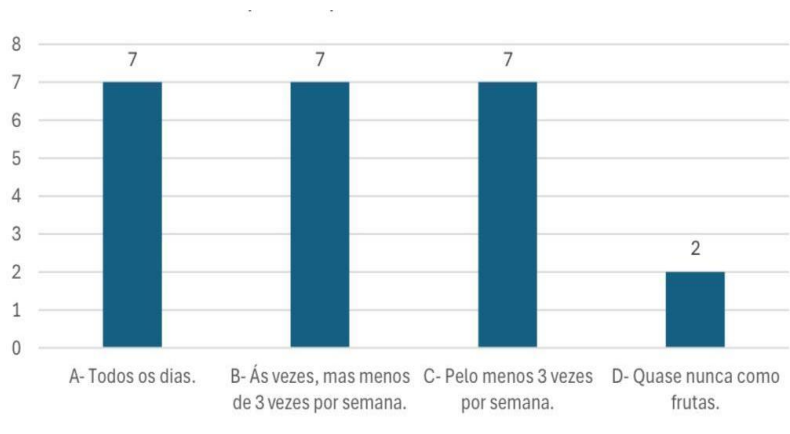
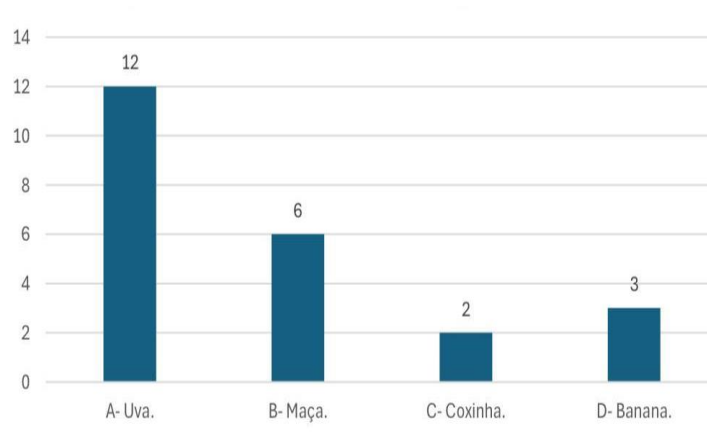


Figure 9 shows that grapes (12 children), apples (6 children) and bananas (3 children) were the preferred foods. While only 2 children stated that they opt for coxinha, which demonstrates a good preference for fruits when there is an option, they also show that practical and easy-to-eat fruits are more consumed at home (Pearson et al. 2009).

Figure 10

Which foods below would you rather eat?

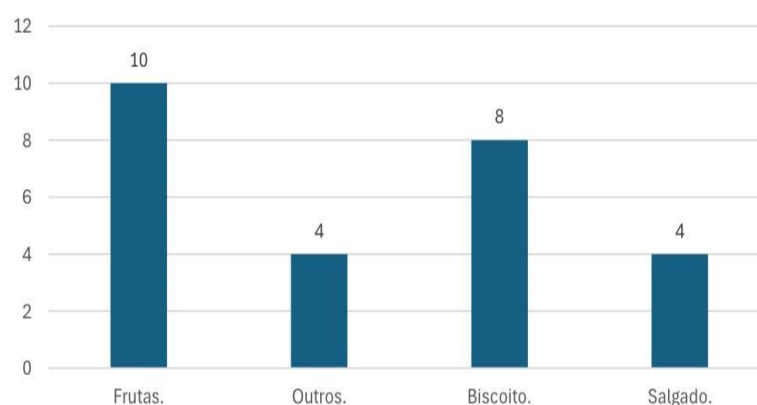


When asked about snacks (Figure 11), fruits (10 children) and cookies (8) were the most mentioned items; snacks (4) and assorted items (4). Considering that cookies, snacks, and part of the "assorted items" tend to be ultra-processed, this indicates that about 62% of children reported less healthy options in snacks, signaling a pattern that is still strongly oriented towards practicality and convenience, to the detriment of nutritional quality. This diagnosis reinforces the urgency of food and nutrition education from an early age, with

integrated actions between family, school and public policies. Recent evidence shows that school-based interventions with greater parental involvement produce better dietary changes in children; Broad reviews also confirm that well-designed policies and programs in the school environment improve multiple diet, health, and learning outcomes (Olgacher et al., 2025). In the Brazilian context, guidelines such as the Food Guide for the Brazilian Population and the PNAE give the guide to prioritize fresh foods and limit ultra-processed foods; National studies indicate that higher consumption of ultra-processed foods in children and adolescents is associated with poorer diet quality and unfavorable cardiometabolic markers, especially in the Northeast. Strengthening access to fruit (price, availability and supply at school), setting the example of adults and adopting clear school standards for snacks are concrete steps to reverse the situation.

Figure 11

Usually what do you eat at snack time?



According to the data in Figure 12, it is observed that most of the children interviewed (12) reported a preference for foods such as bread and butter and sausage products (ham and bologna) for breakfast. In second place, the consumption of fruit or natural juice appears, mentioned by only 6 children. This eating pattern reflects a very common habit among Brazilian families, marked by quick, practical options that are generally more attractive to children's palates, but which, from a nutritional point of view, are not the most appropriate choices for the first meal of the day.

Frequent consumption of ultra-processed foods, such as sausages, is associated with a higher risk of obesity, hypertension, dyslipidemias, and nutritional deficits throughout life (Nobre et al., 2023; Santos et al., 2024). Recent studies confirm that children exposed early to ultra-processed foods tend to consolidate unhealthy eating patterns that extend into adolescence and adulthood. In addition, the low adherence to the consumption of fruits and

natural juices shows the persistence of challenges in promoting healthy eating habits since childhood, despite the recommendations of the Food Guide for the Brazilian Population (Brasil, 2014).

These findings reinforce the need for intersectoral educational actions, involving both the school and the families, in order to encourage more balanced food choices from an early age. Evidence shows that food and nutrition education programs that include parental involvement have the greatest positive impact on children's diet quality (Pearson et al., 2009), while recent reviews confirm that comprehensive school-based interventions are effective in improving dietary patterns and reducing future risks (Silva, Bezerra & Claro, 2025).

Figure 12

Which of these options do you like to eat the most for breakfast?

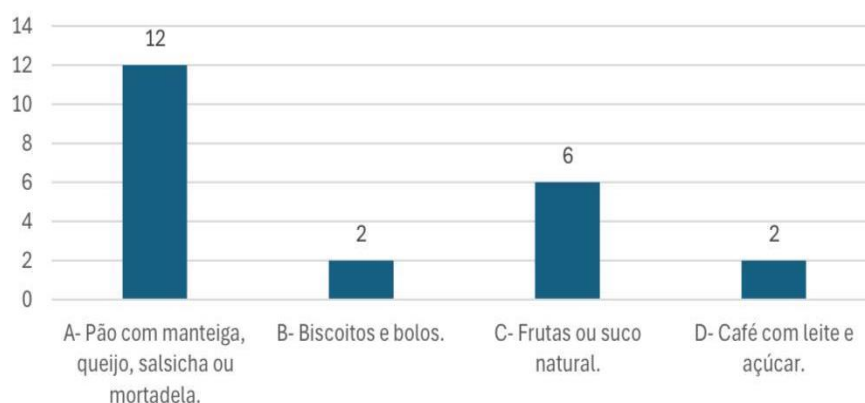
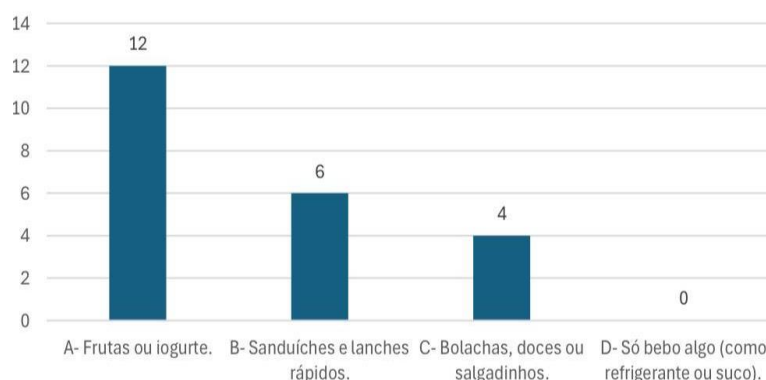


Figure 13 shows that most children opt for fruit or yogurt (12), a positive habit. Others choose sandwiches (6) or sweets and snacks (4). None reported consuming only beverages. Studies such as the one by De Jesus et al. (2020) point out that the availability of ready-to-eat fruits and vegetables in the home environment contributes to the reduction of the intake of ultra-processed snacks among children; However, the high cost of these foods still represents an obstacle for many families, making it difficult to adopt healthier eating habits on a daily basis.

Figure 13

When You Feel Hungry, What Do You Usually Eat?



According to the data in Figure 14, it is observed that the children's answers about the food considered the tastiest were quite balanced. Watermelon was the most mentioned item (7 mentions), followed by coxinha (6), chocolate (5) and banana (4). This panorama reveals a scenario that is both positive and challenging for the promotion of healthy eating in childhood.

On the one hand, the appreciation of fruits stands out, especially watermelon, which leads the ranking, and bananas, also well accepted. This finding reinforces that children's palate can be receptive to fresh foods, when they are offered consistently and inserted into the eating routine (Brasil, 2014). Recent studies confirm that repeated and early exposure to fruits and vegetables increases children's uptake and reduces food selectivity (Dallazen et al., 2022).

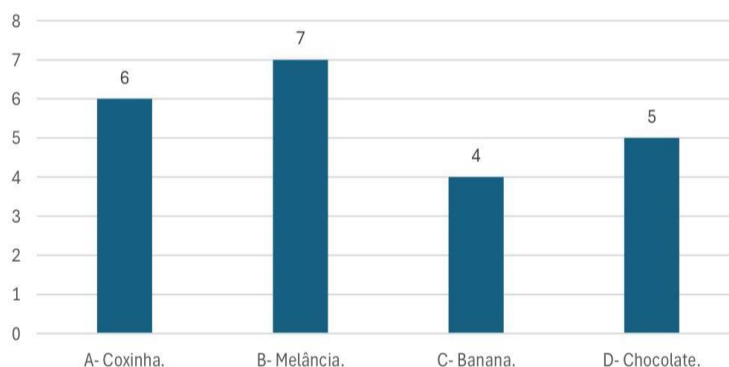
On the other hand, the high preference for coxinha and chocolate, both classified as ultra-processed or of low nutritional value, draws attention. These foods concentrate fat, salt, and/or sugar and have a strong sensory and marketing appeal, factors that explain their high attractiveness among children (Nobre et al., 2023). Recent evidence shows that early and frequent consumption of ultra-processed foods is associated with increased risk of obesity, hypertension, and metabolic alterations in children and adolescents (Santos et al., 2024).

This contrast between the acceptance of fruits and the preference for ultra-processed foods confirms that childhood is a period marked by the coexistence of healthy and unhealthy eating habits, which can make it difficult to consolidate balanced patterns in the long term. As Mennella and Beauchamp (1994) have already pointed out, food preferences are influenced by cultural, emotional and repeated exposure factors, and are strongly modulated by the family and school environment. Current reviews also highlight that intersectoral educational strategies – involving school, family, and public policies – are essential to

strengthen the consumption of fresh foods and reduce the appeal to ultra-processed foods (Silva, Bezerra & Claro, 2025).

Figure 14

For you, which of the foods below is tastier?

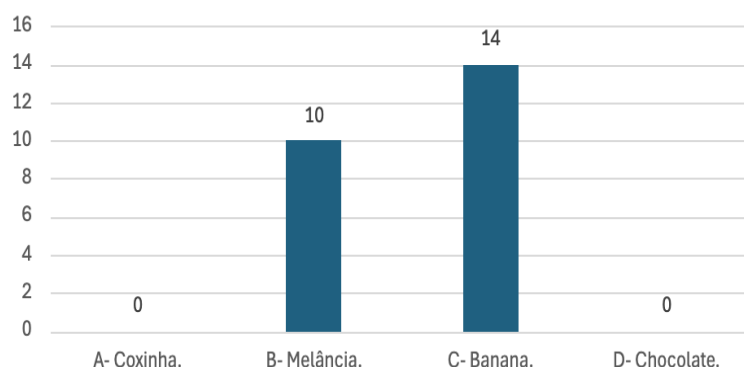


According to the data obtained in Figure 15, bananas and watermelons were pointed out by the children as the healthiest foods, while coxinha and chocolate were not included in this category. This distinction indicates that, even at an early stage of cognitive and dietary development, children already have a certain discernment between what is considered healthy and what is not, demonstrating a basic understanding of the concepts associated with good nutrition. This result is relevant, as it suggests that educational actions promoted by schools, parents or guardians are being, in a way, assimilated by children.

On the other hand, the exclusion of coxinha and chocolate from the category of healthy foods is an indication that children recognize that these items, despite being tasty and frequently consumed, do not bring the same nutritional benefits as fruits. Both foods are high in fat, sugar, and/or sodium, and are widely recognized as ultra-processed, associated with the risk of childhood obesity and other comorbidities when consumed in excess. This perception is supported by the literature by Castromán-Valenti et al. (2019) highlight that food and nutrition education, when conducted in a continuous and contextualized way, has the power to form attitudes and knowledge from childhood, allowing children to develop their own criteria for judging the foods around them. The school, as a formative environment, together with the support of parents, plays a fundamental role in this process, especially by offering balanced meals and coherent information about food.

Figure 15

For you, which of the foods below is healthier?



According to the data obtained, most of the children interviewed (14) stated that they liked chocolate (Figure 16), confirming the wide acceptance of this food among children, something widely documented in the scientific literature (Beauchamp & Cowart, 1987). However, it is important to highlight that these same children reported consuming the candy in moderation, that is, they enjoy the taste, but demonstrate some control over the frequency of ingestion. Only two children reported consuming chocolate whenever possible, evidencing a more permissive and potentially worrisome pattern.

This information is relevant in several aspects. First, they reflect a balanced relationship with a food with high sensory appeal, which can be considered an advance in the contemporary scenario of massive exposure to ultra-processed products and aggressive marketing strategies aimed at children (Monteiro et al., 2019; Cairns et al., 2023). The fact that most children claim to consume chocolate in moderation indicates that dietary guidance strategies and the mediation of parents, caregivers and teachers are contributing to the formation of more conscious habits (Pearson et al., 2009; Silva, Bezerra & Claro, 2025).

According to Beauchamp and Cowart (1987), the taste for sweet foods is natural to human beings, being associated with biological, cultural and environmental factors. However, control over the consumption of added sugars can be learned and socially reinforced, especially in contexts where there is food education, dialogue about health, and diversified food supply (Dallazen et al., 2022). Thus, even though it is natural to like sweets such as chocolate, the ability to regulate consumption according to health or received guidance demonstrates dietary maturity and represents a positive sign of the effects of early nutritional education.

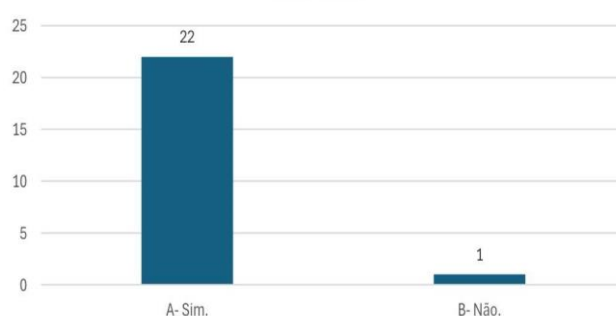
Figure 16

What is your opinion about chocolate?



Figure 17 reveals that almost all the children interviewed (22 out of a total of 24) demonstrate that they know that eating healthy brings health benefits. In addition to recognizing the importance of this behavior, the children were able to correctly relate the concept of healthy eating to the reduction of calories, fats and sugars, showing a significant degree of understanding of the basic principles of balanced nutrition. This finding is in line with the studies of Mennella (2007), which point out that, even in childhood, children are capable of building notions about food health, especially when exposed to consistent educational contexts.

This high level of food awareness among children is quite expressive and can be interpreted as a result of good educational practices both in the school and family environment. Schools that integrate nutritional education content into their pedagogical activities, combined with parents and caregivers who are attentive to their children's food choices, collaborate directly in the formation of healthier values and habits. When children are able to verbalize concepts such as "too much fat is bad" or "too much sugar can harm health," it indicates that they have not only heard these messages, but have assimilated them to a significant degree.

Figure 17*Do you know the benefits of food?*

The analysis of the data reveals a worrying scenario in relation to eating habits during the school period (Figure 18). Only 7 children, out of a total of 24, reported taking healthy snacks on a regular basis. Another 9 said they bought their snacks directly in the school canteen, while the rest reported adopting a combination of healthy and unhealthy foods.

This situation highlights a significant gap in the consistency and quality of school meals, reinforcing the challenge of promoting healthy habits continuously and effectively among children. Although some children have knowledge about what would be an appropriate snack, the data show that this knowledge does not always translate into daily practice.

The influence of the school environment is central to this process. The school is a privileged space for socialization and learning, capable of reinforcing (or compromising) positive behaviors related to health (Pearson, Biddle & Gorely, 2009). Recent studies confirm that integrated school interventions, especially those involving the active participation of families, are more effective in improving the quality of children's diets (Silva, Bezerra & Claro, 2025).

The fact that 9 children buy snacks in the canteen may indicate a restricted supply of healthy options in these establishments. Brazilian evidence shows that, in many schools without strict nutritional regulations, ultra-processed foods rich in sugar, fat, and sodium still predominate, such as snacks, soft drinks, and industrialized sweets (Monteiro et al., 2019; Nobre et al., 2023). This reality contributes to the consolidation of inadequate eating habits from an early age, with negative repercussions on health in the short and long term (Santos et al., 2024).

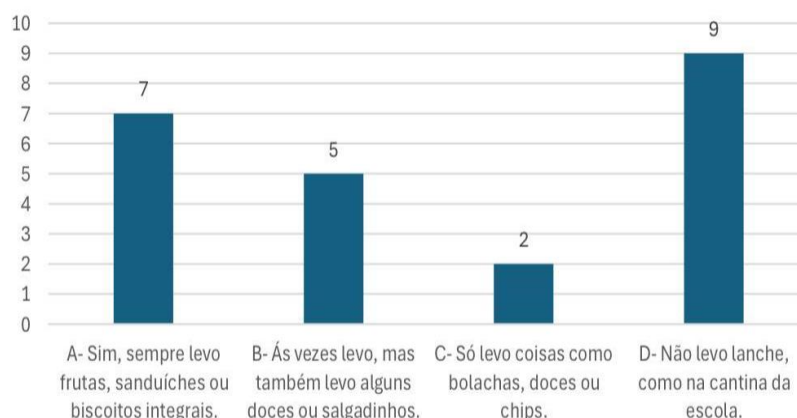
In addition, the choice of part of the students to combine healthy and unhealthy foods demonstrates an attempt at balance, but still without solid guidance or systematic incentive. This scenario may be related to the lack of involvement of families, the absence of stricter

school policies on the type of snack allowed, or even the economic limitation to access healthy foods, such as fruits, yogurts, and homemade preparations (Brasil, 2014).

Thus, the data in Figure 14 reinforce the urgency of intersectoral strategies, involving school, family and public policies, so that school snacks are not only a meal, but also a pedagogical opportunity to consolidate healthy eating practices.

Figure 18

When you go to school, do you bring a healthy snack?



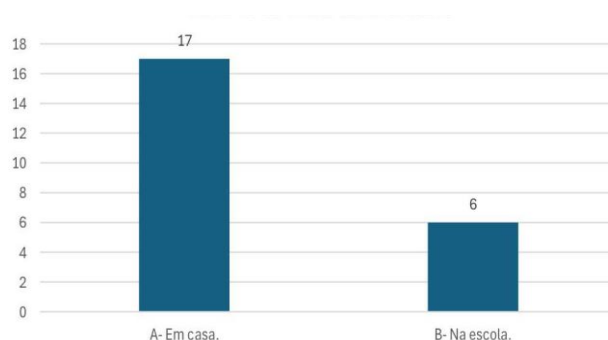
The analysis of Figure 19 shows that most of the children interviewed consume fruit at home (17), reinforcing the role of the family as the main influencer of eating habits. According to Pearson, Biddle and Gorely (2009), parents and caregivers act as essential behavioral models: children who live with adults who regularly consume fruits, vegetables and minimally processed foods are more likely to reproduce these habits throughout life.

The home environment, as the place of the first food experiences, exerts a lasting influence on food preferences and choices (Birch & Ventura, 2009). Thus, the consumption of fruits at home contributes not only to immediate nutritional adequacy, but also to the formation of sustainable healthy eating patterns.

However, it is important to recognize that the promotion of healthy eating at home does not depend only on the will of those responsible. Socioeconomic, cultural, and time constraints strongly influence food choices, which may limit access to fresh fruits and vegetables in some contexts (Brasil, 2014; Jaime et al., 2020). Despite these challenges, the data suggest that when there is a family effort to offer fruits regularly at meals and snacks, the results tend to be positive, configuring a protective factor against inappropriate eating practices.

Figure 19

Where do you eat the most fruit?



When asked if they used to eat fast food (Figure 20), no child consumes it daily. Most do it rarely (13), while 10 consume it 2 to 3 times a week. Although daily consumption is not present among the group evaluated, the fact that almost half of the children attend this type of ultra-processed diet on a weekly basis (2 to 3 times) is already a warning sign, especially considering the cumulative effects of diets rich in saturated fats, sodium and simple sugars, which are striking characteristics of fast food foods.

Studies such as the one by Emond et al. (2020) point out that frequent consumption of fast food in childhood is directly associated with an increased risk of obesity, type 2 diabetes, and other chronic non-communicable diseases, in addition to contributing to the replacement of nutritious meals with options poor in nutritional value. Even though this habit is not yet dominant among the children evaluated, the weekly frequency reported by a significant portion requires attention and preventive intervention. This consumption pattern can be related to family practices, fast-paced routines, ease of access, and even emotional rewards, such as the use of fast food as a form of pleasure. Therefore, food and nutrition education, both in the school and family environment, is essential to deconstruct the association between pleasure and ultra-processed food, and at the same time, encourage healthier and more conscious choices.

Figure 20

How often do you usually eat fast food (hamburgers, pizzas, fried foods)?

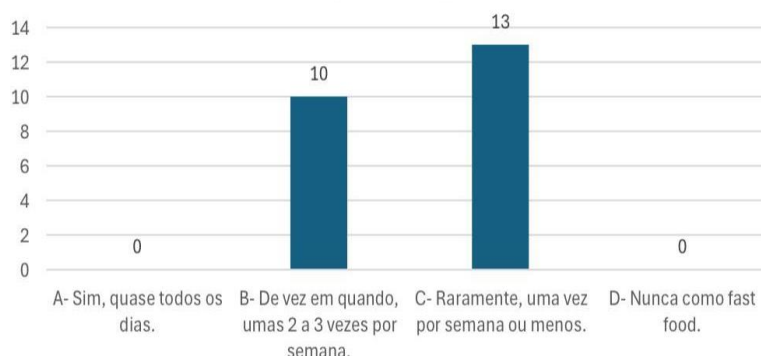
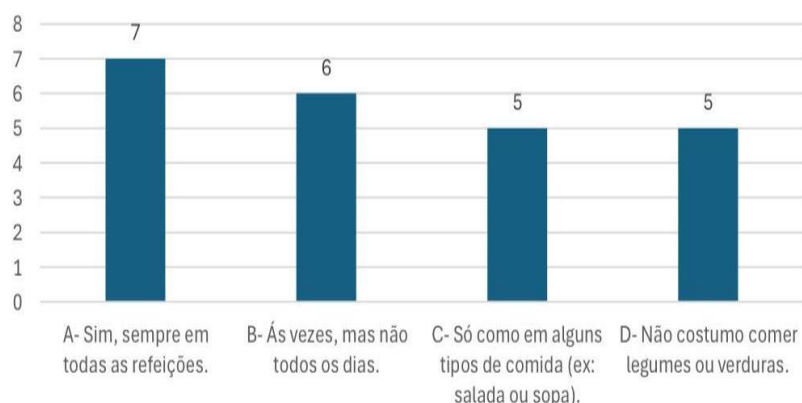


Figure 21 shows that a minority (7) of the children consume vegetables at every meal, another group (6) does not consume them every day, and another 16 consume them rarely or almost never. These numbers point to an important challenge in the formation of healthy eating habits, since the regular consumption of vegetables is directly related to the adequate intake of fiber, vitamins, minerals, and antioxidants, fundamental elements for growth, development, and disease prevention.

According to De Jesus et al. (2020), the home environment plays a determining role in the consumption of healthy foods, especially fruits and vegetables. Children who have greater access to these foods at home and are actively encouraged by parents or guardians to consume them have a higher frequency of intake and develop a preference for these items over time.

The low frequency observed in the consumption of vegetables can be related to several factors, such as lack of regular supply at home, family eating habits, rejection by flavor or texture, little familiarity with these foods or even cultural and socioeconomic aspects. In addition, the cost and perishability of vegetables can represent an obstacle for many families, especially in contexts of social vulnerability.

Figure 21*Do you usually eat vegetables in your meals?*

Almost all the children interviewed (22) consider themselves healthy (Figure 22), which may be related to the awareness acquired in school and family environments that emphasize the importance of good life habits. Recent studies indicate that the perception of health among children can be strongly associated with educational messages, self-care practices, and stimulation of well-being transmitted in daily life (Silva et al., 2024). However, as Lima et al. (2023) point out, this positive perception does not always translate into effective health behaviors, especially when there is still a strong influence of ultra-processed foods on children's eating patterns.

The broader analysis of the data reveals a contradiction: although most children consider themselves healthy, food choices do not fully reflect this understanding. The reduced consumption of vegetables, the high frequency of ultra-processed snacks, and the low adherence to the habit of taking healthy snacks to school illustrate a distance between discourse and practice. This discrepancy has already been observed in other studies, which point out how the subjective perception of health can be biased by valuing some isolated behaviors, but not necessarily by the set of eating and lifestyle practices (Emond et al., 2020; Nobre et al., 2023).

In view of this, the importance of continuous food and nutrition education strategies is reinforced, which go beyond the level of awareness and advance towards concrete changes in the routine, involving both the school and the family as fundamental pillars of this process (Silva, Bezerra & Claro, 2025).

Figure 22

Do you consider yourself someone who eats healthy foods?

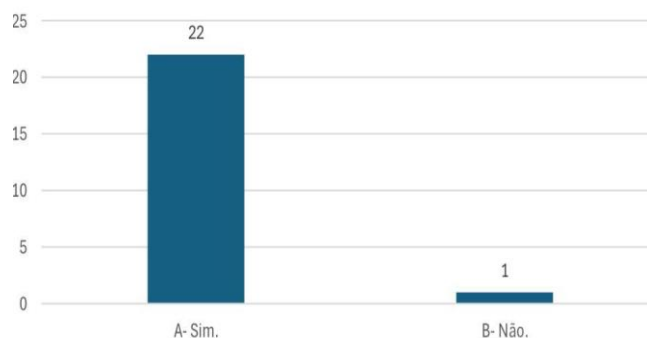


Figure 23 reveals that most children (14) understand healthy eating as the consumption of foods with fewer calories and preservatives, while 8 children associate this concept with the absence of sugar. These results indicate that there is a significant level of knowledge about healthy eating among children, corroborating previous studies that show that children can internalize basic nutritional concepts from an early age (Mennella, 2007).

However, more recent evidence suggests that knowledge does not necessarily guarantee adequate food choices. Research indicates that while children recognize "healthy" foods, factors such as ultra-processed food marketing, sensory preferences, and family influence continue to strongly shape their eating decisions (Emond et al., 2020; Nobre et al., 2023). Thus, the data in the Figure reinforces the importance of continuous educational strategies, which transform knowledge into consistent habits, involving school, family and public policies (Silva, Bezerra & Claro, 2025).

Figure 23

Do you know what healthy foods are?



As demonstrated through the questionnaires and oral observations of the students, the workshops had a positive change in their knowledge about healthy eating, they had interactions with all the "games" focused on learning that were done on the days, this factor demonstrates the interest of the children used for such a project. According to oral reports of the children and their interactions with the games, they were able to discern processed foods and natural/organic foods, foods loaded with fat and foods with low fat contents, demonstrating a great success of the "games" arranged by the project.

An extremely important factor observed was the quality of the students' answers in the "games" that gradually increased with the passing of the techniques and means of learning of the extension students, such as "which food is the richest in sodium", a simple question for the eyes of university students or adults, but not for children so young, And this question proved to be easy to answer orally at the time it was asked, demonstrating a great interest and positive impact on the food understanding of the children who were there, surprising the extension students positively.

Some testimonies of the children who participated in the workshops:

"I really like to eat fruits, especially grapes and apples. Although I don't know what they really know, I know that they are good for their health. Sometimes I also eat cookies or snacks, but now I'm going to try to improve!" (Gabriel, 11 years old, 6th grade).

"I hardly eat vegetables, only when there is soup in the school canteen. At my school, the snack we get is almost always bread, cookies and juices, so at home I eat more fruit." (João, 9 years old, 4th grade).

"I know that chocolate and coxinha are not healthy, but I like it a lot. So I eat only once in a while, like on the weekend. I think eating well helps us grow strong and have energy to play and study. And drink water too! Now I drink more water during the day, I even take my bottle to school." (Alice, 10 years old, 5th grade).

"With this lecture I learned that eating well is not just about not eating sweets, that fruits can be replaced by cookies, I also learned that each color of vegetables and fruits has a different vitamin and to choose what is good for us such as fruits and vegetables of various colors." (Julia, 12 years old, 7th grade).

The extension project provided marked impacts on the training of the students involved, going beyond the learning taught in college. Actively participating in the actions with the children of the communities of Recife awakened in the extension workers a more refined sense of social responsibility and empathy, strengthening their communication, listening and sensitivity to the realities experienced.

During the development of the playful activities of food education, the students were able to exercise and improve skills such as teamwork, creativity in the construction of educational strategies and the ability to adapt to different contexts. In addition, many reported greater confidence in public speaking and a clear and real evolution in the way they express themselves, both orally and in writing, being extremely connected to progress with presentations within the faculty.

The experience also brought important academic gains: students began to become more involved with research and scientific production, as was evident in the preparation of abstracts and reports for scientific events. These records not only reflect the trajectory lived, but also confirm the growth of each participant as a professional in training.

Each extension carried out became a space for genuine exchange, where teaching also meant learning. And, in the end, all participants followed their academic paths carrying with them the marks of this process: more mature, aware of their social role and with a practical background that will certainly contribute to their future performances.

Similar experiences also demonstrate positive results when playful strategies are used as a health education tool with children. A study conducted by Silva et al. (2021), highlights that activities such as games, storytelling, and interactive workshops were effective in promoting changes in the eating behavior of school-age children. As observed in this project, these actions favor active learning, arousing the child's interest and facilitating the understanding of concepts about healthy eating.

In addition, initiatives described by Oliveira et al. (2019) in low-income communities reinforce the importance of outreach as a link between the university and social reality, especially in tackling public health problems, such as poor diet and childhood obesity. The comparison between the projects shows that, regardless of the region, the use of playful approaches, when well planned and culturally adapted, has the potential to generate lasting impacts on the formation of healthy habits and the strengthening of the bond with the community.

Similarly, Santos et al. (2021) highlight that the application of playful strategies in children's food education contributes significantly to the development of critical thinking and children's autonomy in choosing foods. In his project "More Action and Nutrition in Childhood", the use of interactive activities with children aged 4 to 5 years promoted interest in healthy eating and the introduction to new flavors, results that are in line with those observed in the present study. These findings reinforce the importance of playful methodologies adapted to the age group and cultural context of the communities, evidencing their potential to strengthen healthy eating habits from childhood.

3 CONCLUSION

The educational intervention aimed to assess the children's level of knowledge about healthy eating habits and promote awareness through interactive workshops. Throughout the activity, it was possible to perceive the interest and active participation of the children, who demonstrated engagement in the proposed dynamics and presented advances in the understanding of more appropriate food choices. The results reinforce the relevance of promoting healthy habits from childhood, especially in the prevention of chronic non-communicable diseases. It was evident that factors such as inadequate diet and sedentary lifestyle are directly related to the emergence of conditions such as obesity, type 2 diabetes and cardiovascular diseases. In this sense, the educational action contributed positively to the children's learning, using playful resources that facilitated the understanding of the theme in a light and meaningful way.

In view of this, it is considered that the approach worked on has great value for public health, pointing to the need for continuity of educational actions conducted by health professionals in partnership with schools. It is essential that these initiatives are supported by public policies aimed at promoting child health, recognizing that the development of good eating habits in childhood contributes not only to the formation of healthier adults, but also to the dissemination of this knowledge within families and communities.

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TUBERCULOSIS/HIV/AIDS CO-INFECTION IN PARAÍBA: ANALYSIS OF THE DECADE 2014–2024

COINFEÇÃO TUBERCULOSE/HIV/AIDS NA PARAÍBA: ANÁLISE DA DÉCADA 2014 -2024

COINFECCIÓN TUBERCULOSIS/VIH/SIDA EN PARAÍBA: ANÁLISIS DE LA DÉCADA 2014–2024



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ABSTRACT

The co-infection between the Human Immunodeficiency Virus (HIV) and Mycobacterium tuberculosis constitutes a serious Public Health challenge, increasing the morbidity and mortality of immunosuppressed individuals. Therefore, this study aimed to evaluate the number of cases and the epidemiological profile of Tuberculosis/HIV/AIDS co-infection in the State of Paraíba, Northeastern Brazil, from 2014 to 2024. An exploratory study with a quantitative approach was conducted using secondary data from the Notifiable Diseases Information System (SINAN/DATASUS). During the analyzed period, 1,372 cases of co-infection were recorded, with a significant increase of 100.93% in notifications between 2022 and 2024. The results revealed a predominance of male individuals (73.83%), aged between 20 and 39 years (52.33%), and of mixed race/skin color (80.32%). Regarding the socioeducational profile, most patients (57.5%) had low educational attainment or were illiterate. The prevalence of co-infection in the general population of the state was 34.51 per

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100,000 inhabitants, reaching 134.95 per 1,000 among people living with HIV/AIDS. It is concluded that the vulnerability profile for these diseases in the State of Paraíba is concentrated among young men of working age with low levels of formal education.

Keywords: Immunosuppression. Opportunistic Infections. *Mycobacterium tuberculosis*. Acquired Immunodeficiency Syndrome. Health Surveillance.

RESUMO

A coinfeção entre o Vírus da Imunodeficiência Humana (HIV) e *Mycobacterium tuberculosis* constitui um grave desafio à Saúde Pública, elevando a morbimortalidade de indivíduos imunossuprimidos. Diante disso, este estudo objetivou avaliar o número de casos e o perfil epidemiológico da coinfeção Tuberculose/HIV/SIDA no Estado da Paraíba, Nordeste do Brasil, no período de 2014 a 2024. Realizou-se uma pesquisa exploratória de abordagem quantitativa, utilizando dados secundários do Sistema de Informação de Agravos de Notificação (SINAN/DATASUS). No período analisado, registraram-se 1.372 casos de coinfeção, com um crescimento expressivo de 100,93% nas notificações entre 2022 e 2024. Os resultados revelaram a predominância de indivíduos do sexo masculino (73,83%), na faixa etária de 20 a 39 anos (52,33%) e de cor parda (80,32%). No âmbito socioeducacional, observou-se que a maioria dos pacientes (57,5%) possuía baixa escolaridade ou era analfabeta. A prevalência da coinfeção na população geral do estado foi de 34,51 por 100 mil habitantes, atingindo 134,95 por 1.000 entre pessoas vivendo com HIV/AIDS. Conclui-se que o perfil de vulnerabilidade para essas doenças no Estado da Paraíba concentra-se em homens jovens em idade produtiva e com baixo nível de instrução formal.

Palavras-chave: Imunossupressão. Infecções Oportunistas. *Mycobacterium tuberculosis*. Síndrome da Imunodeficiência Adquirida. Vigilância em Saúde.

RESUMEN

La coinfección entre el Virus de la Inmunodeficiencia Humana (VIH) y *Mycobacterium tuberculosis* constituye un grave desafío para la Salud Pública, aumentando la morbimortalidad de los individuos inmunosuprimidos. Ante esto, este estudio tuvo como objetivo evaluar el número de casos y el perfil epidemiológico de la coinfección Tuberculosis/VIH/SIDA en el Estado de Paraíba, Nordeste de Brasil, durante el período de 2014 a 2024. Se realizó una investigación exploratoria con enfoque cuantitativo, utilizando datos secundarios del Sistema de Información de Enfermedades de Notificación (SINAN/DATASUS). Durante el período analizado, se registraron 1.372 casos de coinfección, con un crecimiento expresivo del 100,93% en las notificaciones entre 2022 y 2024. Los resultados revelaron el predominio de individuos del sexo masculino (73,83%), en el grupo etario de 20 a 39 años (52,33%) y de color pardo (80,32%). En el ámbito socioeducativo, se observó que la mayoría de los pacientes (57,5%) tenía baja escolaridad o era analfabeta. La prevalencia de la coinfección en la población general del estado fue de 34,51 por cada 100 mil habitantes, alcanzando 134,95 por cada 1.000 entre las personas que viven con VIH/SIDA. Se concluye que el perfil de vulnerabilidad para estas enfermedades en el Estado de Paraíba se concentra en hombres jóvenes en edad productiva y con bajo nivel de instrucción formal.

Palabras clave: Inmunosupresión. Infecciones Oportunistas. *Mycobacterium tuberculosis*. Síndrome de Inmunodeficiencia Adquirida. Vigilancia en Salud.

1 INTRODUCTION

The human immunodeficiency virus (HIV-1) is a retrovirus that infects cells of the mononuclear system and can lead, if there is no treatment, to Acquired Immunodeficiency Syndrome (AIDS). Infection with this pathogen paves the way for the so-called opportunistic diseases. In this sense, co-infection with HIV and *Mycobacterium tuberculosis*, which causes tuberculosis, represents a challenge to Public Health, as it increases clinical severity and deaths in immunosuppressed people (Santos et al., 2009; Bekker et al., 2023).

Tuberculosis manifests itself chronically and has a global distribution. Clinically, the disease is divided into latent and active forms. In the latter, the presentation can be pulmonary or extrapulmonary. Transmission occurs primarily in the pulmonary form, through the elimination of bacilli in the secretions of the respiratory tract (Busatto, 2015). Although the *M. tuberculosis complex* includes *M. bovis*, a zoonotic agent whose clinical manifestation in humans is indistinguishable from the classical form, the actual proportion of the participation of each agent in human cases still needs to be further elucidated (Thoen, 2009).

According to the WHO, in 2024, approximately 11 million people contracted tuberculosis and 1.2 million died. The situation is more serious in poor countries, where treatment is scarce, in addition to the insidious nature of the disease and the high prevalence of AIDS (Vieira, 2014). In the global context, tuberculosis therefore assumes a reemerging character. In addition to the AIDS epidemic, factors such as poverty, aging, and immigration challenge disease control (CDC, 2025).

In Brazil, the presence of tuberculosis has been constant since the colonial period. This characteristic, added to the factors also found in underdeveloped nations, represents an even greater challenge to the Unified Health System (SUS) (Ruffino-Netto, 2002). In this context, the weakness of the immune system caused by HIV increases the chances of infection by the *Mycobacterium tuberculosis* complex by up to 37 times, as well as progression from the latent form to the active form (Barbosa, 2014). This risk remains even after the recovery of helper T lymphocytes (CD4), making it necessary to monitor, follow-up, and improve health services (Brasil, 2024). Therefore, this study aimed to evaluate the number of cases and the epidemiological profile of Tuberculosis/HIV/AIDS co-infection in the State of Paraíba, Northeast Brazil, between 2014 and 2024.

2 MATERIAL AND METHODS

This is an exploratory study, with a quantitative approach, based on secondary data from the Notifiable Diseases Information System (SINAN), extracted from DATASUS using the TabWin software. The selected variables were: "Federative Unit: Paraíba", "tuberculosis

investigation", "years 2014 to 2024", "age group (less than 1 year to 80 years or older)", "HIV/AIDS infection", "sex", "race" and "schooling".

The data were organized in an Excel spreadsheet for visualization. After that, for data analysis, the epidemiological prevalence rates were calculated, according to the following formula: number of cases of the disease, divided by the total population, based on the 2022 demographic census. Subsequently, the prevalence rates for each pathology were calculated separately to estimate the population of the stone. Data available in SINAN and in the HIV/AIDS Epidemiological Bulletin 2024 were used. After obtaining the epidemiological rates for the two pathologies, simple descriptive analysis calculations were applied in order to identify the highest proportions of cases over time.

3 RESULTS

Between 2014 and 2024, 1,372 cases of HIV/AIDS and Tuberculosis co-infection were reported in the State of Paraíba in DATASUS. Of the total, about 17.71% (243/1372) were registered in 2024, being the period with the highest incidence, followed by 2023, with 12.24% (168/1372), 2020 with 9.18% (126/1372), 2021 with 8.53% (117/1372) and 2022 with 8.45% (116/1372). The data point to a 100.93% increase in case notifications between 2022 and 2024.

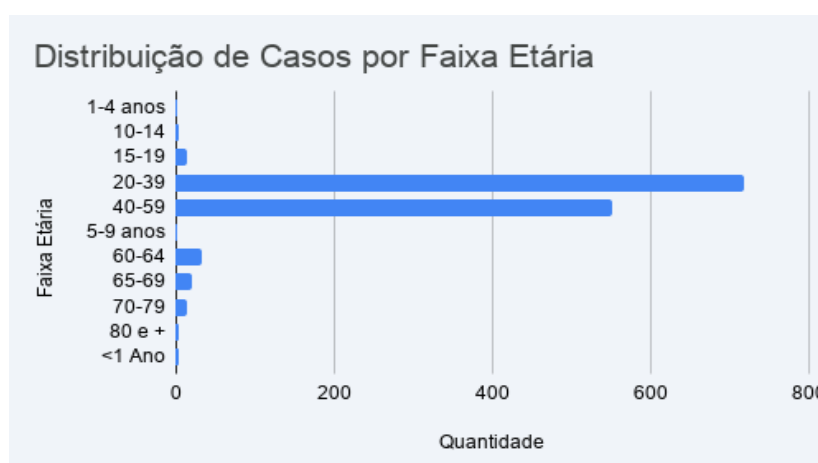
The results of the age groups analyzed are presented in descending order (Figure 1). The age group between 20 and 39 years had the highest number of cases throughout the observed period, with a total of 718 cases reported, followed by the age groups of 40 to 59 years (553), 60 to 64 (33), 65 to 69 (20), 70 to 79 (14), 15 to 19 (14), 10 to 14 years (5), less than 1 year old (5), 80 or older (5), 5 to 9 (2) and from 1 to 4 (3).

Regarding the profile of the 1,372 cases analyzed, there was a predominance of males, with 73.83% (1,013/1372) in relation to females, with 26.16% (359/1372). Regarding social determinants, most individuals (789) had a low level of education or were illiterate.

In terms of color/race, the brown population was the most affected, accounting for 80.32% (1,102/1372) of the notifications, followed by the white population, with 9.69% (133/1372) and black, with 6.77% (93/1372). The prevalence of co-infection in the population of the state was 34.51 per 100 thousand inhabitants, while in the seropositive population it was 134.95 per 1000 and 85.47 per 1000 in the population with tuberculosis.

Figure 1

Distribution of cases by age group



4 DISCUSSION

The results showed a predominance of tuberculosis/AIDS co-infection among males aged 20 to 39 years, representing 73.83% and 52.33% of the confirmed cases in the State of Paraíba, respectively. These findings are in line with the epidemiological profile observed in other national studies, reinforcing the vulnerability of men of working age (Prado et al., 2011).

Although the variable "sexual orientation" was not available in the database analyzed, the literature points to a high frequency of infection among men who have sex with men (MSM), as well as an association with drug use and multiple partners (Pereira, 2014). The epidemiological profile observed in Paraíba, with 73.83% of cases occurring in men, is very similar to that found in other Brazilian states. However, it differs from that observed in other developing nations, such as Mozambique and South Africa. In these countries, in addition to the incidence and prevalence being substantially higher than in Brazil, there is a process of feminization of AIDS, with women making up the majority of diagnosed cases (Vieira, 2014). This phenomenon differs from the male concentration pattern identified in the present study.

The predominant involvement of young people, aged between 20 and 39 years, can be explained by the socioeconomic context, especially the intermittent use of condoms, associated with lower income and low education. In this study, 789 of the 1,372 individuals had, at most, incomplete secondary education or were illiterate, a condition already related in other studies to increased vulnerability to new infections. Similarly, Araújo (2023) identified, in Paraíba, an association between HIV/AIDS infection in young people and low educational levels and/or lack of literacy, a situation that compromises access to information, limits citizenship, and hinders access to health services.

In addition to the sociodemographic profile identified, it was possible to observe a significant increase in notifications between 2022 and 2024, in the order of approximately 100%. This finding suggests that the trend of a 0.3% reduction in TB/HIV/AIDS co-infection observed in Brazil at the end of the 2010s was not maintained in Paraíba. If this trend persists, it may jeopardize the achievement of the goals of eliminating tuberculosis as a public health problem in the country by 2030 (BRASIL, 2026; BRAZIL, 2024).

However, this increase may also reflect advances in epidemiological investigations and health surveillance, especially in view of the need for HIV testing in tuberculosis patients, as well as the investigation of latent tuberculosis infection in HIV-positive people (SÃO PAULO, [n.d.]; Jamal, 2019). Thus, the results indicate not only the persistence of co-infection as an important public health problem in Brazil, but also the need to strengthen prevention actions, early diagnosis, integrated testing, and clinical follow-up of the most vulnerable groups.

5 CONCLUSION

In view of the data obtained, it is concluded that the vulnerability profile for TB/HIV/AIDS co-infection in the State of Paraíba is concentrated in young men, of working age, of brown color and with a low level of formal education. The significant increase in notifications in the 2022-2024 biennium reinforces the need to intensify public policies aimed at this specific population.

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OPERATIONAL PERFORMANCE INDEXES IN HOSPITALS: CONTROL TOOL FOR AUDITING

ÍNDICES DE DESEMPENHO OPERACIONAL EM HOSPITAIS: FERRAMENTA DE CONTROLE PARA AUDITORIA

ÍNDICES DE DESEMPEÑO OPERATIVO EN HOSPITALES: HERRAMIENTA DE CONTROL PARA AUDITORÍA



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ABSTRACT

This study aimed to identify indices that enable the audit system to evaluate the performance of hospital care, through electronic patient records (EPRs). The audit system can contribute to improving the performance of hospital care, based on measurement of indices of services performed. Based on a review of the literature on the operational performance of hospital activities and analysis of EPRs, we identified indices that were subsequently submitted to specialist evaluation through a questionnaire. This resulted in the construction of a new questionnaire, with all indexes systematized, which was submitted to experts to analyze and indicate their relevance. As a result, this study presents 20 indices, subdivided into structure (4), process (9), and result (7) indices, suitable for evaluating operational performance through hospital electronic medical record systems, consisting of a tool to be used by auditors, when analyzing EPRs, to evaluate operational performance, contributing to the management of hospital organizations. The indices also contribute to evaluating the quality and performance of care provided in healthcare organizations.

Keywords: Health Audit. Operational Performance Indicators. Electronic Patient Record. Health Management. Hospital Management.

RESUMO

Este estudo teve como objetivo identificar índices que permitam ao sistema de auditoria avaliar o desempenho da assistência hospitalar, por meio do prontuário eletrônico do paciente (PEP). O sistema de auditoria pode contribuir para a melhoria do desempenho da assistência hospitalar, com base na mensuração de índices dos serviços executados. A partir de uma revisão da literatura sobre o desempenho operacional das atividades hospitalares e da análise de PEPs, identificamos índices que, posteriormente, foram submetidos à avaliação de especialistas por meio de um questionário. Isso resultou na

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construção de um novo questionário, com todos os índices sistematizados, o qual foi submetido a especialistas para analisar e indicar sua relevância. Como resultado, este estudo apresenta 20 índices, subdivididos em índices de estrutura (4), processo (9) e resultado (7), adequados para avaliar o desempenho operacional por meio de sistemas de prontuário eletrônico hospitalar. Trata-se de uma ferramenta a ser utilizada por auditores, ao analisarem os PEPs, para avaliar o desempenho operacional, contribuindo para a gestão das organizações hospitalares. Os índices também contribuem para avaliar a qualidade e o desempenho da assistência prestada nas organizações de saúde.

Palavras-chave: Auditoria em Saúde. Indicadores de Desempenho Operacional. Prontuário Eletrônico do Paciente. Gestão em Saúde. Gestão Hospitalar.

RESUMEN

Este estudio tuvo como objetivo identificar índices que permitan al sistema de auditoría evaluar el desempeño de la atención hospitalaria mediante el Prontuario Electrónico del Paciente (PEP). El sistema de auditoría puede contribuir a la mejora del desempeño de la atención hospitalaria a partir de la medición de índices de los servicios ejecutados. A partir de una revisión de la literatura sobre el desempeño operativo de las actividades hospitalarias y del análisis de los PEP, se identificaron índices que posteriormente fueron sometidos a la evaluación de especialistas mediante un cuestionario. Esto dio lugar a la construcción de un nuevo cuestionario con todos los índices sistematizados, el cual fue sometido a especialistas para analizar e indicar su relevancia. Como resultado, este estudio presenta 20 índices, subdivididos en índices de estructura (4), proceso (9) y resultado (7), adecuados para evaluar el desempeño operativo mediante sistemas de prontuario electrónico hospitalario. Se trata de una herramienta que debe ser utilizada por auditores al analizar los PEP para evaluar el desempeño operativo, contribuyendo a la gestión de las organizaciones hospitalarias. Los índices también contribuyen a evaluar la calidad y el desempeño de la atención prestada en las organizaciones de salud.

Palabras clave: Auditoría en Salud. Indicadores de Desempeño Operativo. Prontuario Electrónico del Paciente. Gestión en Salud. Gestión Hospitalaria.

1 INTRODUCTION

Hospitals, as crucial entities in the health system, play a fundamental role in the global effort to achieve the Sustainable Development Goals (SDGs) (Bastos, Bonato, Gomes, 2019; Parente; Parente, 2019; WHO, 2024). The quality of hospital management directly impacts the effectiveness of the health system. In the face of limited resources, the health system necessitates efficient hospital management to serve the population both qualitatively and quantitatively. The challenges of resource scarcity and management excellence in the context of hospital organizations are increasingly prevalent and growing in Brazil (Teixeira, 2019). With this in mind, our study aims to develop operational performance indexes to enhance control over the hospital management system, leading to more efficient service management and resource utilization. We posit that operational performance is intricately linked to the operations control quality, as control mechanisms provide valuable feedback on hospital management (Oliveira et al., 2018).

The primary control mechanism is the audit system, which depends on records about the patients' health-disease process: patient records, where the procedures and medications administered are recorded. The medical record is an essential source of information, and reading it allows one to understand the quality of hospital activities performance. However, for an objective information analysis, it is important to use indexes, which make it possible to systematize information and indexes to measure the services provided quality, enabling their comparability (Assi, 2020; Mutti; Macagnan, 2022; Ribeiro et al., 2018; Silva, Ferreira; Almeida, 2020). In this sense, the reliability of the audit work results would be related to the choice of indexes used to analyze hospital operational performance (Rahimi et al., 2014; Rahimi et al., 2017).

It is worth highlighting that indexes are representations of attributes and dimensions, which make it possible to objectively identify these characteristics (Nikjoo et al., 2013). Indexes are complex representations ranging from simple numerical counting to more complex calculations (maffissoni, 2020). Operational Performance Indexes help to compare results, enabling managers to act to implement improvements in the system (Nikjoo et al., 2013; Khalifa; Khalid, 2015) and are key pieces for analyzing, monitoring, and improving management processes, operational and decision-making tools (Miranda, 2022).

Of the 4,466 private Brazilian hospitals, 63% are philanthropic or non-profit cooperative organizations. In 2022, Brazil had 263,793 beds in these hospitals, with a density of 1.99 for every 1,000 inhabitants. The average recommended by the World Health Organization (WHO) is 3.2 (FBH/CNSaúde, 2022). Therefore, on the one hand, Brazil has a significant number of private hospitals and beds, which demands management controls; on

the other hand, there is a low density of beds, which requires efficient management to meet the demands of the Brazilian population. The lack of resources in hospitals, the size of the population, and the different types of diseases, given the geographic size of Brazil, make hospital management complex. This requires a control system that contributes to improving the hospital management system. Hence, the relevance of researching indexes that make it possible to contribute to more efficient and qualitative management.

The construction of indexes began by identifying them through a literature review and then analyzing electronic medical records. It ended with applying a questionnaire validated by five researchers on the subject. The questionnaire was applied using the adapted Delphi method, through social networks and corporate emails, via the Google form and allowed 32 responses in the first round and 20 responses in the second round from health professionals working in the regions of Missões, Noroeste Colonial, and Fronteira Noroeste of the Rio Grande do Sul State. The Missões region is made up of 25 municipalities. It has a total of 255,399 inhabitants. The Northwest Colonial region comprises 11 municipalities and has 184,928 inhabitants, while the Northwest Border region comprises 20 municipalities and has 220,270 inhabitants (FEE, 2022).

The operational performance indexes for hospital management were formed into three categories related to the health system's three components: 1. Structures, 2. Processes, and 3. Results (Donabedian, 1966; Gilbert, 2015). With the variety in each category, the study resulted in a total of twenty indexes, distributed as follows: four for structure, nine for processes, and seven for results. All indexes were created to establish the possibility of analyzing hospital operational performance through auditing Electronic Patient Records (EPRs) and can be used as a management tool.

Next, this article presents the formulation of the study's premise, the methodological procedures used, the main findings and results discussion, the final considerations, and the references used.

2 RATIONALES OF THE STUDY

Given the scarce resources designated by the Brazilian State, the health system demands hospitals to be efficiently managed. Management efficiency involves using tools that enable planning, organization, direction, and control. More specifically, control is a mechanism that contributes to management whenever it allows an analysis of evidence that makes it possible to identify aspects to be improved while also providing comparable information (Santos et al., 2020; Braga Neto et al., 2008). To effectively manage processes, considering the human resources and materials involved, hospitals must map their activities

and implement improvements and controls over their performance (Carini et al., 2020; Montini Costa, 2020; Silva et al., 2019). Performance in health services means quality, efficiency, and effectiveness, encompassing evidence-based practices, continuity and integration in health services, health promotion, and orientation to patients' needs and expectations (Ioan; Nestian; Tita, 2012; Khalifa; Khalid, 2015). Hospitals are organizations that have specific characteristics that deserve attention.

To meet the demands of hospital organizations, a management model is necessary that can optimize the management process (Ioan, Nestian, Tita, 2012; Oliveira; Toda, 2013; Silva; Ferreira; Almeida, 2020). It is worth noting that the contemporary hospital sets goals that go beyond treating and curing patients. It needs to include the well-being of its users and offer comfort like that offered in hotels. In this model, the hospital organization must present differences in providing services beyond efficiency in patient prognosis and treatment (Montini; Costa, 2020). Therefore, the hospital organization that wants to remain sustainable in the long term needs to develop and implement planning based on control tools with continuous monitoring.

For a long time, the printed medical record was the only instrument for collecting and storing information regarding patients treated in health services. With advances in information technology, electronic medical records emerge, enabling an information network that creates spaces for new ways of using information in health services, improving the quality of care provided (Millen, 2022; Neves et al., 2020). In this sense, the electronic patient record (EPR) is a tool that assists health and hospital management and provides better control through the audit system, which is a primary source of information for monitoring the health-disease process of the patient (Ribeiro et al., 2018). The EPR is a source of information, with records of the individual's health history, from birth to the moment of death (Neves et al., 2020; Silva, 2021; Granja et al., 2022), also supporting managers in decision-making. In other words, the EPR is a source of information that allows hospital organizations to carry out control activities, such as operational auditing, generating complementary information for management. The audit aims to analyze the conformity of operations, investigate specified requirements, analyze signs of non-conformities, evaluate the lack of corrective practices or improvements to be applied, suggesting solutions to remove existing non-conformities (Brasil, 2000). This control activity can cover the entire hospital area and serve governance with reliable and independent information from service fronts (Fleischmann, 2019).

From this perspective, operational auditing is an organizational evaluation and control activity intended to review operations as a service provided to the administration. It

constitutes a management control that works through the analysis and evaluation of the efficiency of other controls (Crepaldi; Crepaldi, 2019). It comprises examinations, analyses, evaluations, surveys, and proofs, methodologically structured to assess the integrity, adequacy, effectiveness, efficiency, and economics of processes, information systems, and internal controls integrated into the environment and risk management, with aimed at assisting the organization's administration in achieving its objectives (Adriano, 2020). The audit activity is structured in procedures, with a technical, objective, systematic, and disciplined focus, providing support for improving processes, management, and internal controls through the recommendation of solutions for non-conformities identified in audit reports we forward to the managers of the organizations. Thus, the audit is a tool that validates the information and ensures that internal controls are adequate (Prudente; Evangelista; Toth, 2020), adding value to the organization.

Therefore, operational auditing is a management tool that is essential for healthcare organizations to survive with quality and financial balance and transparency, contributing to the governance system (Teixeira, 2019; Batista, 2021). The audit system promotes control over the quality of care provided to the patient and the organization's management costs within acceptable standards of care, satisfying the patient with the expected quality (Loureiro et al., 2018). Management must be established based on indexes for effective control, contributing to an objective analysis by classifying information. The indexes allow an objective analysis of the evidence and assist decision-making, identifying points for improvement in the services provided (Silva; Ferreira; Almeida, 2020).

Therefore, operational health auditing must use previously defined indexes to evaluate the organization's operational performance. Indexes are information that represents attributes and concepts and make it possible to understand, describe, and compare aspects of reality and project the future (Bittar, 2001.; Oliveira et al., 2018; Prates; Ospina, 2004; Robbins; Decenzo, 2007). Each index must contain a goal to be achieved, comparing what was planned with what was accomplished (Brasil, 2017; ANVISA, 2021). Indexes are a practice strengthened by organizations' current management systems (Azevedo, 2020; Khalifa; Khalid, 2015).

The indexes can reflect a population's health situation, monitor health conditions, and assist in hospital management. When analyzed and related, the correlation between indexes can become instruments to support decision-making, helping to manage resources and processes. In the Brazilian hospital context, according to Ordinance GM 3390/2013, the indexes must be used to monitor actions and serve as a basis for obtaining standards of excellence (Brasil, 2013; Silveira et al., 2015), as they show trends and explain how

improvements are being made over time (Khalifa; Khalid, 2015). To evaluate health services and the quality of care, the leading operational performance indexes can be classified into three components of the health system: structures, processes, and results (Donabedian, 1996; Gilbert, 2015).

Structure indexes represent the context in which healthcare is provided, including hospital buildings, personnel, and equipment. Process indexes include all transactions between patients and healthcare providers throughout healthcare delivery. Result indexes refer to the effects of care on patients' health (Donabedian, 1966; Gilbert, 2015; Khalifa; Khalid, 2015). Therefore, the guiding premise of this study is that operational performance indexes are fundamental for audit activities in EPRs and hospital management control. They enable the assessment of hospital operational performance, providing governance support for the decision-making process and strategic realignments that mean better operational results.

However, constructing indexes is a complex process (Maffissoni, 2020), which must have quality and be timely, precise, and relevant to assist in monitoring and progressing objectives and goals (Prates; Ospina, 2004). The literature review is inconclusive about which indexes should be collected and analyzed to understand hospital performance (ANVISA, 2021; Carini et al., 2020). From this perspective, we developed the study based on a literature review on the topic, using keywords: operational audit and care quality and performance indexes, operational performance indicators, and hospital audit. We also reviewed the official websites of regulatory bodies, current legislation, and field research using a questionnaire detailed in the next item.

3 METHODOLOGICAL PROCEDURES

The methodological development comprised diverse sources of evidence. Firstly, we developed a literature review on hospital operational performance indicators and indexes (Andolhe, 2013; Andrade; Benevides, 2019; Anschau et al., 2017; Araújo; Guerreiro, 2020; Blankart, 2021; D'Aquino, 2017; Dodo et al., 2020; Faria et al., 2010; 2019; Machado et al., 2013; Nunes, 2018; 2021; Viana, et al., 2016). We also reviewed the legislation and standards relating to the healthcare system in Brazil (Brasil, 2002; ANVISA, 2019). Analyzing these two sources made it possible to identify the first list of operational performance indexes for hospital organizations.

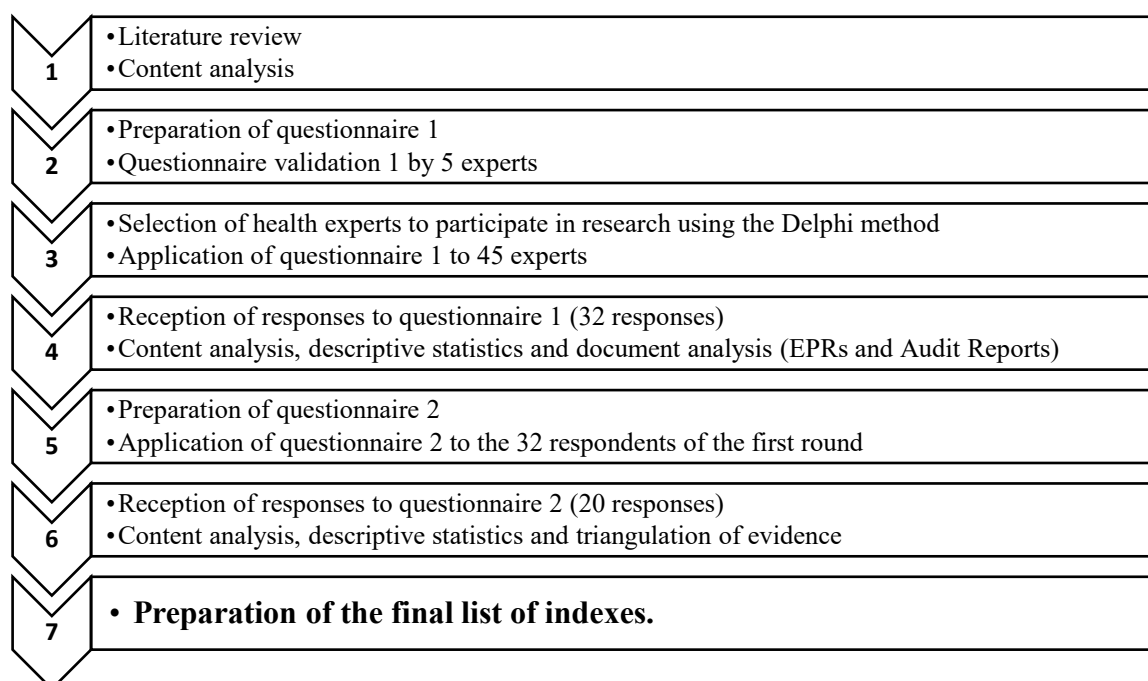
Next, we develop the analysis of audit reports. To do so, we use the content analysis technique. We organize the *corpus* for the analysis and interpretation of evidence. Next, we organized and analyzed electronic medical records in a new study stage. We also used the

content analysis technique. The audit reports and electronic medical records are from a medium-sized hospital in the Northwest Region of the State of Rio Grande do Sul (RS), owned by the second largest medical cooperative in the State and one of the primary cooperatives in the health sector in the Country. With the content analyses completed, we prepared the first list of indexes, leading to another research development stage: preparing the first questionnaire.

The first stage of preparing the questionnaire was based on the analyses developed so far, consisting of a review of literature, laws, standards, and regulations, followed by the analysis of audit reports and electronic records, providing a first version of the questionnaire. The questionnaire consisted of open and closed questions, which referred to the concepts and representativeness of indexes. The closed questions were created based on the previous stages of the study, and the open questions aimed to include other indexes considered relevant, not estimated in the literature, and excluded those considered irrelevant for the assessment of hospital operational performance.

Subsequently, five experts and researchers submitted this questionnaire for evaluation. The experts' suggestions were analyzed and considered for adjustments to the questionnaire. After validation of the indexes by researchers on the topic was completed, the questionnaire was sent to three groups of health professionals in two distinct stages, following the Delphi method, with adaptations. Firstly, the questionnaire was sent to 45 specialized professionals chosen for accessibility, namely 15 auditors, 15 hospital managers, 15 health researchers, and all doctors or nurses. In the first round, 32 responded to the questionnaire, including 16 auditors, four managers, and 12 teachers. Subsequently, the second questionnaire was sent to the same group, as recommended by the Delphi method, which made it possible to obtain 20 responses in the second round, coming from 10 auditors, two managers, and nine health researchers.

The evidence obtained from the questionnaires was analyzed qualitatively and quantitatively, which characterized the consensus among experts on the indexes, making another round of questions unnecessary. The qualitative form was carried out using the content analysis technique, which made it possible to identify relevant indexes that would remain in the final list. We developed quantitative analysis at a descriptive statistical level. Subsequently, triangulation (Vergara, 2015) was carried out between the data collected by the questionnaires, the literature review, and documentary research to prepare the final list of hospital operational performance evaluation indexes for carrying out audits in the EPRs. Below, figure 1 shows the flowchart of the research's methodological procedures:

Figure 1*Flowchart of methodological procedures*

Next, we present and discuss the research results with the reviewed literature.

4 MAIN FINDINGS AND DISCUSSION OF RESULTS

The literature review made it possible to identify the recommendation for the use of nine operational performance indexes in hospital management systems, named as follows:

1. *Cesarean sections* (Ferreira; Nascimento, 2021; Nunes, 2018; Reis et al., 2020; Rahimi et al., 2014)
2. *Surgeries* – performance and suspension (Lobo et al., 2019; Nunes, 2018; Rahimi et al., 2014; 2017; Silva et al., 2019),
3. *Hospitalization and Discharge from the hospital* (Andrade; Benevides, 2019; Brasil, 2002; Grala et al., 2020; Nikjoo et al., 2013; Nunes, 2018; Silva et al., 2017; Silva; Queiroz; Maia, 2021. Vieira, et al., 2006),
4. *Adverse events* (Andolhe, 2013; Ioan et al., 2012; Machado et al., 2013; Mansour, 2012)

One of the key findings from our review is the crucial role of key performance indicators in-hospital evaluation. The literature, including studies by Anschau et al. (2017), Gomes et al. (2010), and Machado et al. (2013), consistently emphasizes the importance of these indicators, underlining the urgency of their practical implementation in healthcare settings.

6. *Permanence hospital* (Anschau et al., 2017; ANVISA, 2019; Blankart, 2021; Brasil, 2002); Would Make et al. 2010; Ferreira et al. 2021; Ioan et al., 2017; Nikjoo, et al., 2013; Nunes, 2018; Rahimi, et al., 2014; Kings; Birth, 2021; Vieira, et al., 2006).
7. *Records in Nursing* (Dodo et al., 2020; Hess, 2010; Merli et al., 2013; Motorbike, 2021; Silva et al., 2019; Viana et al., 2016)
8. *Readmission hospital* (Merli et al., 2013; Mota, 2021; Santos, 2018).
9. *Bed Turnover* (Anschau et al., 2017; D'Aquino, 2017; Ferreira et al., 2021; Nikjoo et al., 2013; Nunes, 2018).

These indexes enable the recognition of the attribute and allow the creation of indexes that measure the quality, the recognition possible failures of our services in health, monitoring the actions carried out, in short, that contributed to hospital management (Anschau et al., 2017; Azevedo, 2020; Brasil, 2013; Machado et al., 2013; Silveira; et al., 2015). For example, the indicator of Hospital Occupancy makes it possible to calculate the occupancy index, which is related to the replacement interval of these beds. It is the average in permanence. The target audience for analysis is the patients hospitalized in hospitals. Your use It consists of assessing the efficiency of the management of operational beds in hospitals and the use of hospital beds in healthcare service systems health (Brasil, 2002; Nikjoo et al., 2013). Legislation recommends an occupancy rate between 75% and 85%. Higher than these percentages can mean the emergence of adverse events such as hospital infection and reduced safety in the care environment (Brasil, 2002). On the other hand, the indicator of Discharge from the hospital is associated with the degree of humanization and can mean a faster recovery for the patient and the rationalization of the use of hospital beds (Grala; Araújo; Guerreiro, 2002; Silva; Queiroz; Maia, 2021). Healthcare costs are very high, making it a reality among countries to provide priority for hospital beds for acute or decompensated pathologies (Andrade; Benevides, 2019; Nikjoo et al., 2013).

The bed occupancy turnover index is obtained by the relationship between the number of patients leaving the hospital and the number of active beds in the same period. The higher the index, the better the yield per bed, which signals efficiency in the use of resources available (D'Aquino, 2017; Nunes, 2018). Therefore, bed occupancy turnover is inversely related to patients' average length of stay. Reducing the length of hospital stay can increase the number of patients served (Ferreira; Fiorotto; Brilinger, 2021; Rahimi et al., 2014; 2017).

The average Hospital Stay index focuses on the patient's hospitalization. This index makes it possible to analyze the efficiency of the management of bed operations, assessment of time average inpatient permanence, and good practices assistance. It is operational bed turnover (ANVISA, 2019). In large hospitals, the average Ideal General Stay

varies from 4 to 5 days, which may vary depending on hospitalization clinics. It is surgical. However, when the O period in hospitalization is prolonged, one increases costs and a reduction in bed turnover, indicating administration and assistance (Blankart, 2021; Moraes et al., 2017). Thus, when relating the average hospital stay of a patient to the Diagnosis Related Groups (DRG), we have the average indicator between the type of patient treated in the hospital and their respective hospital cost (Blankart, 2021). The use of DRG makes the realization possible compared to that of the assistance hospital. Your costs make productivity analysis possible through the relationship between your assistance and economic results. The effectiveness measured by the DRG in an organization can be compared with other hospital organizations, creating opportunities to improve performance (Albareda, 2020; Blankart, 2021).

The Mortality indicator expresses a crucial dimension of the quality of care provided: the result (Gomes et al., 2010; Rahimi et al., 2014; 2017). From this perspective, Nunes (2018) states that assessing hospital deaths is the central concern of identifying the deaths that can be avoided. The index: Unscheduled Readmission is a readmission of the patient which was not foreseen when Discharged from the hospital for one period until 30 days after the high (Ioan; Nestian; Tita, 2012; Merli; Lopes; Macharelli, 2013). The reasons that lead a patient to readmission in less time than a month are complex, and we must consider using tools that allow us to identify patients at the highest risk (Mota, 2021).

Despite all the advances in patient safety, human error causing adverse effects is one of the factors to consider. Adverse events are undesirable, although predictable, in nature harmful or harmful, compromising patient safety under the care of healthcare professionals. health (Andolhe, 2013; Ioan; Nestian; Tita, 2013; Mansour, 2012). Error or incident can be defined as the event or circumstance that could have resulted in damage unnecessary to the patient. When no reach patients are reached or are identified in advance, they are recognized as near misses (almost errors). When they reach the patient, but no cause damage is discernible, they are called a no-damage incident. When they result in discernible damage, they are named as an adverse event (Mansour, 2012). Controlling this is related to the set of activities that aim to monitor the activities in operations and deal with eventual deviations at the flat original, allowing identity and correcting irregularities, leading to more appropriate care for patients' needs and offering more effective services (Nunes, 2018).

Thus, as the hospital is an establishment responsible for the healing process and treatment of patients, carrying out activities such as hospitalizations, surgeries, and births (Brasil, 1998), such activities must be constantly monitored, with views to the improvement of the procedures in question it is the obtaining in best results (Nunes, 2018). Paschoal and

Gatto (2006) emphasize the importance of controlling and investigating reasons for suspension to eliminate or minimize the occurrence of suspension in surgeries. A high rate of suspended surgeries indicates the need for managers to review organizational procedures (Rahimi et al., 2014; 2017). Another indicator that can highlight the need to investigate errors in procedures in hospitals refers to the number of cesarean sections performed, and this quantity is used as an important indicator of perinatal health (Ferreira; Nascimento, 2021; Nunes, 2018).

Nursing information is fundamental and corresponds to around 50% of patient care records. These records enable control, exercised through the audit system, facilitating planning and decision-making (Dodo et al., 2020; Hess, 2010; Mota, 2021). One of the problems faced in the realization of the audit in accounts is the nonconformity or absence of nursing records at the medical record level. This causes discrepancies in the charge's hospitals, causing avoidable waste and indicating possible failures in the process assistance. It breaks the aspects of ethics. It is excellent for professionals (Vigna; Ruiz; Lime, 2020). Below, we present indexes identified from the literature review on the performance of hospital organizations.

1. *Average hospital stay* (Anschau et al., 2017; ANVISA, 2019; Blankart, 2021; Brasil, 2002; Ferreira et al., 2021; Ioan et al., 2012; Machado et al., 2013; Moraes et al., 2017).
2. *Average hospital stay for surgical beds* (Faria et al., 2010; Lang, 2018; Maldonado et al., 2021).
3. *Average hospital stay in clinical beds* (Anschau et al., 2017; Faria et al., 2010; Ioan et al., 2012; Lang, 2018).
4. *Average length of stay related to the DRG* (Albareda, 2020; Blankart, 2021; Serufo Filho; Couto, 2016).
5. *Rotation of bed use* (Anschau et al., 2017; D'Aquino, 2017; Ferreira et al., 2021; Nikjoo et al., 2013; Nunes, 2018).
6. *Cesarean section rate* (Ferreira; Nascimento, 2021; Nunes, 2018; Rahimi, et al., 2014; 2017; Reis, et al., 2020).
7. *Discharge from hospital rate* (Andrade; Benevides, 2019; Silva et al., 2021; Silva et al., 2017).
8. *Rate of adverse events* (Andolhe, 2013; Ioan et al., 2012; Mansour, 2012; Machado et al., 2013. Nascimento et al., 2008).
9. *Mortality rate* (Anschau et al., 2017; Gomes et al., 2010; Ioan et al., 2012; Machado et al., 2013; Nikjoo et al., 2013; Nunes, 2018; Rahimi et al., 2014; Vieira et al., 2006).

10. *Hospital Occupancy Rate* (Brasil, 2002; Grala et al., 2020; Rahimi et al., 2014; 2017; Nunes, 2018; Vieira et al., 2006).
11. *Unscheduled Readmission Rate* (Ioan et al., 2012; Merli et al., 2013; Mota, 2021; Nikjoo et al., 2013; Rahimi et al., 2014; 2017; Santos, 2018).
12. *Surgical suspension rate* (Lobo et al., 2019; Nunes, 2018; Rahimi et al., 2014; 2017; Silva et al., 2019).

Nursing records (Dodo et al., 2020; Hess, 2010; Merli et al., 2013; Mota, 2021; Viana et al., 2016) remain qualitatively analyzed as they present diverse patient information. This information can be compared when illnesses are similar regarding the use of medications and forms of treatment, among others.

The questionnaire respondents analyzed the indexes found in the literature review. The first question contained indexes identified, which experts chose and judged suitable for evaluating operational performance in hospital electronic medical record systems. The number of responses obtained for each index is shown in Table 1 below.

Table 1

Indexes for evaluation of performance

Number	Indexes for assessment in performance	Number of responses	Percentage
1	The rate in Events Adverse	30	94%
2	The rate in Hospital Occupation	26	81%
3	Average of Hospital Stay	24	75%
4	Average of Hospital Stay – Beds clinicians	22	69%
5	Average of Permanence Hospital – Beds surgical	20	63%
6	Average in Related stay to DRG	20	63%
7	The rate of Discharge from the hospital	20	63%
8	Records in Nursing	18	56%
9	Rate in Mortality	18	56%
10	The rate in Readmission no Scheduled	18	56%
11	Turnover of the Giro bed	16	50%
12	The rate of Suspension in Surgeries	16	50%
13	The rate of Cesarean sections	10	31%

Table 1 shows that 94%, 81%, and 75% of respondents pointed to Adverse Event Rate, Hospital Occupancy Rate, and Average Hospital Stay as the leading indexes to evaluate operational performance. On the other hand, 31% of respondents understood that the Cesarean Rate index is the least relevant for such an assessment. Next, it was asked whether the experts would exclude indexes and what they would be. Three respondents suggested excluding nursing records, the average length of stay related to DRG, and the surgery suspension rate. However, considering the confirmatory percentage of maintenance of these indexes and the percentage suggesting exclusion, we maintained them. When experts were asked to suggest indexes that they considered relevant to evaluate the

performance of the hospital, in addition to the cited in question 1, we got the following answers:

Table 2

Suggestion of indexes for operational performance assessment

Number	Indexes
1	The average permanence in obstetrics is pediatrics.
2	Turnover of the team nursing
3	Level of satisfaction of the patients It is users of the System of Health
4	The rate of complications per event adverse
5	The rate of infection related to Assistance to Health (IRAS)
6	The rate of mortality from IRAS
7	The rate of use of antimicrobials

From this perspective, respondents suggested seven more indexes to evaluate hospital operational performance in addition to those indicated in the literature.

In the second round of application of the questionnaire, considering the indexes included the relationship Based on the suggestions of previous respondents, respondents gave an evaluation on a scale from 01, when the indicator would be considered terrible, to 05, when it would be considered excellent for the assessment operational performance of hospital activities. The results obtained are presented in table 3 below:

Table 3

Assessment of Hospital Operational Performance Indexes

	Indexes	1	2	3	4	5	P*	R**
1	Satisfaction of patients and users of the healthcare system				2	18	98	1st
2	Adverse event rate				2	18	98	1st
3	Healthcare-associated infection rate				2	18	98	1st
4	The rate of complications due to adverse events				4	16	96	2nd
5	Mortality rate				4	16	96	2nd
6	HAI mortality rate				4	16	96	2nd
7	Average hospital stays			2	2	16	94	3rd
8	Antimicrobial use rate				6	14	94	3rd
9	Hospital occupancy rate			2	4	14	92	4th
10	Average hospital stay – surgical beds			2	6	12	90	5th
11	Average hospital stay – clinical beds			2	6	12	90	5th
12	Nursing records			2	1	7	45	5th
13	Nursing team turnover				12	8	88	6th
14	Unscheduled readmission rate			4	6	10	86	7th
15	Bed rotation turnover			4	8	8	84	8th
16	The average length of stay related to DGR		2	6	4	8	78	9th
17	Discharge from hospital rate		2	4	8	6	78	9th
18	Surgery suspension rate			8	8	4	76	10th
19	Average length of stay in obstetrics and pediatrics		2	4	8	6	72	11th
20	Cesarean section rate		6	4	6	4	68	12th

Average ***	0%	3%	11.5%	26%	59.5%		
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Note: * means the total sum of points obtained by the index, the number of answers multiplied by the weight.

**means the position of the index in the Ranking, obtained by the number of points.

*** represents the percentage of responses for each importance attribution.

According to the results, it was observed that three indexes were considered excellent for evaluating hospital operational performance by 90% of respondents, coming first in the ranking: Satisfaction of patients and users of the health system, Rate of adverse events, and Healthcare-associated infection rate. Three other indexes obtained 96 points from experts, reaching second place in the ranking: Mortality rate, Rate of complications due to adverse events, and HAI mortality rate. On the other hand, the indexes that obtained the lowest number of points for evaluating hospital operational performance were the Cesarean section rate, 68 points, and the last position in the ranking, and the Average length of stay in obstetrics and pediatrics, 72 points, and the penultimate position. On average, the indexes were considered excellent for evaluating hospital performance by 59.5% of the experts; none of the experts considered any index to be terrible, and only 3% of the experts considered an index with weight 2 to evaluate hospital operational performance.

It is noteworthy that, although there were suggestions to remove some indexes as they were not relevant to the assessment of operational performance, in the responses to the first questionnaire, the number of specialists was not significant, nor did the results of this stage corroborate to exclude them from the final list of indexes to evaluate performance hospital operational, for through audit activities in EPRs.

The nursing records index is considered essential for evaluating performance. It is worth highlighting your medical records. They are remarkable documents, so much for administrative and financial aspects. This process is fundamental to a procedural model of quality nursing from the planning, implementation, and evaluation of problem situations of patients (Dodo et al., 2020; Mota, 2021; Silva et al., 2019). Nursing records correspond to approximately 50% of information on nursing care recorded in medical records. Therefore, its central role in communication stands out among the multidisciplinary team, as it generates information that supports the conduct of other professionals, makes it easier to plan, and is the outlet for decisions. It is the continuity of care (Silva et al., 2019).

The search for Reis and Nascimento (2021) about the index, average in permanence related to the DRG, pointed out its importance and confirmed the inefficiency of using the bed hospital. It is consumption in daily above of foreseen, so much in DRG's clinicians how much surgical. Gonçalves' study et al. 2020 highlights that the index surgery suspension rate increases the organization's operational and financial costs, reducing the efficiency of the

service offered. They conclude that surgeons and anesthetists frequently suspend surgeries in public hospitals in the state of Rio de Janeiro. January (Gonçalves, et al., 2020). This leads to inferring the usefulness of the indexes for hospital management.

Below, we present the three categories of indexes related to the three components of the health system: structure, processes, and results, constructed from the triangulation of analyses carried out, considering literature review, documentary analysis, and responses obtained by quizzes applied to the experts, which made it possible to build 20 indexes to be used to control operational performance in EPRs.

Table 4

Structure Indexes

Number	Index	Description
1	Records of nursing	Quality of assistance provided documentation accuracy, completeness, and lost revenue welcome from the hospitalization.
2	Turnover of the team nursing	Variation in personnel entry and exit; free flow
3	Turnover of the beds	Relationship between the number of patients discharged from the hospital and the number of active beds in the same period.
4	Hospital Occupancy Rate	Relationship between the number of patient days and the number of bed days in a certain period

We highlight that structure indexes describe the context in which healthcare is provided, including hospital buildings, personnel, financing, and equipment (Khalifa; Khalid, 2015). When evaluating the structure, the environment in which health care takes place and the instruments of which it is a product are assessed, in addition to the management processes that support and guide the provision of care (Donabedian, 1966). The absence of key structural components supporting care needs to be translated into action items that relate to care processes and better outcomes (Gilbert, 2015).

Table 5

Process Indexes

Number	Indexes	Description
1	Average length of stay in obstetrics and pediatrics	Average time in days that patients remain hospitalized in Maternity/Obstetrics.
2	Average hospital stays	Relationship between total patient days and the number of patients who left the hospital in the determined period, including your deaths. Represents the average time in days that a patient stayed hospitalized at the hospital
3	Average hospital stays for surgical beds.	The time during which, on average, a patient remains admitted to the hospital in the surgical clinic
4	Average hospital stays in clinical beds.	The time that, on average, a patient stays in a hospital in medical clinic beds

5	Average stay DRG	Classification of DRGs about the median length of hospital stay according to the American criteria of days of hospitalization
6	Cesarean section rate	Abdominal surgical intervention to extract the conceptus from the mother's uterus during labor.
7	Rate of complications due to adverse events	Unforeseen, undesirable, or potentially dangerous occurrence.
8	Adverse event rate	Undesirable occurrences of a harmful or harmful nature but predictable
9	Healthcare-associated infection rate (HAI)	Infections acquired after the patient undergoes a healthcare procedure or hospitalization may be related to these events.

Process indexes include all transactions between patients and providers during the delivery of healthcare (Khalifa; Khalid, 2015). Process evaluation consists of evaluating whether what is considered adequate, indicated, and complete as health care, obtained from the health system's history, was used for each type of case (Donabedian, 1966). Gilbert (2015) highlights that identifying operational quality deficits, such as gaps in key care processes, should serve as a basis for adjustments aimed at better care and better results for healthcare organizations.

Table 6

Result indexes

Number	Index	Description
1	Satisfaction of patients and users of the Health System	Degree of satisfaction from the patients' point of view and perspective regarding the quality of services provided
2	Discharge from hospital rate	Release of the patient for home treatment.
3	Mortality rate	Relationship between the number of deaths in the hospital and the release of the patient in each period.
4	HAI mortality rate	HAI is considered the most significant cause of death in the hospital environment.
5	Unscheduled readmission rate	Unplanned readmissions of a patient to the investigated hospital or another in the public or private healthcare system within up to 30 days after discharge from the hospital.
6	Surgery suspension rate	Any surgery scheduled but not performed on the scheduled date.
7	Antimicrobial use rate	Use of antimicrobials in healthcare services to ensure the pharmacotherapeutic effect, reducing the occurrence of adverse events, preventing the spread of Microbial Resistance (MR), and reducing unnecessary healthcare costs

Outcome indexes refer to the effects of healthcare on patients' health status (Khalifa; Khalid, 2015). By obtaining better performance results through these indexes, indicative of recovery, restoration of functions, and survival, it is established that the structure and processes are interconnected to provide the results obtained (Donabedian, 1966; Gilbert, 2015). Measures of structure, process, and results that evaluate the context and setting of

care, how care is provided, and the effects of that care have become the main pillars of evaluating the operational performance of healthcare organizations (Gilbert, 2015).

The indexes in performance operational are elements fundamentals for the measurement of performance, like this as for the definition of variables that better represent efficiency in the use of resources in one organization (Ioan; Nestian; Tita, 2012; Khalifa; Khalid, 2015). They enable operational performance control of the operational activities of hospitals concerning efficient patient care, with the lowest related costs and the best results in terms of health.

The indexes are summary measures containing information relevant to state dimensions in health, goods, and the health system's performance. The aim is to quantify your results. It is to assess O greeting in goals. Its goals demonstrate the operational situation, with economic and financial consequences for these organizations, which need to remain to ensure the continuity of health services provided to the community where they are inserted. Per that, the indexes become useful for showing detours in one situation considered normal, serving as one important flare gun for the process in question to be reviewed and prevent the installation of any problem that affects the sustainability of the hospital organization.

Furthermore, the list final in indexes created the leave from revising the literature from the analysis documentary. It is the analysis of experts; It is one tool that the auditors can use to analyze your medical records. The patients' electronics are used to assess operational performance, contributing to the organization management of hospitals.

5 FINAL CONSIDERATIONS

Indexes are essential tools for organizational management, and they make it possible to measure the current situation of a given phenomenon or problem, make comparisons, and check for changes or trends, in addition to evaluating the execution of planned actions over a period. Hospital organizations, like any other organization, need to track and monitor their operational performance, aiming to minimize costs and, at the same time, obtain efficient health outcomes for their patients. Thus, this study aimed to identify control indexes that can be used in audit activities to evaluate operational performance in hospital EPR systems.

The study made it possible to identify, in addition to the thirteen identified in the literature in the area, the inclusion of seven more indexes, namely: turnover or turnover of the nursing team; average length of stay in obstetrics and pediatrics; satisfaction of patients and users of the Health System; rate of complications due to adverse events; healthcare-associated infection rate (HAI); mortality rate from HAIs; and rate of antimicrobial use, thus

totaling a list of 20 indexes. Document analysis made it possible to obtain information through EPRs, which also contributed to the research results.

It is worth highlighting that the study focused on identifying operational performance indexes of hospital organizations and obtaining information from electronic patient records (EPRs). It did not focus on other possibilities for identifying indexes. Furthermore, the study did not consider questioning hospital patients, which could be studied in another project. It is also noteworthy that the experts questioned work in interior regions of the state of Rio Grande do Sul, in medium-sized hospital organizations and universities, which offer medicine, nursing, and pharmacy courses, among others in the health area. In their portfolios.

In this sense, based on the limitations of this research, future studies are suggested that fill the gaps left, such as analyzing other types of indexes, in addition to operational ones, such as economic-financial ones, to observe the sustainability and continuity of these organizations in the communities where they operate. Search for specialists from less needy regions regarding hospital units to serve the population. It is also important to analyze the performance of other healthcare organizations and look at other information sources beyond audit reports and EPRs. Additionally, the number of experts to be questioned can be increased, and it can also be obtained randomly and not due to accessibility, as was the case in this research. Furthermore, studies can be carried out based on the perception of hospital patients, which would enable comparative studies of hospital operational performance, considering both perspectives.

Finally, this research contributes to identifying appropriate indexes to evaluate operational performance in hospital electronic medical record systems. Thus, the final list of indexes consists of a tool that can be used by internal auditors when analyzing electronic patient records to evaluate operational performance and contribute to the management of hospital organizations. Furthermore, it contributes to evaluating the quality and performance of care provided in healthcare organizations in search of continuous improvements in management processes. It also contributes to the literature and knowledge on the subject, leaving another study as a source of future research.

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IMPACT OF SCHOOL LIFESTYLE ON SPINAL HEALTH IN CHILDREN AND ADOLESCENTS

IMPACTO DO ESTILO DE VIDA ESCOLAR NA SAÚDE DA COLUNA EM CRIANÇAS E ADOLESCENTES

IMPACTO DEL ESTILO DE VIDA ESCOLAR EN LA SALUD DE LA COLUMNA VERTEBRAL EN NIÑOS Y ADOLESCENTES



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ABSTRACT

This study aimed to identify the main habits that negatively interfere with the spinal health of children and adolescents, analyze school and extracurricular factors associated with postural changes, and evaluate preventive strategies applicable in the educational environment. This is an integrative literature review conducted in the PubMed, LILACS, and SciELO databases, with the selection of articles published between 2021 and 2025. After applying the inclusion and exclusion criteria, eight international studies were analyzed. The results show that factors such as inappropriate backpack use, prolonged sitting posture, non-adapted school furniture, and the absence of corrective practices in the school environment negatively influence spinal health in children and adolescents. In addition, extracurricular habits such as sedentary behavior, excessive use of electronic devices, and poor posture during daily activities intensify these effects. Evidence also demonstrates that interventions in the school environment, such as postural education programs, physical exercise, and active breaks, are effective in promoting spinal health, although they depend on continuity and student adherence.

Keywords: Spinal Health. Posture. Ergonomics. Prevention. Posture Correction.

RESUMO

Este estudo teve como objetivo identificar os principais hábitos que interferem negativamente na saúde da coluna de crianças e adolescentes, analisar fatores escolares e extraescolares associados às alterações posturais e avaliar estratégias preventivas aplicáveis no ambiente educacional. Trata-se de uma revisão integrativa da literatura, realizada nas bases de dados PubMed, LILACS e SciELO, com seleção de artigos publicados entre 2021 e 2025. Após aplicação dos critérios de inclusão e exclusão, foram

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analisados oito estudos internacionais. Os resultados evidenciam que fatores como uso inadequado de mochilas, permanência prolongada em postura sentada, mobiliário escolar não adaptado e ausência práticas corretivas no ambiente escolar, influenciam negativamente para a saúde da coluna em crianças e adolescentes. Além disso, hábitos extraescolares, como sedentarismo, uso excessivo de dispositivos eletrônicos e má postura nas atividades diárias, potencializam esses efeitos. As evidências também demonstram que intervenções no ambiente escolar, como programas de educação postural, exercícios físicos e pausas ativas, são eficazes na promoção da saúde da coluna, embora dependam da continuidade e da adesão dos estudantes.

Palavras-chave: Saúde da Coluna. Postura. Ergonomia. Prevenção. Correção de Postura.

RESUMEN

Este estudio tuvo como objetivo identificar los principales hábitos que interfieren negativamente en la salud de la columna vertebral de niños y adolescentes, analizar factores escolares y extraescolares asociados a las alteraciones posturales y evaluar estrategias preventivas aplicables en el entorno educativo. Se trata de una revisión integradora de la literatura, realizada en las bases de datos PubMed, LILACS y SciELO, con selección de artículos publicados entre 2021 y 2025. Tras la aplicación de los criterios de inclusión y exclusión, se analizaron ocho estudios internacionales. Los resultados evidencian que factores como el uso inadecuado de mochilas, la permanencia prolongada en postura sentada, el mobiliario escolar no adaptado y la ausencia de prácticas correctivas en el ambiente escolar influyen negativamente en la salud de la columna vertebral en niños y adolescentes. Además, hábitos extraescolares como el sedentarismo, el uso excesivo de dispositivos electrónicos y la mala postura en las actividades diarias potencian estos efectos. Las evidencias también demuestran que las intervenciones en el entorno escolar, como programas de educación postural, ejercicios físicos y pausas activas, son eficaces para promover la salud de la columna vertebral, aunque dependen de la continuidad y de la adhesión de los estudiantes.

Palabras clave: Salud de la Columna Vertebral. Postura. Ergonomía. Prevención. Corrección Postural.

1 INTRODUCTION

Changes in contemporary life habits, especially related to the frequent use of electronic devices such as cell phones, tablets and computers, associated with the demands of the school environment, are relevant factors in the daily lives of children and adolescents, and can directly impact the health of the spine. Other factors such as the absence of adequate ergonomic conditions in the school environment, such as classroom desks, and the lack of attention of educational institutions to the postural education of the student population, have contributed negatively to the adoption of incorrect postures of the student population.

The frequent transport of school backpacks with high loads also contributes significantly to the development of discomfort, pain, and changes in the musculoskeletal system (RICARDO et al., 2024). In addition, the demands of student life, often associated with high levels of stress and tension, can intensify muscle tension, further aggravating the impacts on spine health. In this scenario, it is essential to understand how these factors influence the physical development of young people and children.

The school phase is a decisive period for the formation of habits, including postural ones, which can have repercussions throughout life. Thus, inadequate practices adopted early can favor the emergence of chronic dysfunctions in adult life. The importance of implementing structural and behavioral changes in the school environment is highlighted, through the adoption of positive practices aimed at health promotion. International studies show (VIEIRA, 2019) that the insertion of systematized postural correction programs, combined with the regular practice of physical activity in the school context, contributes significantly to the prevention of musculoskeletal changes (SANTOS et al., 2017).

In this sense, the experience of health promotion in some schools demonstrates that the incorporation of postural correction in physical education classes, together with the obligation of physical activity and a perspective of comprehensive health. (SOMHEGYI, 2022).

The purpose of this study is to investigate the factors related to the school environment and the students' lifestyle, which is essential for the identification of risks and for the proposition of preventive strategies. From the peak strategy, a survey of articles that could address such elements was made, in order to be able to raise content on the subject, and elucidate essential practices for changing these conditions.

2 HYPOTHESIS

Factors of the academic routine, such as ergonomic absence, inadequate posture and carrying excessive loads, are part of the school routine and cause damage to the health of the spine, as well as the constant tension that student life promotes, reflecting in muscle tension, leading to pain and musculoskeletal changes. However, changes can be made in the environment and also in postural habits, in order to improve the quality of spine health.

3 JUSTIFICATION

The present study is justified by the increasing incidence of postural alterations and complaints of back pain in children and adolescents, associated with daily school habits and a sedentary lifestyle that is increasingly common in this age group. The school environment requires long periods in the sitting position, often on inadequate furniture, in addition to the daily transport of backpacks with excessive weight, factors that can contribute to musculoskeletal overloads and postural deviations.

In addition, the school environment goes beyond the physical limits of the school, extending to the home context, where the prolonged use of electronic devices, the performance of tasks in inappropriate places and the reduction of the practice of physical activities intensify the risks to the health of the spine. Considering that inadequate postural habits acquired in childhood and adolescence can persist into adulthood, increasing the predisposition to chronic pain and musculoskeletal dysfunctions, it is essential to investigate these factors early.

4 OBJECTIVES

4.1 GENERAL

- Identify the main habits that can negatively interfere with the health of the spine of children and adolescents.

4.2 SPECIFIC

Identify everyday school actions that can interfere with spine health;

- Analyze factors external to school that also influence spine health;
- Discuss the strategies normally used in the school environment to improve postural quality and prevent back problems.

5 METHODOLOGY

For this study, we used the structure referring to the integrative review with the theme "Impact of school lifestyle on spine health in children and adolescents.", which is an evidence study.

At the time of defining the guiding questions, it was thought about how these questions would select a certain group of articles that could fit the object of study. It was decided to use the PICO strategy that is presented below in the format of a flowchart table. The PICO strategy is used to construct research questions that can be of different natures. An adequate search question will enable the correct definition of search, thus expanding the results in the databases, optimizing the search and focusing the scope of the search, which will avoid unnecessary searches (NOBRE, PIMENTA and SANTOS, 2007).

For its execution, studies related to the theme were selected that could answer the research question: "Which school habits among children and adolescents can negatively interfere with spine health?", the key terms of the research were defined, namely: Spine health; School. After defining these terms, searches began in previously selected databases, PubMed, Latin American and Caribbean Literature on Health Sciences (LILACS) in the Plus classification and Scientific Electronic Library Online (SciELO), the study was carried out during the month of March 2026.

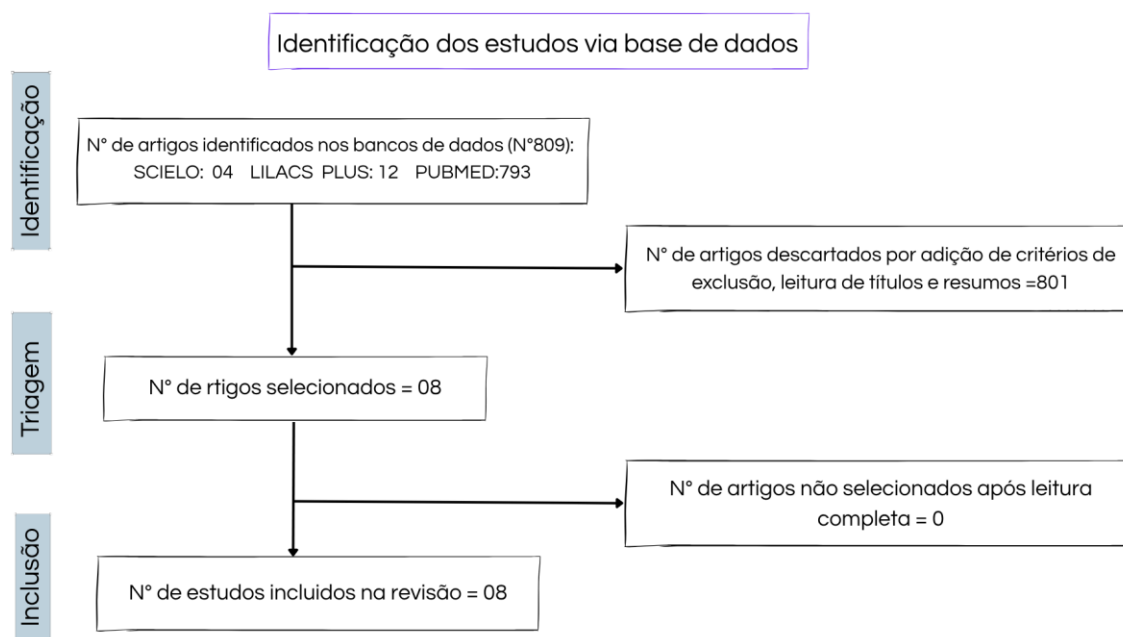
As inclusion criteria, we searched for articles with less than five (5) years of publication, which had in their content the correlation between posture and/or spine health with the activities of the target audience, being high school and elementary school students, who relate school activities as factors of interference in spine health, as well as methods, analyses, suggestions or comparisons of possible prevention strategies aimed at improving posture and spine health.

The exclusion criteria were articles with more than five (5) years of publication; those with a focus on diagnosis unrelated to spine or posture, genetic conditions, paid jobs or restricted access to paid login accounts, isolated case studies, those in which they are not related to the school environment or practices, as well as those not associated with elementary and/or high school students, those in which the target audience diverges from those of the objective of this study.

Articles that met the exclusion criteria or did not fit the inclusion criteria were discarded, resulting in a final selection of 08 publications, which were used for the present review.

Figure 1

PRISMA flowchart for the identification, screening and inclusion of the publications selected for this integrative review. Eunápolis, BA, Brazil, 2026.



Source: Survey data, 2026.

After selection, the articles were read and analyzed, with the aim of responding to the previously determined objectives.

6 RESULTS

The articles covered portray studies between the years 2021 and 2025, are international productions from several countries, including: one from Germany, two from China, one from Spain, one from Hungary, one from Iran, one from Paraguay and one from Portugal, which have different approaches, namely: a clinical trial, a pilot study, a case-control study, one literature review and four cross-sectional studies. Its main characteristics are described in the table below:

Table 1

Table identifying the main characteristics of the publications selected for this integrative review. Eunápolis, BA, Brazil, 2026

Original title	Translated title	Author/Year/Place	Type of study	Findings	DOI/PMID
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The effect and durability of postural education and corrective games on the alignment of the thoracic and cervical spine and the daily habits in children.	Effect and durability of postural education and corrective games on thoracic and cervical spine alignment and daily habits in children.	Majid Barzegari & Ali Shamsi Majelan / 2025/ Baharestan - Iran	Clinical Trial	Both exercise and control interventions significantly reduced kyphosis angle, head-forward posture, and shoulder-forward posture, while improving daily activity patterns, with no notable differences in effectiveness. Sample number: 60 participants.	DOI: https://doi.org/10.1038/s41598-025-29071-6
Postural evaluation and factors associated with spinal changes in schoolchildren with daily backpack use: a cross-sectional study.	Postural assessment and factors associated with spinal changes in schoolchildren who use backpacks daily: a cross-sectional study.	Willian Ricardo Cabañas & Akira Kikuchi Hisaoka, / 2024 / San Lorenzo - Paraguay	Cross-sectional study	The prevalence of postural abnormalities was significant, predominantly in males. Inappropriate use of backpacks and previous injuries are important risk factors. Preventive programs focused on postural education and the correct use of school bags are needed. Sample number: 192 students between 6 and 14 years old, students from private schools.	DOI: https://doi.org/10.18004/anales/2024.057.03.28

Epidemiology of spinal pain in a population of schoolchildren from Spain.	Epidemiology of spinal pain in a population of school children in Spain.	Fraiz Barbeito M, Rey Veiga S, González Y, Da Cuña Carrera I, et al / 2021/ Galicia - Spain	Cross-sectional study	School-age children reported spinal pain, which was mild and short-lived, often in the cervical region. The association with risk factors indicates that children who reported pain have better postural habits.	DOI: http://dx.doi.org/10.5546/aap.2021.eng.364
Prevalence, characteristics, and impact of spinal and lower limb recurrent pain at age 13	Prevalence, characteristics, and impact of recurrent pain in the spine and lower limbs at 13 years of age.	Rodrigues, Elisa et al / 2024 / Portugal	Cross-sectional study	More than half of the adolescents reported recurrent pain in the spine or lower limbs, with back pain being more frequent, intense and lasting. However, lower limb pain resulted in more concomitant limitations.	PMID: 38956994.
Increased backpack weight might lead to increased trunk stiffness during walking in primary school aged children: A pilot study	Increased backpack weight may lead to increased trunk stiffness during walking in primary school-aged children: A pilot study.	Mueller, Juliane et al. / 2025/ Trier – Germany	Pilot Study	The additional weight of the backpack led to a more flexed trunk posture during the standing position and reduced trunk movement in the transverse and frontal planes, stride length, and	DOI: 10.1016/j.gaitpost.2025.09.004

				gait speed during walking. These adjustments probably compensate for the dorsal shift of the center of mass and minimize energy expenditure by reducing the angular momentum of the trunk and backpack during walking.	
Sagittal imbalance of the spine is associated with poor sitting posture among primary and secondary school students in China: a cross-sectional study	Sagittal spinal imbalance is associated with poor sitting posture in middle and high school students in China: a cross-sectional study.	Li, Chaoqun et al. / 2022 / China	Cross-sectional study	There was a significant correlation between the sagittal angle of the spine in different postures. Poor sitting posture, associated with abnormalities in the sagittal angle, impacts the shape of the spine, so that sagittal imbalance was also observed when students were in a natural upright posture. Height is an important factor that affects the shape of the students' spine when they are sitting.	DOI: 10.1186/s12891-022-05303-y

Posture correction as part of holistic health promotion in Hungarian schools	Postural correction as part of holistic health promotion in Hungarian schools.	Annamária Sonhegyi / 2022/ Hungary	Literature review	Postural correction exercises that develop, automate, and maintain a biomechanically correct posture. Postural correction could be monitored by the school health service using the Matthiass test ²⁶ , which is a semi-objective clinical test to detect postural muscle weakness.	DOI: 10.18071/isz.75.0151
Academic-related factors and daily lifestyle habits associated with adolescent idiopathic scoliosis: a case-control study	Academic factors and daily life habits associated with adolescent idiopathic scoliosis: a case-control study	Dou Q, Zhu Z, Zhu L, et al. / 2023 / Shenzhen - China	Case Study - Control	Academic factors and daily lifestyle habits have been associated with Inappropriate Attachment Syndrome (IAS) among Chinese adolescents . It is recommended that schools, families and related institutions take steps to develop effective SAI prevention and management strategies that integrate the	doi:10.1265/ehpm.22-00243

				"Student-Family-School-Education-Health-Sport" pillars.	
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Source: Survey data, 2026.

The studies address that the health of the spine in children and adolescents can indeed have interference with the school lifestyle, since the incorrect use of backpacks associated with overweight is linked to complications of postural dysfunctions and significant pain, as well as ergonomic aspects of school furniture, where they remain seated for long periods and without breaks in chairs and tables with anthropometric characteristics that generate the adoption of unfavorable postures. However, it is not the only factor that negatively interferes with the health of the spine, what happens is a set of out-of-school and school habits. What generates dysfunctions and pain are not just isolated acts, but constancy, when this becomes a habit, the result of a convergence of risky behavior, inside and outside the school environment. (CABAÑAS et al., 2024; BARBEITO et al., 2021)

Outside the school environment, the set that generates sedentary lifestyle, such as inadequate posture for long periods of time in daily activities, excessive use of screens and consoles combined with poor diet generate significant impairments that will intensify the damage to the health of the spine, increasing the susceptibility to deformities, such as idiopathic scoliosis, due to reduced bone density and poor muscle nutrition, in addition, the absence of physical activity generates muscle weakness contributing to overloads in the vertebral structure. (DOU Q, et al., 2023; BARZEGARI, M., et al.2025)

Evidence indicates that inadequate reading and writing posture, which occur both inside and outside the school environment, promotes significant changes in the physiological curvatures of the spine, with an increase in thoracic kyphosis and a reduction in lumbar lordosis, and may even lead to the disappearance of this curvature in a prolonged sitting position. (LI, Chaoqun et al., 2022)

Although changes in extracurricular habits are of paramount importance, there are interventions that can be applied in the educational environment, with the aim of reducing such harm and promoting postural health, studies show that the implementation of a schedule with active breaks during the school period, practice of physical activity and corrective games (physical education), bring benefits, correcting postural vices and reducing muscle weakness. Promoting positive changes in habits, which although not the complete solution, since these changes should extend to daily life as a whole, already helps in the

maintenance of the spine, even more so if associated with constancy. (BARZEGARI, M.; MAJELAN, A., 2025).

7 DISCUSSION

The findings of this study show that postural changes in children and adolescents result from the interaction between school and extracurricular factors, reinforcing the multifactorial character of musculoskeletal dysfunctions. While the home environment contributes to sedentary habits, excessive use of electronic devices, and inadequate postures, the school environment also plays a relevant role in both the emergence and prevention of these problems. In this context, factors such as prolonged sitting position, ergonomic inadequacy of furniture, and incorrect use of backpacks are directly associated with increased overload on the spine and the development of back pain. When associated with inappropriate habits maintained outside of school, these factors potentiate the negative effects on the biomechanics of the spine (ROSSI et al., 2021; CABAÑAS et al., 2024).

In view of this scenario, the implementation of preventive strategies in the school environment is fundamental. Postural education programs stand out as one of the main interventions, promoting students' awareness of the adoption of more appropriate habits in their daily lives. Evidence indicates that these actions contribute to the improvement of postural behavior and reduction of musculoskeletal complaints, although their effectiveness depends on the continuity of practices and student adherence (BATISTÃO et al., 2019).

The inadequacy of school furniture, which often does not respect the anthropometric characteristics of students, generates relevant impacts. This mismatch leads to postural compensations, such as anterior flexion of the trunk and projection of the head, contributing to changes in spinal alignment over time. Ergonomically adjusted environments contribute to better body alignment and reduced spine overload, although their implementation is still limited in many school contexts (CABAÑAS; KIKUCHI HISAOKA, 2024).

In addition, the inadequate transport of school bags is one of the main risk factors. Studies show that excess weight and incorrect use of backpacks are associated with an increased incidence of back pain and postural changes in schoolchildren (FERNÁNDEZ et al., 2021). The transport of excessive loads, combined with asymmetric use, reinforces the need for continuous educational interventions, since punctual changes tend not to generate lasting impact (ROSSI et al., 2021).

Another relevant point refers to the encouragement of the practice of physical activity and the insertion of active breaks during the school period. These strategies contribute to reducing the time spent in static posture, promoting improved postural control, muscle

strengthening, and reducing overload on the spine, and are considered accessible and feasible measures in the school context (BATISTÃO et al., 2019). The absence of postural education in the school environment is also a relevant factor.

The lack of guidance on appropriate habits favors the perpetuation of harmful behaviors throughout growth. In this context, recent studies indicate that structured interventions with exercise and health education promote improvements in muscle endurance and postural behavior (WEIGEL; GRIFKA; JANSEN, 2025).

Finally, the importance of an integrated approach, involving the articulation between school and family, is highlighted. Thus, it is observed that the factors of daily school life do not act in isolation, but in a multifactorial way. The association between sedentary lifestyle, inadequate ergonomics, mechanical overload, and lack of orientation contributes significantly to the development of postural changes and back pain, highlighting the need for preventive strategies in the school environment (FERNÁNDEZ et al., 2021; CABAÑAS; KIKUCHI HISAOKA, 2024; WEIGEL; GRIFKA; JANSEN, 2025).

8 CONCLUSION

Therefore, it can be concluded that spine health in children and adolescents is influenced by a multifactorial set, involving the school environment and daily habits.

It was possible to identify that actions of daily school life, such as the inappropriate use of backpacks, prolonged sitting and the inadequacy of ergonomic school furniture, exert an important influence on spine health. At the same time, factors external to the school, such as a sedentary lifestyle, excessive use of electronic devices, poor posture in daily activities and low practice of physical activity and/or few and/or non-existent practices in schools aimed at postural corrections, potentiate these negative impacts.

From this perspective, it was observed that strategies applied in the school environment, such as postural education programs, insertion of active breaks and encouragement of physical activity, present positive results in the promotion of spine health and in the prevention of postural changes. It is important to note that its efficiency will only occur when such practices are being carried out continuously, in order to actually integrate healthy and corrective habits for posture, so that they can occur outside the school environment.

Thus, there is a need for an integrated approach between school, family and health professionals, aiming to promote behavioral changes for spine health. The implementation of educational policies that include ergonomics, more appropriate furniture for ergonomics in schools and health education, and the encouragement of physical activity is essential to

reduce the incidence of postural problems for the healthy development of the school population.

Finally, the importance of practices and policies aimed at spinal health in schools is reinforced, and therefore, a study of the area should be carried out to enhance preventive strategies directed to the reality of the context to be inserted, to promote a better quality of life from childhood to adolescence.

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TIRZEPATIDE AND THE RISKS OF USE WITHOUT MEDICAL PRESCRIPTION

TIRZEPATIDA E OS RISCOS DO USO SEM PRESCRIÇÃO MÉDICA

TIRZEPATIDA Y LOS RIESGOS DEL USO SIN PRESCRIPCIÓN MÉDICA



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ABSTRACT

Tirzepatide represents a milestone in metabolic pharmacotherapy as the first dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Although it has demonstrated unprecedented efficacy in reducing glycated hemoglobin (HbA1c) and body weight in the treatment of type 2 diabetes and obesity, its growing popularity has generated a concerning phenomenon of non-prescribed use without medical supervision. The objective of this study is to conduct a literature review on tirzepatide, emphasizing the risks associated with its use without prescription. The analysis of the safety profile indicates that the most frequent adverse events are gastrointestinal (nausea, diarrhea, and vomiting), in addition to serious and rare risks such as acute pancreatitis, gallbladder disease, acute kidney injury, and warnings regarding suicidal ideation and thyroid C-cell tumors. It is concluded that use without supervision eliminates the screening of absolute contraindications, predisposes individuals to inappropriate dose titration, nullifies the monitoring of serious drug interactions, and exposes users to the dangers of the unregulated market, including counterfeit products and improper storage.

Keywords: Tirzepatide. Dual GIP/GLP-1 Agonist. Self-Medication. Adverse Effects. Patient Safety.

RESUMO

A tirzepatida representa um marco na farmacoterapia metabólica como o primeiro agonista duplo dos receptores do polipeptídeo insulínotropo dependente de glicose (GIP) e do peptídeo semelhante ao glucagon-1 (GLP-1). Embora tenha demonstrado uma eficácia sem precedentes na redução da hemoglobina glicada (HbA1c) e na perda de peso corporal no tratamento do diabetes tipo 2 e da obesidade, sua crescente popularização gerou um fenômeno preocupante de uso não prescrito e sem supervisão médica. O objetivo deste trabalho é realizar uma revisão bibliográfica sobre a tirzepatida, enfatizando os riscos de

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seu uso sem prescrição. A análise do perfil de segurança aponta que os eventos adversos mais frequentes são gastrointestinais (náuseas, diarreia e vômitos) , além de riscos graves e raros, como pancreatite aguda, doença biliar, lesão renal aguda e advertências sobre ideação suicida e tumores de células C da tireoide. Conclui-se que o uso sem supervisão elimina a triagem de contraindicações absolutas , predispõe a uma titulação inadequada de doses , anula o monitoramento de interações medicamentosas graves e expõe o usuário aos perigos do mercado não regulamentado, incluindo produtos falsificados e armazenamento inadequado.

Palavras-chave: Tirzepatida. Agonista Dual GIP/GLP-1. Automedicação. Efeitos Adversos. Segurança do Paciente.

RESUMEN

La tirzepatida representa un hito en la farmacoterapia metabólica como el primer agonista dual de los receptores del polipéptido insulínico dependiente de glucosa (GIP) y del péptido similar al glucagón tipo 1 (GLP-1). Aunque ha demostrado una eficacia sin precedentes en la reducción de la hemoglobina glucosilada (HbA1c) y en la pérdida de peso corporal en el tratamiento de la diabetes tipo 2 y la obesidad, su creciente popularización ha generado un fenómeno preocupante de uso sin prescripción y sin supervisión médica. El objetivo de este trabajo es realizar una revisión bibliográfica sobre la tirzepatida, enfatizando los riesgos de su uso sin prescripción médica. El análisis del perfil de seguridad indica que los eventos adversos más frecuentes son gastrointestinales (náuseas, diarrea y vómitos), además de riesgos graves y raros como pancreatitis aguda, enfermedad biliar, lesión renal aguda y advertencias sobre ideación suicida y tumores de células C de la tiroides. Se concluye que el uso sin supervisión elimina el cribado de contraindicaciones absolutas, predispone a una titulación inadecuada de las dosis, anula el monitoreo de interacciones medicamentosas graves y expone al usuario a los peligros del mercado no regulado, incluidos productos falsificados y almacenamiento inadecuado.

Palabras clave: Tirzepatida. Agonista Dual GIP/GLP-1. Automedicación. Efectos Adversos. Seguridad del Paciente.

1 INTRODUCTION

Tirzepatide represents a milestone in metabolic pharmacotherapy as the first dual agonist of GIP (glucose-dependent insulintropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors approved for clinical use.^{[1][2]} Approved by the FDA in May 2022 for the treatment of type 2 diabetes and later in 2023 for obesity, tirzepatide has demonstrated unprecedented efficacy in reducing glycated hemoglobin (HbA1c) and losing body weight.^{[3][4]}

However, the growing popularization of this drug has been accompanied by a worrying phenomenon: its use without prescription and without adequate medical supervision. This course completion work aims to carry out a comprehensive literature review on tirzepatide, with special emphasis on the risks associated with its use without a medical prescription, providing scientific support for the understanding of the dangers of this practice.

The relevance of this topic for biomedicine lies in the need to understand not only the pharmacological mechanisms and clinical efficacy of tirzepatide, but also the risks inherent to its inappropriate use, contributing to health education and the prevention of avoidable adverse events.

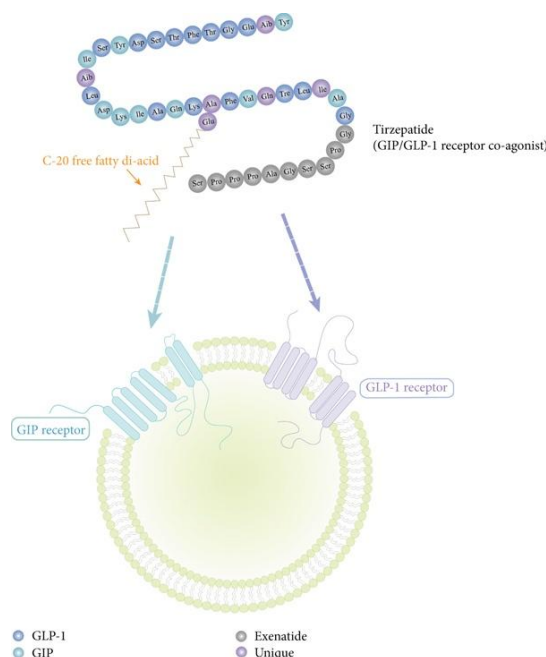
2 MOLECULAR STRUCTURE AND MECHANISM OF ACTION

2.1 CHEMICAL STRUCTURE

Tirzepatide is a synthetic acylated peptide composed of 39 amino acids, whose structure is based primarily on the sequence of the native GIP.^{[1][4]} A distinctive feature of its structure is the presence of a C20 di-acid fatty acid chain attached to a lysine residue, a modification that facilitates binding to albumin and significantly prolongs the half-life of the molecule.^{[2][5]}

Figure 1

The structure of tirzepatide. undefined



This structural modification allows a half-life of approximately 116.7 hours (about 5 days), making it possible to administer subcutaneously weekly.^{[1][2]} The molecular structure has been engineered to activate both GIP receptors and GLP-1 receptors, albeit with different affinities—it has comparable affinity to GIP receptors, but weaker binding to GLP-1 receptors compared to native GLP-1.^[5]

2.2 DUAL MECHANISM OF ACTION

The mechanism of action of tirzepatide involves the simultaneous activation of two complementary incretin systems:^{[1][6]}

GLP-1 Receptor Activation: GLP-1 is an incretin hormone that stimulates insulin secretion in hyperglycemic states, suppresses glucagon secretion in hyperglycemic or euglycemic conditions, slows gastric emptying, decreases appetite, and reduces body weight.^[1] GLP-1 receptors are expressed in pancreatic beta cells and in brain regions that regulate dietary intake.^{[1][2]}

GIP Receptor Activation: GIP is the main incretin hormone in healthy individuals and has insulinotropic properties. Unlike GLP-1, GIP is glucagonotropic in a glucose-dependent manner - in hyperglycemic conditions, it stimulates insulin release and reduces glucagon levels; In euglycemic or hypoglycemic conditions, glucagon levels are increased.^[1] GIP receptors are abundant in adipose tissue, where GIP enhances the postprandial lipid

buffering capacity of white adipose tissue and insulin sensitivity, potentially preventing ectopic fat deposition.^[1]

Synergy of Mechanisms: Preclinical studies have shown that the combined agonism of GIP and GLP-1 produces robust weight loss effects independent of insulin sensitivity and lipid metabolism.^[4] In diet-induced obese mice, combined agonism showed greater anorexic action compared to semaglutide, increasing satiety and satiety, reducing preference for high-fat diets, and decreasing preference for sweet taste.^[4]

The hypothesis is that the GIP component of dual agonism acts centrally to potentiate the GLP-1-induced reduction in food intake.^[1] This synergistic action results in superior effects on glycemic control and body weight reduction compared to selective GLP-1 agonists.^{[6][3]}

2.3 PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic properties of tirzepatide have been characterized in clinical studies:^[2]

- **Absorption:** Weekly subcutaneous administration
- **Half-life:** Approximately 5 days (116.7 hours)
- **Metabolism:** Metabolites are excreted through urine and feces
- **Dose adjustments:** The pharmacodynamic and pharmacokinetic properties of tirzepatide were similar in patients with renal and hepatic impairment, and no dose adjustment was required in these conditions^{[2][7][8]}

Tirzepatide increases insulin secretion, reduces glucagon release in a glucose-dependent manner, decreases fasting and postprandial glucose levels, promotes satiety, decreases body weight, and delays gastric emptying.^[2]

3 CLINICAL EFFICACY

3.1 EFFICACY IN TYPE 2 DIABETES: SURPASS PROGRAM

The SURPASS phase III clinical trial program (SURPASS-1 to SURPASS-6) evaluated the efficacy and safety of tirzepatide in patients with type 2 diabetes.^{[3][4][9][10]}

SURPASS-1 (Monotherapy): This double-blind, randomized, phase 3 study evaluated tirzepatide as monotherapy in patients with type 2 diabetes.^[4] Placebo-adjusted reductions in HbA1c were 21 mmol/mol (1.91%), 21 mmol/mol (1.93%), and 23 mmol/mol (2.11%) with tirzepatide 5, 10, and 15 mg weekly, respectively.^[9] Notably, 87–92% of participants met the American Diabetes Association's target of 7.0% HbA1c, and 31–52%

achieved normoglycemia (HbA1c 5.7%) with no increased risk of clinically significant hypoglycemia.^[4]

Relative to body weight, tirzepatide demonstrated significant mean reductions at all doses. The proportion of participants who achieved weight loss $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ was substantial, demonstrating benefits beyond glycemic control.^[4]

SURPASS-2 (Comparison with Semaglutide): This study directly compared tirzepatide with semaglutide 1.0 mg weekly, a selective GLP-1 agonist.^[1] Tirzepatide has demonstrated superiority in both glycemic control and weight loss. Weight reductions were 8.5%, 11.0%, and 13.0% at the 5, 10, and 15 mg doses of tirzepatide, respectively, compared to 6.7% with semaglutide 1 mg.^[1]

SURPASS-6 (Addition to Basal Insulin): This study evaluated tirzepatide versus insulin lispro added to basal insulin in patients with type 2 diabetes.^[10] Tirzepatide demonstrated significant superiority in reducing HbA1c and body weight. In addition, the incidence of clinically significant hypoglycemia was substantially lower with tirzepatide (9-12% of participants) compared to insulin lispro (48%), with event rates of 0.4 versus 4.4 events/patient-year.^[10] **Meta-analysis of the SURPASS Program:** A meta-analysis including seven clinical trials with 6,609 participants confirmed the dose-dependent superiority of tirzepatide in HbA1c reduction versus all comparators, with mean differences ranging from -17.71 mmol/mol (-1.62%) to -22.35 mmol/mol (-2.06%) versus placebo.^[3]

3.2 EFFICACY IN OBESITY: SURMOUNT PROGRAM

The SURMOUNT program specifically investigated the efficacy of tirzepatide for the treatment of obesity.^{[11][12]}

SURMOUNT-1: This 72-week study evaluated tirzepatide in participants with obesity without type 2 diabetes.^[12] The highest dose (15 mg) resulted in an average weight reduction of 22.5%, with nearly 40% of participants losing $\geq 25\%$ of body weight. The rates of participants achieving weight loss $\geq 5\%$ ranged from 67-78%, $\geq 10\%$ from 31-47%, and $\geq 15\%$ from 13-27%.^[12]

The most frequent adverse events were gastrointestinal (nausea, diarrhoea, and constipation), occurring in more participants in the tirzepatide groups than in the placebo group, being generally transient, mild to moderate in severity, and occurring mainly during the dose escalation period.^[12]

SURMOUNT-2: In patients with obesity and type 2 diabetes, tirzepatide reduced weight by an average of 12.8% and 14.7% at doses of 10 and 15 mg, respectively, with a

reduction in HbA1c of 2.2%. Almost half of the participants achieved normal HbA1c values (5.7%).^[11]

SURMOUNT-3 and SURMOUNT-4: These studies demonstrated that combining tirzepatide with intensive lifestyle intervention or continuing treatment for 88 weeks resulted in weight reduction of up to 26.6% and 26%, respectively.^[11] In SURMOUNT-3, discontinuation rates due to adverse events were 10.5% in the tirzepatide group versus 2.1% in the placebo group.^[11]

3.3 DIABETES PREVENTION AND OTHER INDICATIONS

Diabetes Prevention: A recent study published in 2025 evaluated tirzepatide for obesity treatment and diabetes prevention in participants with prediabetes.^[13] The results demonstrated significant efficacy in reducing weight and preventing progression to type 2 diabetes. Four cases of adjudication-confirmed pancreatitis were reported, evenly distributed between the treatment groups, including placebo, and none were classified as severe.^[13]

Obstructive Sleep Apnea: In December 2024, tirzepatide became the first prescription drug approved for the treatment of moderate to severe obstructive sleep apnea in adults with obesity.^[14] The studies demonstrated significant improvement in sleep apnea parameters, with a safety profile consistent with previous studies.^[14]

3.4 ADDITIONAL CARDIOMETABOLIC BENEFITS

In addition to glycemic control and weight loss, tirzepatide has demonstrated improvements in multiple cardiometabolic risk factors:^{[9][4]}

- **Lipid profile:** Reduction of total cholesterol, triglycerides, VLDL and LDL, with an increase in HDL^[4]
- **Insulin sensitivity:** Significant improvement in insulin resistance as assessed by HOMA-IR^[4]
- **Blood pressure:** Reduction of systolic blood pressure- **Hepatic fat:** Improvement of liver fat content and reduction of visceral and subcutaneous abdominal adipose tissue^[9]
- **Cardiovascular safety:** Pre-specified post-hoc analyses showed that tirzepatide did not increase the risk of MACE (major adverse cardiovascular events) in participants with type 2 diabetes compared to controls^{[3][9]}

4 SAFETY PROFILE AND ADVERSE EVENTS

4.1 GASTROINTESTINAL ADVERSE EVENTS

The most frequent adverse events with tirzepatide are gastrointestinal, including nausea, diarrhea, constipation, and vomiting.^{[13][12][11][10][5][14]} These events were generally mild to moderate, transient, and occurred primarily during the dose-escalation period.^{[13][12][11]}

In SURMOUNT-1, nausea occurred in 24.6-33.3% of participants on tirzepatide versus 9.5% on placebo; diarrhea in 18.7-23.0% versus 7.3%; and vomiting in 8.3-12.2% versus 1.7%.^[12] In SURMOUNT-3, the three most common adverse reactions were nausea (tirzepatide: 39.7%; placebo: 14.0%), diarrhea (tirzepatide: 31.0%; placebo: 9.2%), and constipation (tirzepatide: 23.0%; placebo: 6.8%).^[11] In SURPASS-6, the most frequent gastrointestinal events with tirzepatide included nausea (14-26%), diarrhea (11-15%), and vomiting (5-13%).^[10] Most cases were mild to moderate in severity, transient, and occurred during the dose escalation period.^[10]

Meta-analyses confirmed increased odds of gastrointestinal events, particularly nausea, with tirzepatide compared to other long-acting GLP-1 agonists.^[9] Interestingly, some studies suggest that tirzepatide may have a slightly lower frequency of gastrointestinal side effects than selective GLP-1 agonists, possibly due to its unbalanced dual agonist effect favoring GIPR activity over GLP-1R.^[5]

4.2 SERIOUS ADVERSE EVENTS

Pancreatitis: Rare cases of acute pancreatitis have been reported.^{[13][12][8][14]} In SURMOUNT-1, there were four adjudication-confirmed cases, evenly distributed among treatment groups, including placebo, and none were classified as severe.^[12] In the diabetes prevention study, four cases were reported (three in the tirzepatide groups and one in the placebo group).^[13] In SURPASS-6, there were no cases of adjudicated pancreatitis.^[10] In the sleep apnea studies, there were two confirmed cases of acute pancreatitis in the tirzepatide group of trial 2.^[14]

Biliary Disease: The incidence of cholelithiasis was generally similar between the tirzepatide and placebo groups, although cholecystitis and acute cholecystitis were reported more frequently in the tirzepatide groups, with low incidences ($\leq 0.6\%$).^[12] In SURPASS-6, nine participants treated with tirzepatide and two treated with insulin lispro reported cholelithiasis.^[10] There is a small increased risk of gallbladder or biliary diseases that may be associated with GLP-1 agonists, and may be dose-dependent, duration, or indication-dependent.^[8]

Hypoglycemia: When used as monotherapy or without sulfonylureas/insulin, tirzepatide does not increase the risk of hypoglycemia.^{[7][5]} In SURPASS-1, there were no cases of clinically significant (54 mg/dL) or severe hypoglycemia with tirzepatide.^[4] In patients with type 2 diabetes, hypoglycemia occurs in about 4%, but is rare (0.5%) in patients without diabetes.^[7] In SURPASS-6, when added to basal insulin, the incidence of clinically significant hypoglycemia was substantially lower with tirzepatide (9-12%) compared to insulin lispro (48%).^[10]

Acute Kidney Injury: Has occurred rarely according to postmarketing reports, particularly in patients with nausea, vomiting, diarrhea, or dehydration.^[7]

Cardiovascular Events and Mortality: In SURMOUNT-1, eleven deaths were reported: 4 (0.6%) in the tirzepatide 5 mg group, 2 (0.3%) in the 10 mg group, 1 (0.2%) in the 15 mg group, and 4 (0.6%) in the placebo group.^[12] In the diabetes prevention study, ten deaths were reported, with seven occurring in the tirzepatide groups and three in the placebo group.^[13] None of the deaths were considered treatment-related by the investigators.^[10]

Mental Health: Based on experience with other weight loss medications, tirzepatide carries warnings about increased behavior and suicidal ideation.^{[11][7]} In the sleep apnea studies, there were five cases of major depressive disorder or suicidal ideation/behavior in both studies (two with tirzepatide and three with placebo).^[14] Patients should be monitored and the drug should not be prescribed to patients with a history of suicidal attempts or active ideation.^{[11][7]}

4.3 DISCONTINUATION FEES

Discontinuation rates due to adverse events varied between studies. In SURMOUNT-1, 4.3-7.1% of participants on tirzepatide discontinued versus 2.6% on placebo.^[12] In the combined SURMOUNT-1 and -2 studies, discontinuation due to adverse events occurred in 4.8%, 6.3%, and 6.7% of patients receiving tirzepatide 5 mg, 10 mg, and 15 mg, respectively, and 3.4% of patients receiving placebo.^[11] In SURMOUNT-3, 10.5% and 2.1% of patients in the tirzepatide and placebo groups, respectively, discontinued treatment due to adverse events.^[11] In SURMOUNT-4, the proportions were 1.8% and 0.9%.^[11]

The 15 mg dose had a higher discontinuation rate regardless of the comparator.^[12] Discontinuations due to gastrointestinal adverse events in SURPASS-1 were 2-7% with tirzepatide versus 1% with placebo.^[4]

4.4 CONTRAINDICATIONS AND WARNINGS

Black-Box Warning: Tirzepatide has a black-box warning on thyroid C-cell tumors, based on rat data of uncertain significance for humans. It is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).^{[11][7][5][8]}

Additional Precautions:

- Caution in patients with a history of biliary disease or pancreatitis^[8]
- Caution in patients with a history of diabetic retinopathy
- Delayed gastric emptying may alter the absorption of oral medications, particularly oral contraceptives. Non-oral contraception or barrier method is recommended for 4 weeks after initiation and after each dose escalation^{[11][7][8]}
- Should not be used in pregnant women and should be discontinued if pregnancy occurs^{[7][8]}
- Insufficient data on presence in breast milk^{[7][8]}
- Not studied in children^{[7][8]}
- Does not require dose adjustment in patients with renal or hepatic impairment^{[7][8]}

4.5 POST-MARKETING PHARMACOVIGILANCE DATA

An analysis of the FDA's adverse event reporting system (FAERS) investigated the actual safety profile of tirzepatide.^[15] The study detected disproportionate reporting of gastrointestinal events (nausea with ROR 4.01, 95% CI 3.85-4.19), pancreaticobiliary disorders (pancreatitis with ROR 3.63, 95% CI 3.15-4.19), diabetic retinopathy (ROR 4.14, 95% CI 2.34-7.30), and medullary thyroid carcinoma (ROR 13.67, 95% CI 4.35-42.96).^[15]

However, tirzepatide exhibited a similar risk of gastrointestinal events and medullary thyroid carcinoma and a lower risk of most pancreaticobiliary adverse events and diabetic retinopathy versus GLP-1 agonists.^[15] The safety profile was similar to that of GLP-1 agonists, with no increased risk of pancreaticobiliary adverse events, diabetic retinopathy, and medullary thyroid carcinoma.^[15]

5 RISKS OF USE WITHOUT A MEDICAL PRESCRIPTION

5.1 ABSENCE OF SCREENING FOR CONTRAINDICATIONS

The use of tirzepatide without medical supervision eliminates essential screening for absolute contraindications, including:

History of Medullary Thyroid Carcinoma or MEN 2: Tirzepatide is absolutely contraindicated in patients with a personal or family history of Medullary Thyroid Carcinoma

or multiple endocrine neoplasia syndrome type 2.^{[11][7][5][8]} Without proper medical evaluation, individuals with these conditions may inadvertently use the drug, exposing themselves to serious risks.

History of Pancreatitis: Although pancreatitis is rare with tirzepatide, patients with a prior history of pancreatitis require special caution.^[8] Unsupervised use prevents proper assessment of this risk.

History of Biliary Disease: Patients with a history of biliary disease require careful monitoring as there is an increased risk of cholecystitis and cholelithiasis.^{[12][8]}

Mental Health: Tirzepatide should not be prescribed to patients with a history of suicidal attempts or active ideation.^{[11][7]} Without adequate psychiatric evaluation, vulnerable individuals may use the drug without the necessary monitoring.

5.2 INADEQUATE TITRATION AND GASTROINTESTINAL ADVERSE EVENTS

Tirzepatide requires careful titration starting at 2.5 mg weekly with monthly tapering to minimize gastrointestinal adverse events.^{[4][11]} The optimized escalation schedule was developed specifically to improve gastrointestinal tolerability.^[4]

Risks of Improper Titration:

- **Severe gastrointestinal events:** Severe nausea, vomiting, and diarrhea may occur in up to 3% of patients. Without proper titration, these events can be more frequent and severe^[7]
- **Dehydration and electrolyte imbalances:** Serious gastrointestinal events can lead to significant dehydration and electrolyte imbalances, particularly dangerous in vulnerable patients- **Acute kidney injury:** Dehydration secondary to gastrointestinal events can precipitate acute kidney injury, as reported in post-marketing data^[7]
- **Premature discontinuation:** Serious adverse events due to improper titration can lead to premature discontinuation of treatment, preventing patients who could benefit from the drug from using it properly

5.3 LACK OF MONITORING OF ORAL CONTRACEPTIVE DRUG INTERACTIONS

Tirzepatide delays gastric emptying, which may reduce the efficacy of oral contraceptives.^{[11][7][8]} Patients should use non-oral contraception or add barrier method for 4 weeks after initiation and after each dose escalation.^{[11][7][8]} Without medical advice, women of childbearing age may experience contraceptive failure.

Sulfonylureas and Insulin: When tirzepatide is used in combination with sulfonylureas or insulin, there is a significantly increased risk of hypoglycemia.^{[10][5]} In

SURPASS-6, the incidence of clinically significant hypoglycemia was 9-12% with tirzepatide versus 48% with insulin lispro when added to basal insulin.^[10] Without medical supervision, patients may not properly adjust the doses of these medications, resulting in severe hypoglycemia.

Other Oral Medications: Delayed gastric emptying may affect the absorption of several oral medications.^{[11][8]} Without medical evaluation, clinically significant interactions may go unnoticed.

5.4 USE IN UNSTUDIED POPULATIONS

Pregnancy: Tirzepatide should not be used in pregnant women and should be discontinued if pregnancy occurs.^{[7][8]} Data are insufficient to determine risk in pregnant women.^[8] Without medical supervision, women may inadvertently use tirzepatide during pregnancy, exposing the fetus to unknown risks.

Lactation: There are no data on the presence of tirzepatide in breast milk.^{[7][8]} Without medical advice, breastfeeding women may use the drug without knowledge of the potential risks to the infant.

Children and Adolescents: Tirzepatide has not been studied in children.^{[7][8]} Unsupervised use in pediatric populations exposes developing individuals to unknown risks.

Elderly: Only small proportions of patients in clinical trials were over 65 years of age.^[7] Elderly patients may be more vulnerable to adverse events, particularly dehydration and acute kidney injury.

5.5 IMPOSSIBILITY OF MANAGING COMPLICATIONS

Acute Pancreatitis: Although rare, acute pancreatitis is a potentially serious complication that requires prompt recognition and management.^{[13][12][8][14]} Without medical supervision, patients may not recognize symptoms or seek appropriate care in a timely manner.

Acute Kidney Injury: As reported in postmarketing data, acute kidney injury may occur, particularly in the context of dehydration.^[7] Without medical monitoring, this complication can progress to severe kidney failure.

Acute Biliary Disease: Acute cholecystitis requires appropriate medical or surgical management.^{[12][10]} Patients without medical supervision may not recognize symptoms or seek appropriate treatment.

Severe Hypoglycemia: In patients using tirzepatide with sulfonylureas or insulin, severe hypoglycemia may occur.^[10] Without guidance on recognizing and managing

hypoglycemia, patients are at risk for serious complications, including loss of consciousness, seizures, and death.

5.6 SPECIFIC RISKS OF THE UNREGULATED MARKET

Counterfeit Products: The unregulated market may contain counterfeit products without the proper active ingredient, with incorrect dosages, or contaminated with hazardous substances.

Inadequate Storage: Tirzepatide requires proper refrigerated storage. Products obtained outside of regulated channels may have been improperly stored, compromising efficacy and safety.

Lack of Traceability: Products obtained without a medical prescription lack traceability in case of recalls or identification of problematic batches.

Improper Administration Technique: Without medical or nursing advice, patients may use inappropriate injection technique, resulting in erratic absorption, injection site infections, or other complications.

6 ETHICAL AND LEGAL CONSIDERATIONS

Tirzepatide is a prescription drug approved by the FDA and international regulatory agencies. Their dispensation without a medical prescription violates health regulations and exposes suppliers to legal sanctions. Health professionals, including biomedical professionals, have an ethical responsibility to promote the rational use of medications and educate the population about the risks of unsupervised use of prescription medications. It is essential to develop public health education strategies to make the population aware of: The risks of using over-the-counter medications; The importance of medical supervision in the treatment of obesity and diabetes; Safe and effective alternatives to us treatments.

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OMEGA-3 IN REDUCING CARDIOMETABOLIC RISK IN PATIENTS WITH DYSLIPIDEMIA AND METABOLIC SYNDROME: CURRENT CLINICAL EVIDENCE

ÔMEGA-3 NA REDUÇÃO DO RISCO CARDIOMETABÓLICO EM PACIENTES COM DISLIPIDEMIA E SÍNDROME METABÓLICA: EVIDÊNCIAS CLÍNICAS ATUAIS

LOS ÁCIDOS GRASOS OMEGA-3 CONTRIBUYEN A REDUCIR EL RIESGO CARDIOMETABÓLICO EN PACIENTES CON DISLIPIDEMIA Y SÍNDROME METABÓLICO: EVIDENCIA CLÍNICA ACTUAL



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ABSTRACT

Metabolic syndrome and dyslipidemia are important risk factors for the development of cardiovascular diseases and represent a major global public health concern. In this context, omega-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been extensively investigated due to their potential cardiometabolic effects. This study aimed to critically analyze current clinical evidence regarding the use of omega-3 in reducing cardiometabolic risk in patients with dyslipidemia and metabolic syndrome. This is an integrative literature review based on scientific articles published between 2016 and 2025 and indexed in the PubMed/MEDLINE, SciELO, and Scopus databases. Original studies, systematic reviews, meta-analyses, and clinical trials addressing the effects of omega-3 on lipid profile, inflammation, insulin resistance, endothelial function, and cardiovascular risk were included. The findings demonstrated consistent results mainly in reducing serum triglyceride levels, partially improving inflammatory markers, and potentially decreasing residual cardiovascular risk. However, significant methodological heterogeneity was observed among the studies, including differences in administered doses, EPA and DHA formulations, supplementation duration, and characteristics of the evaluated populations. In addition, the effects on insulin resistance, glycemic control, and major cardiovascular outcomes remain partially controversial. It is concluded that omega-3 has promising potential as a complementary strategy in the management of dyslipidemia and metabolic syndrome, especially in controlling hypertriglyceridemia and modulating inflammation. Nevertheless, more robust and standardized clinical studies are still needed to better define therapeutic indications, ideal dosages, and the most effective formulations in the context of cardiometabolic prevention.

Keywords: Omega-3. Dyslipidemia. Metabolic Syndrome. Cardiometabolic Risk. EPA. DHA.

RESUMO

A síndrome metabólica e a dislipidemia configuram importantes fatores de risco para o desenvolvimento de doenças cardiovasculares, representando um relevante problema de saúde pública mundial. Nesse contexto, os ácidos graxos poli-insaturados ômega-3, especialmente o ácido eicosapentaenoico (EPA) e o ácido docosahexaenoico (DHA), vêm sendo amplamente investigados devido aos seus potenciais efeitos cardiometabólicos. O presente estudo teve como objetivo analisar criticamente as evidências clínicas atuais acerca da utilização do ômega-3 na redução do risco cardiometabólico em pacientes com dislipidemia e síndrome metabólica. Trata-se de uma revisão integrativa da literatura, realizada a partir de artigos científicos publicados entre 2016 e 2025, indexados nas bases de dados PubMed/MEDLINE, SciELO e Scopus. Foram incluídos estudos originais, revisões sistemáticas, meta-análises e ensaios clínicos relacionados aos efeitos do ômega-3 sobre perfil lipídico, inflamação, resistência à insulina, função endotelial e risco cardiovascular. Os achados demonstraram resultados consistentes principalmente na redução dos níveis séricos de triglicerídeos, melhora parcial de marcadores inflamatórios e possível diminuição do risco cardiovascular residual. Entretanto, observou-se significativa heterogeneidade metodológica entre os estudos, incluindo diferenças nas doses administradas, formulações de EPA e DHA, tempo de suplementação e características das populações avaliadas. Além

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disso, os efeitos sobre resistência insulínica, glicemia e eventos cardiovasculares maiores ainda permanecem parcialmente controversos. Conclui-se que o ômega-3 apresenta potencial promissor como estratégia complementar no manejo da dislipidemia e da síndrome metabólica, especialmente no controle da hipertrigliceridemia e modulação inflamatória. Contudo, ainda são necessários estudos clínicos mais robustos e padronizados para definição mais precisa das indicações terapêuticas, doses ideais e formulações mais eficazes no contexto da prevenção cardiometabólica.

Palavras-chave: Ômega-3. Dislipidemia. Síndrome Metabólica. Risco Cardiometabólico. EPA. DHA.

RESUMEN

El síndrome metabólico y la dislipidemia son factores de riesgo significativos para el desarrollo de enfermedades cardiovasculares, lo que representa un importante problema de salud pública a nivel mundial. En este contexto, los ácidos grasos poliinsaturados omega-3, especialmente el ácido eicosapentaenoico (EPA) y el ácido docosahexaenoico (DHA), han sido ampliamente investigados debido a sus potenciales efectos cardiometabólicos. Este estudio tuvo como objetivo analizar críticamente la evidencia clínica actual sobre el uso de omega-3 para reducir el riesgo cardiometabólico en pacientes con dislipidemia y síndrome metabólico. Se trata de una revisión bibliográfica integradora, basada en artículos científicos publicados entre 2016 y 2025, indexados en las bases de datos PubMed/MEDLINE, SciELO y Scopus. Se incluyeron estudios originales, revisiones sistemáticas, metaanálisis y ensayos clínicos relacionados con los efectos de los omega-3 sobre el perfil lipídico, la inflamación, la resistencia a la insulina, la función endotelial y el riesgo cardiovascular. Los hallazgos demostraron resultados consistentes, principalmente en la reducción de los niveles séricos de triglicéridos, la mejora parcial de los marcadores inflamatorios y la posible disminución del riesgo cardiovascular residual. Sin embargo, se observó una heterogeneidad metodológica significativa entre los estudios, incluyendo diferencias en las dosis administradas, las formulaciones de EPA y DHA, el tiempo de suplementación y las características de las poblaciones evaluadas. Además, los efectos sobre la resistencia a la insulina, la glucemia y los eventos cardiovasculares mayores siguen siendo parcialmente controvertidos. Se concluye que los omega-3 muestran un potencial prometedor como estrategia complementaria en el manejo de la dislipidemia y el síndrome metabólico, especialmente en el control de la hipertrigliceridemia y la modulación de la inflamación. No obstante, aún se necesitan estudios clínicos más sólidos y estandarizados para una definición más precisa de las indicaciones terapéuticas, las dosis ideales y las formulaciones más efectivas en el contexto de la prevención cardiometabólica.

Palabras clave: Omega-3. Dislipidemia. Síndrome Metabólico. Riesgo Cardiometabólico. EPA. DHA.

1 INTRODUCTION

Metabolic syndrome represents one of the main contemporary public health challenges, characterized by a set of metabolic alterations associated with a significant increase in cardiovascular risk and the development of type 2 diabetes mellitus. Among the main components of this condition are central obesity, high blood pressure, insulin resistance, and dyslipidemia, especially hypertriglyceridemia, and low levels of high-density lipoprotein (HDL-cholesterol). Patients with metabolic syndrome are more predisposed to the development of atherosclerotic cardiovascular diseases, making it essential to adopt effective therapeutic strategies aimed at controlling cardiometabolic risk factors (GUO et al., 2017). In this context, omega-3 polyunsaturated fatty acids have been widely investigated due to their potential beneficial effects on lipid metabolism, systemic inflammation, and cardiovascular protection, although part of the literature still presents divergent results regarding the magnitude of these effects in different clinical populations.

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are bioactive nutrients found primarily in cold-water fish and marine products. Recent studies have shown that these compounds exert an important action in reducing serum triglyceride levels, in addition to having anti-inflammatory, antioxidant, and antithrombotic properties. A meta-analysis involving more than seven thousand participants showed that omega-3 supplementation promotes a significant reduction in plasma triglyceride concentrations, especially in individuals with hypertriglyceridemia (CALDER, 2017). In addition, it was observed that doses higher than 2 g/day of EPA and DHA are more effective in improving lipid parameters in individuals with metabolic syndrome (BASIRAT; MERINO-TORRES, 2025). However, methodological differences between studies, including time of intervention, clinical profile of participants, and different formulations of EPA and DHA, make it difficult to standardize results and limit direct comparisons between available clinical trials.

In addition to the effects on the lipid profile, omega-3s also demonstrate a relevant influence on inflammatory and endothelial mechanisms related to the progression of atherosclerosis. Chronic low-grade inflammation is one of the main pathophysiological mechanisms associated with metabolic syndrome and cardiovascular diseases. Diets enriched with omega-3 polyunsaturated fatty acids contribute to improved endothelial function and reduction of inflammatory markers in patients with metabolic syndrome (BERTORELLO; EYNARD; DEFAGÓ, 2022). Likewise, EPA can act to stabilize atherosclerotic plaques and reduce residual cardiovascular risk, especially in patients undergoing treatment with statins (MANUBOLU; BUDOFF; LAKSHMANAN, 2022). Despite

this, clinical studies still show inconsistencies regarding long-term cardiovascular outcomes, especially when comparing formulations containing EPA alone with associations of EPA and DHA.

However, despite favorable evidence related to triglyceride reduction and inflammatory modulation, some metabolic effects of omega-3 supplementation remain controversial in the scientific literature. Studies have shown that fish oil supplementation does not promote significant improvement in insulin sensitivity in the general population, although benefits have been observed in individuals with pre-existing metabolic alterations (GAO et al., 2017). Other authors point out that the effects on insulin resistance and blood glucose still present inconsistent results, depending on the dose used, intervention time, composition of lipid formulations, and clinical profile of patients (STELLA et al., 2018). In addition, some studies report a slight increase in LDL-cholesterol levels after supplementation with certain omega-3 formulations, evidencing the complexity of the metabolic response associated with these compounds. These findings reinforce the need for further investigations to clarify the mechanisms of action and clinical effectiveness of omega-3 in different cardiometabolic contexts.

Given this scenario, it is relevant to deepen the analysis of current scientific evidence on the use of omega-3 to reduce cardiometabolic risk in patients with dyslipidemia and metabolic syndrome. Considering the increasing prevalence of these conditions and their impact on cardiovascular morbidity and mortality, understanding the clinical effects of EPA and DHA supplementation can significantly contribute to complementary therapeutic strategies in the management of these diseases. Thus, the present study aims to critically analyze the contemporary clinical evidence related to the effects of omega-3 on cardiometabolic parameters in individuals with dyslipidemia and metabolic syndrome, through an integrative review of the scientific literature published in the last ten years, with emphasis on the main metabolic, inflammatory, and cardiovascular outcomes described in clinical trials, systematic reviews, and meta-analyses.

2 METHODOLOGY

This is an integrative descriptive literature review with a qualitative approach, developed with the objective of critically analyzing the current scientific evidence on the effects of omega-3 on the reduction of cardiometabolic risk in patients with dyslipidemia and metabolic syndrome. The review was conducted according to the methodological steps proposed by Mendes, Silveira and Galvão (2008) for integrative reviews, including definition

of the theme and guiding question, establishment of inclusion and exclusion criteria, search and selection of studies, data extraction and analysis, and synthesis of results.

The guiding question of the study was defined as follows: "What is the current clinical evidence on the effects of omega-3 in reducing cardiometabolic risk in patients with dyslipidemia and metabolic syndrome?". To respond to this problem, a bibliographic survey was carried out in internationally recognized scientific databases, including PubMed/MEDLINE, SciELO and Scopus, as they are widely used in the indexing of studies in the area of health sciences.

The search for articles took place between May and June 2026, using the following descriptors in Portuguese and English, combined using the Boolean operators AND and OR: "omega-3", "omega-3 fatty acids", "dyslipidemia", "metabolic syndrome", "cardiometabolic risk", "EPA", "DHA" and "hypertriglyceridemia". Studies published in the period from 2016 to 2025, available in full, in Portuguese, English or Spanish, were considered.

As inclusion criteria, original scientific articles, systematic reviews, meta-analyses, and clinical trials that addressed the effects of omega-3 on cardiometabolic parameters related to dyslipidemia and metabolic syndrome, including lipid profile, inflammation, insulin resistance, endothelial function, and cardiovascular risk, were selected. Duplicate studies, incomplete articles, term papers, dissertations, theses, congress abstracts, experimental studies in animals, and publications that were not directly related to the research objective were excluded.

After applying the eligibility criteria, the titles, abstracts and, subsequently, the full texts of potentially relevant articles were read. At the end of the selection process, 12 scientific studies considered relevant to the proposed theme were included. The extracted data included information regarding the authors, year of publication, type of study, population analyzed, main interventions performed, and cardiometabolic outcomes observed.

The analysis of the studies was carried out in a descriptive and comparative way, seeking to identify convergences, divergences and methodological limitations present in the current scientific literature. Aspects such as differences between EPA and DHA formulations, doses administered, duration of supplementation, and heterogeneity of cardiovascular and metabolic outcomes found in the selected studies were considered. Thus, the integrative review enabled a broad and critical understanding of the use of omega-3 as a complementary strategy to reduce cardiometabolic risk in patients with dyslipidemia and metabolic syndrome.

3 RESULTS AND DISCUSSION

This integrative review analyzed 12 scientific studies published between 2016 and 2025, including systematic reviews, meta-analyses, and clinical trials aimed at investigating the effects of omega-3 on cardiometabolic parameters in individuals with dyslipidemia and metabolic syndrome. In general, the studies have shown favorable results, especially in relation to the reduction of serum triglyceride levels, partial improvement of inflammatory markers, and a possible contribution to the reduction of residual cardiovascular risk. However, considerable methodological heterogeneity was observed among the studies analyzed, involving differences in the doses administered, duration of supplementation, clinical profile of the participants, sample size, and composition of formulations containing EPA and DHA, factors that hinder direct comparisons and standardization of clinical findings. In addition, evidence suggests that regular consumption of polyunsaturated fatty acids may be associated with reduced risk of developing metabolic syndrome, although the mechanisms involved are not yet completely elucidated (GUO et al., 2017).

The results related to the lipid profile were the most consistent among the selected studies. Calder (2017) identified an approximate mean reduction of 38.6 mg/dL in plasma triglyceride levels after omega-3 supplementation, especially in individuals with hypertriglyceridemia. Similarly, Basirat and Merino-Torres (2025) observed that doses higher than 2 g/day were more effective in reducing triglycerides, especially in medium and long-term interventions. Similar results were also described by Fogacci et al. (2020), who identified a significant improvement in the lipid profile after omega-3 supplementation in patients with metabolic alterations. These findings reinforce the use of omega-3 as a complementary strategy in the treatment of dyslipidemia, especially in patients with metabolic syndrome, in whom hypertriglyceridemia represents an important cardiovascular risk factor. Despite this, some studies have reported a slight increase in LDL-cholesterol levels after supplementation, particularly in formulations with higher DHA concentration, showing that the effects on lipid metabolism do not occur uniformly in all patients. In addition, although the reduction in triglycerides is consistent, this effect does not always translate proportionally into an objective reduction in major cardiovascular events.

In addition to lipid alterations, it was observed that omega-3 fatty acids also exert influence on inflammatory and endothelial processes associated with the progression of atherosclerosis. Bertorello, Eynard, and Defagó (2022) demonstrated significant improvement of endothelial markers and reduction of systolic and diastolic blood pressure in individuals with metabolic syndrome undergoing omega-3-enriched diets. These effects may be related to the anti-inflammatory action of EPA and DHA on inflammatory cytokines,

oxidative stress, and vascular function. Fazelian et al. (2021) also observed improvement in cardiometabolic parameters and reduction in oxidative stress after omega-3 supplementation, reinforcing the anti-inflammatory potential of these formulations. Manubolu, Budoff, and Lakshmanan (2022) highlighted that purified EPA-based formulations showed additional benefits in stabilizing atherosclerotic plaques and reducing residual cardiovascular risk in patients on statins. However, there are still relevant divergences in the literature regarding the clinical superiority of EPA alone compared to combined formulations of EPA/DHA, especially in studies with different populations and follow-up times. These inconsistencies suggest that the cardioprotective effects of omega-3 may depend not only on the composition of the supplementation, but also on the metabolic and therapeutic context of the individuals evaluated. Additionally, studies involving plant sources of omega-3 also demonstrate potentially beneficial effects on cardiovascular health, although there are still limitations regarding the direct comparison between different types of omega-3 fatty acids (SALA-VILA et al., 2022).

Regarding glycemic parameters and insulin resistance, the results were less consistent. Gao et al. (2017), in a meta-analysis involving 17 clinical studies, found that fish oil supplementation did not promote a significant improvement in insulin sensitivity in the general population. However, discrete benefits were observed in individuals who already had metabolic alterations, such as obesity, metabolic syndrome, and insulin resistance. Similar results were described by Stella et al. (2018), who pointed out inconsistencies related to the influence of omega-3 on blood glucose and insulin metabolism. Salek et al. (2019) also identified variable metabolic effects related to the use of omega-3s in conditions associated with insulin resistance, suggesting that the clinical response may vary according to individual metabolic characteristics. Such divergences can be partially explained by the broad methodological heterogeneity of the studies, including differences in the doses used, duration of interventions, dietary adherence, concomitant use of medications, and clinical characteristics of the populations evaluated. In addition, many studies had a short follow-up period, limiting the assessment of longer-lasting metabolic effects.

Another relevant aspect identified in the present review refers to the differences between the omega-3 formulations used in clinical studies. Recent evidence suggests that formulations containing purified EPA may have greater cardiovascular benefit when compared to the associations of EPA and DHA, especially in patients with high cardiometabolic risk. However, there is still no definitive consensus on the ideal doses, duration of supplementation, and profile of patients with the best therapeutic response. In addition, some of the studies included have important methodological limitations, such as

small sample size, short follow-up period, and lack of standardization of intervention protocols, factors that reduce the broad clinical applicability of the results and hinder the universal extrapolation of the findings to different population contexts. In addition, studies involving different types of fatty acids demonstrate that the cardiometabolic response to omega-3 can vary according to the formulation used and the previously established metabolic conditions (LI et al., 2018).

In general, the findings of this integrative review demonstrate that omega-3 supplementation has relevant potential as a complementary strategy in reducing cardiometabolic risk, especially due to its ability to reduce plasma triglycerides and modulate inflammatory processes associated with metabolic syndrome. Even so, the inconsistencies observed in certain metabolic and cardiovascular outcomes highlight the need for more robust clinical studies, with greater methodological standardization, longitudinal follow-up, and more precise definition of the formulations used. In this way, it will be possible to establish more consistent therapeutic recommendations regarding the use of EPA and DHA in patients with dyslipidemia and metabolic syndrome, expanding the clinical applicability of the currently available evidence.

4 CONCLUSION

The present integrative review showed that supplementation with omega-3 fatty acids, especially EPA and DHA, has relevant potential as a complementary strategy to reduce cardiometabolic risk in patients with dyslipidemia and metabolic syndrome. The main benefits observed in the scientific literature are concentrated in the reduction of serum triglyceride levels, partial improvement of inflammatory markers, and possible contribution to cardiovascular protection, especially in individuals with hypertriglyceridemia and high atherosclerotic risk. These findings reinforce the clinical relevance of omega-3 in complementary metabolic management, especially in contexts of persistent residual cardiovascular risk.

The studies analyzed showed that higher doses of omega-3, especially higher than 2 g/day, tend to produce more expressive metabolic responses, especially in medium and long-term interventions. In addition, recent evidence suggests that formulations containing purified EPA may have superior cardiovascular benefits when compared to combined formulations of EPA and DHA. However, the results still remain partially controversial, especially regarding the effects on insulin resistance, glycemic control, and effective reduction of major cardiovascular events. Part of these divergences may be related to methodological

differences between the studies, as well as to the lack of standardization regarding the formulations used and the clinical profiles of the populations evaluated.

Significant methodological heterogeneity was also observed among the included studies, involving differences in the populations analyzed, doses administered, supplementation time, clinical trial design, and composition of the formulations used. These limitations make it difficult to standardize the findings and restrict the broad extrapolation of the results to different clinical contexts. In addition, some studies have reported a slight increase in LDL-cholesterol levels after certain supplementations, reinforcing the complexity of the metabolic effects associated with the use of omega-3 and the need for cautious interpretation of the observed benefits.

Thus, it is concluded that omega-3 has promising applicability in the complementary management of dyslipidemia and metabolic syndrome, especially in the control of hypertriglyceridemia and inflammatory modulation. However, the current findings still indicate the need for therapeutic individualization, considering factors such as metabolic profile, cardiovascular risk, dose administered, and composition of the supplementation used. In addition, more robust clinical trials are needed, with greater methodological standardization and longitudinal follow-up, capable of clarifying the cardiovascular and metabolic effects of different formulations of EPA and DHA in a more consistent manner. The advancement of this evidence may contribute to more accurate and clinically applicable therapeutic recommendations in the context of cardiometabolic prevention.

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DIABETES MELLITUS AND MENTAL HEALTH: DEVELOPMENT OF EDUCATIONAL MATERIALS FOR INTEGRATED CARE

DIABETES MELLITUS E SAÚDE MENTAL: ELABORAÇÃO DE MATERIAL DE DIVULGAÇÃO CIENTÍFICA EM REDE PARA UMA ASSISTÊNCIA INTEGRADA

DIABETES MELLITUS Y SALUD MENTAL: DESARROLLO DE MATERIAL DE DIFUSIÓN CIENTÍFICA EN LÍNEA PARA LA ATENCIÓN INTEGRAL



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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic condition characterized by hyperglycemia, requiring continuous management, including insulin therapy in type 1 diabetes mellitus (DM1) and the use of oral antidiabetic drugs, with or without insulin, in type 2 diabetes mellitus (DM2). In this context, the demanding routine of self-management can favor the development of emotional disorders, negatively impacting glycemic control and adherence to treatment. This study aimed to develop online scientific dissemination materials focused on promoting mental health in people with diabetes. The research adopted a two-stage methodological approach: (1) integrative literature review; and (2) content production for the @glicogotas Instagram profile, associated with netnographic analysis using the platform's Insights feature. Seventeen scientific articles selected in the review were used in the development of the materials, which highlighted the influence of sleep quality and emotional management on glycemic control. The posts reached an average of 1,085 views, with the content on "Type 1 Diabetes and Depression" standing out as having the highest engagement (1,470 views and 46 interactions). The analysis indicated that content related to subjective experiences and practical strategies for emotional coping generates greater public interest. Therefore, the developed online science outreach materials prove to be strategic tools for strengthening diabetes education on social media, transforming the virtual space into an environment of affective and humanized education and bringing the public closer to scientific discourse.

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Keywords: Diabetes Mellitus. Mental Health. Diabetes Education. Sleep. Science Communication Online.

RESUMO

O diabetes mellitus (DM) é uma condição metabólica crônica caracterizada por hiperglicemia, que exige manejo contínuo, incluindo insulinoterapia no diabetes mellitus tipo 1 (DM1) e uso de antidiabéticos orais, associados ou não à insulina, no diabetes mellitus tipo 2 (DM2). Nesse contexto, a rotina exigente de autogestão pode favorecer o desenvolvimento de transtornos emocionais, impactando negativamente o controle glicêmico e a adesão ao tratamento. Este estudo teve como objetivo desenvolver materiais de divulgação científica em rede voltados à promoção da saúde mental em pessoas com diabetes. A pesquisa adotou abordagem metodológica em duas etapas: (1) revisão integrativa da literatura; e (2) produção de conteúdos para o perfil @glicogotas no *Instagram*, associada à análise netnográfica por meio do recurso *Insights* da plataforma. Na elaboração dos materiais, utilizaram-se 17 artigos científicos selecionados na revisão, os quais evidenciaram a influência da qualidade do sono e do manejo emocional no controle glicêmico. As publicações alcançaram média de 1.085 visualizações, com destaque para o conteúdo sobre “DM1 e depressão”, que apresentou maior engajamento (1.470 visualizações e 46 interações). A análise indicou que conteúdos relacionados a experiências subjetivas e estratégias práticas de enfrentamento emocional despertam maior interesse do público. Assim, os materiais de divulgação científica em rede desenvolvidos mostram-se ferramentas estratégicas para fortalecer a educação em diabetes nas redes sociais, transformando o espaço virtual em ambiente de educação afetiva e humanizada e aproximando o público do discurso científico.

Palavras-chave: Diabetes Mellitus. Saúde Mental. Educação em Diabetes. Sono. Divulgação Científica em Rede.

RESUMEN

La diabetes mellitus (DM) es una enfermedad metabólica crónica caracterizada por hiperglucemia, que requiere un manejo continuo, incluyendo la insulinoterapia en la diabetes mellitus tipo 1 (DM1) y el uso de antidiabéticos orales, con o sin insulina, en la diabetes mellitus tipo 2 (DM2). En este contexto, la exigente rutina del autocontrol puede favorecer el desarrollo de trastornos emocionales, impactando negativamente el control glucémico y la adherencia al tratamiento. Este estudio tuvo como objetivo desarrollar materiales de difusión científica en línea enfocados en promover la salud mental en personas con diabetes. La investigación adoptó un enfoque metodológico de dos etapas: (1) revisión integradora de la literatura; y (2) producción de contenido para el perfil de Instagram @glicogotas, asociado con un análisis netnográfico utilizando la función Insights de la plataforma. Diecisiete artículos científicos seleccionados en la revisión se utilizaron en el desarrollo de los materiales, los cuales resaltaron la influencia de la calidad del sueño y el manejo emocional en el control glucémico. Las publicaciones alcanzaron un promedio de 1085 visualizaciones, destacando el contenido sobre "Diabetes tipo 1 y depresión" por su alta interacción (1470 visualizaciones y 46 interacciones). El análisis indicó que el contenido relacionado con experiencias subjetivas y estrategias prácticas para el manejo emocional genera mayor interés público. Por lo tanto, los materiales de comunicación científica en línea desarrollados demuestran ser herramientas estratégicas para fortalecer la educación sobre diabetes en redes sociales, transformando el espacio virtual en un entorno de educación afectiva y humanizada, y acercando al público al discurso científico.

Palabras clave: Diabetes Mellitus. Salud Mental. Educación Sobre Diabetes. Sueño. Comunicación Científica en Línea.

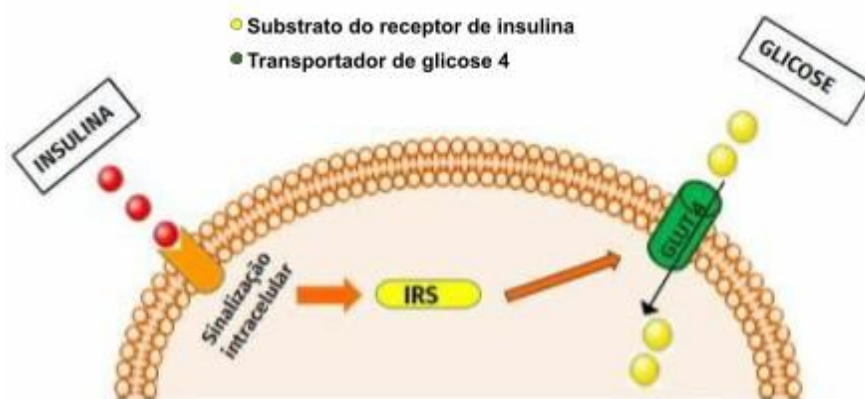
1 INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus (DM) is a chronic metabolic condition characterized by high blood glucose levels, resulting from endocrine alterations in insulin production, which plays a central role in the regulation of blood glucose, stimulating glucose uptake by peripheral tissues, especially skeletal muscle and adipose tissue. This process occurs through the translocation of the glucose transporter GLUT4, located in vesicles in the cytoplasm of cells, to the plasma membrane, mediated by the activation of the Insulin Receptor Substrate (IRS), as shown in the intracellular signaling cascade in Figure 1. In the absence of adequate insulin secretion or in the presence of resistance to its action, glucose uptake is impaired, resulting in hyperglycemia and, in decompensated cases, glycosuria (presence of glucose in the urine). Treatment consists mainly of insulin therapy and/or the use of oral antidiabetic drugs (International Diabetes Federation, 2025; Nelson; Cox; Hoskins, 2022).

Figure 1

Demonstration of the mechanism of action of insulin in glucose uptake



Source: Oliveira et al, 2021

The main types of DM are type 1 (DM1) and type 2 (DM2). DM1 results from an autoimmune response, in which the body's defense mechanisms mistakenly recognize the β cells of the pancreas, responsible for the production of insulin, as antigens and fight them, leading to partial or total deficiency of this hormone (Nelson; Cox; Hoskins, 2022). Although this form of diabetes can appear at any age, it is one of the most frequent chronic conditions in children and adolescents. Its management requires continuous glycemic monitoring, a balanced diet, and strict adherence to treatment, aiming to prevent acute complications, such as diabetic ketoacidosis, and chronic complications, such as diabetic retinopathy and chronic kidney disease (Brutsaert, 2025; International Diabetes Federation, 2025; Nelson; Cox; Hoskins, 2022).

On the other hand, T2DM, responsible for more than 90% of global cases, is characterized by insulin resistance of the body's cells, leading to hyperglycemia (International Diabetes Federation, 2025). Over time, there may be progressive loss of pancreatic capacity to produce insulin due to this resistance. As for symptoms, they tend to be milder than in DM1 and may be absent for long periods, which hinders early diagnosis and delays treatment. This type of diabetes is more common in adults and is associated with obesity, sedentary lifestyle, aging, and family history (International Diabetes Federation, 2025; Nelson; Cox; Hoskins, 2022; Perrin *et al.*, 2017).

According to the International Diabetes Federation (2025), worldwide, there are about 589 million diabetics between 20 and 79 years of age. In Brazil, there are approximately 16.7 million carriers. Among these, approximately 499 thousand are DM1, which places the country in 4th position in the world ranking (International Diabetes Federation, 2025).

1.2 DIABETES AND MENTAL HEALTH

DM is strongly associated with mental health impacts, with a higher risk of developing psychological disorders such as anxiety and depression. These conditions can compromise treatment adherence and thus increase the risk of serious complications (Watanabe *et al.*, 2024). Depression, for example, affects about 20% of patients, and has multifactorial causes. It is characterized by symptoms such as deep sadness, fatigue, and changes in sleep and appetite, and can be assessed by instruments such as the Beck Depression Inventory (BDI), the Hamilton Depression Scale (HDRS), and structured clinical interviews (Brasil, 2022; Curcio *et al.*, 2012; Fráguas; Soares; Bronstein, 2009; Rodrigues *et al.*, 2025). Anxiety, in turn, may be related to the fear of hypoglycemic crises and the need for constant monitoring, leading some patients to maintain higher glycemic levels than recommended (Brasil, 2022). In addition, the management of the condition can generate a state of hypervigilance and continuous worry, significantly compromising the quality of life of these individuals. Anxiety can also be assessed by validated psychometric instruments, such as the Beck Anxiety Inventory (BAI) and the Hamilton Anxiety Scale (HARS) (Cunha, 2001).

A relevant aspect of mental health in diabetics is diabetes distress (DD), defined as an emotional response specific to the management of DM (Rodrigues *et al.*, 2025). This situation involves concerns about glycemic control, continuous treatment, the relationship with health professionals, and the social impacts of the condition. In this sense, it can be assessed by the Diabetes Distress Scale (DDS), an instrument composed of 17 items divided into 4 subscales: emotional burden, stress with treatment, insecurity in relation to the doctor and impact on interpersonal relationships (Fráguas; Soares; Bronstein, 2009; Rodrigues *et*

al., 2025).

Sleep also plays an important role in metabolic, cognitive, and emotional regulation in diabetics. Its imbalance is associated with hyperglycemia and worsening of the glycemic condition, negatively impacting self-management (Donga *et al.*, 2010; Vézina-Im *et al.*, 2024). In individuals with T1D, sleep disruptions include the need to wake up to treat nocturnal hypoglycemia, while in T2DM, sleep may be impaired by obstructive sleep apnea (Vézina-Im *et al.*, 2024). In addition, hyperglycemia can compromise the circadian cycle, through the possible reduction of melatonin synthesis, a hormone responsible for regulating sleep (Amaral *et al.*, 2014; Corrado *et al.*, 2024).

In this context, educational methodologies focused on diabetes have demonstrated efficacy not only in the physical management of the condition, but also in supporting mental health and sleep quality, by promoting knowledge about the condition and self-care, favoring treatment adherence and contributing to minimize symptoms of depression and diabetes distress (Pereira *et al.*, 2012). Education for self-management, according to the North American model Diabetes Self-Management Education (DSME), should be centered on individual needs, considering biopsychosocial aspects, in line with the principles of Paulo Freire's problem-solving education, which places the patient as the protagonist of the learning process through critical reflection on their reality, promoting autonomy and self-management of health (Pereira *et al.*, 2012). Thus, the use of educational materials, both printed, such as booklets and booklets, and digital materials stand out as relevant strategies to improve the quality of life of patients (Damaceno *et al.*, 2023; Primadani; Susanti; Oktavia, 2025).

In view of the above, the @glicogotas page on the social network Instagram, is configured as an initiative for scientific dissemination in a network with a playful, educational and interactive approach, expanding access to knowledge about DM1 for the general public. The analysis of the posts demonstrates the potential of social networks as spaces for education, awareness, and emotional support in the context of health, especially when addressing complex topics related to mental health, such as depression, anxiety, stress, and diabetes distress, in an accessible way.

In this sense, as highlighted by Santos *et al.* (2023), social media, especially Instagram, have consolidated themselves as important tools for scientific dissemination and mental health promotion, by allowing the dissemination of information through a light, visual, and interactive language, which brings the public closer to the topics covered. However, the authors point out the risks of indiscriminate use of social networks, such as the dissemination of fake news and the negative influence on the mental health of users. In this context, digital

health education plays an essential role in mitigating such effects, promoting the critical and conscious use of networks. This perspective is reflected in the actions of Glicogotas, which uses Instagram in a responsible and formative way, transforming it into a healthy learning environment.

1.3 OBJECTIVES

1.3.1 General objective

The present study aims to develop material for scientific dissemination in a network focused on the mental health of people with DM1, aiming at integrated care between these aspects.

1.3.2 Specific objectives

- 1- To conduct a bibliographic survey on the prevalence of psychological disorders in people with type 1 diabetes mellitus;
- 2- Develop materials for scientific dissemination for posting and social networking;
- 3- Analyze the influence of Instagram posts on the dissemination of information about mental health and diabetes.

2 METHODOLOGY

2.1 BIBLIOGRAPHIC SURVEY

The bibliographic survey was conducted through an integrative review, using the PubMed, LILACS and SciELO databases. For the search, descriptors combined by Boolean operators (AND, OR) were used, with the objective of optimizing the sensitivity and specificity of the results obtained (Table 1). In the PubMed database, the descriptors were refined with MeSH (Medical Subject Headings) terms, ensuring a more precise and comprehensive search, however, "diabetes education" and "psychological disorders" did not present results, being searched as free keywords.

Table 1

Descriptors and Boolean method used in database searches

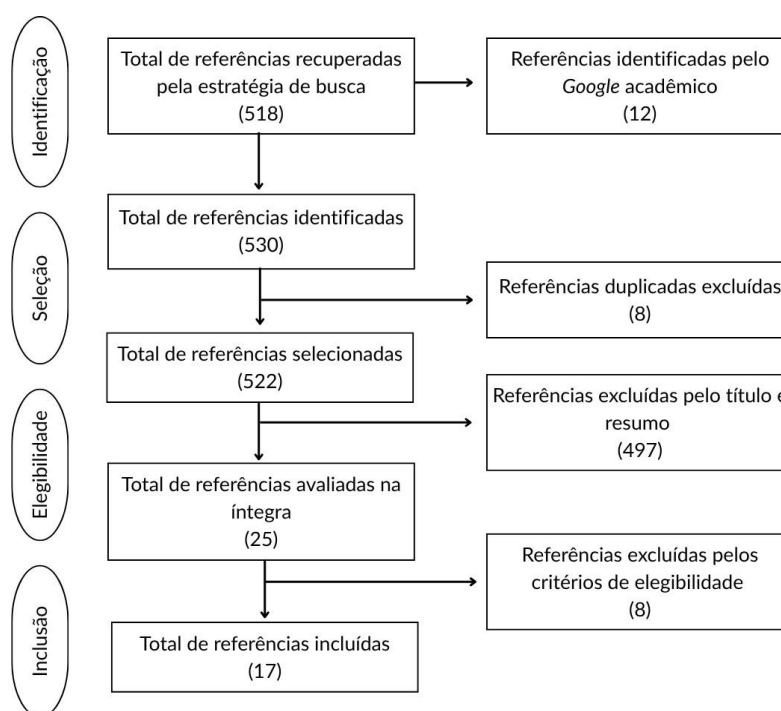
Database	Descriptors and Boolean method
PubMed	("Diabetes Mellitus, Type 1"[MeSH] OR "diabetes education"[MeSH]) AND ("Health Education"[MeSH] OR "Sleep"[MeSH] OR "Mental Health"[MeSH] OR "psychological disorders"[MeSH])
LILACS	("Type 1 Diabetes Mellitus" OR "diabetes education") AND ("health education" OR "sleep" OR "mental health" OR "psychological disorders")
SciELO	((("type 1 diabetes" OR "diabetes education") AND ("health education" OR "sleep" OR "mental health" OR "psychological disorders"))

Source: Autoral, 2025

To ensure quality and relevance, filters were applied for period (2012–2024), language (Portuguese and English), and species (humans), in addition to the exclusion of preprints and paid articles in PubMed. The selection took place in four stages, as illustrated in Figure 2.

Figure 2

Flowchart of the selection of searches in the databases



Source: Autoral, 2025

2.2 SOCIAL NETWORK POSTING AND NETNOGRAPHIC ANALYSIS

The material for posts on social networks was developed in the Canva tool, following the visual identity of the Glicogotas project, which includes typography, colors and its own illustrations. The publications incorporate graphic elements of the platform and authorial materials. The content of the posts was prepared from the reading of the scientific articles

selected during the bibliographic survey, books and lectures with specialists, ensuring theoretical foundation and accuracy of the information. The posts were made on the @glicogotas Instagram profile of the project "Glicogotas: The drops of glucose that we don't count!", developed since 2023 by professors and students from the Federal Institute of Rio de Janeiro (IFRJ), which investigates social and emotional aspects of DM1 and uses educational and playful strategies to promote self-care. Currently, it has a partnership with the IFB and the Health Department of the Federal District (SES-DF). The performance analysis of the posts was based on Insights, a tool made available by Instagram, and made it possible to quantitatively evaluate the reach of the educational materials developed, their ability to generate engagement and public interest around the theme of DM1 and mental health. Thus, these data complement the qualitative evaluation of the project's actions on social networks.

3 RESULTS AND DISCUSSIONS

3.1 BIBLIOGRAPHIC SURVEY

The integrative review (Table 2), composed of 17 studies, shows that DM1 has an intrinsic relationship with mental health, in which psychological, behavioral, and physiological factors interact dynamically, directly impacting treatment adherence, glycemic control, and quality of life. In addition, people with diabetes have about twice the risk of developing depression (Ducat; Philipson; Anderson, 2014). This scenario is aggravated by the emotional strain of ongoing DM management, including glycemic monitoring, insulin use, and fear of complications. In addition, diabetes-specific suffering, which is often more prevalent than depression, is associated with worsening adherence and a higher risk of complications (Ducat *et al.*, 2015). In children and adolescents, family, social, and emotional factors intensify this vulnerability, reinforcing a bidirectional cycle between mental health and metabolic control (Buchberger *et al.*, 2016; Smaniotto; Pascolat, 2022). Sleep also stands out as a critical factor, since changes resulting from the management of the condition impair metabolic and emotional balance (Farabi, 2016; Vézina-Im *et al.*, 2024; Soares *et al.*, 2025). In view of this, educational interventions associated with emotional support show a positive impact on autonomy, self-care and quality of life (Ferreira *et al.*, 2018; Murillo *et al.*, 2017), being enhanced by strategies such as social networks, educational materials and playful resources, as long as they all have reliable and verifiable information (Nass *et al.*, 2019; Pedrinho *et al.*, 2021; Gonçalves *et al.*, 2019). The Social Cognitive Theory highlights self-efficacy as a central element for therapeutic success (Lima *et al.*, 2018), while continuous psychological follow-up is essential to avoid overdiagnosis and strengthen resilience (Fisher

et al., 2016). Despite the methodological limitations of the studies, such as the predominance of cross-sectional designs and gaps in the integration between sleep, mental health, and education, there is a consensus that integrated and participatory strategies are essential to promote humanized, sustainable, and patient-centered care throughout the life of DM1.

Table 2

Bibliographic Survey

Title	Author(s)	Year	Language	Theme	Type	Main result	ABNT Reference
Type 1 Diabetes and Sleep	Sarah S. Farabi	2016	English	Sleep	Review	Evidence from the literature supports the likelihood that individuals with T1DM have reduced sleep quality.	FARABI, Sarah S. Type 1 Diabetes and Sleep. Diabetes Spectrum. v. 29 n. 1 p. 10-13, 2016.
Characterizing sleep in adults with Type 1 and Type 2 diabetes.	Lydi-Anne Vézina-Im <i>et al.</i>	2024	English	Sleep	Research	People with diabetes, especially with T2DM and lower income, have poorer sleep quality.	VÉZINA-IM, Lydi-Anne <i>et al.</i> Characterizing sleep in adults with Type 1 and Type 2 diabetes. Sleep Epidemiology. Vol. 4, 2024.
A review of the mental health issues of diabetes conference	Lee Ducat <i>et al.</i>	2015	English	Mental health	Review	The review highlights the prevalence of mental health problems among individuals with diabetes, emphasizing the need for integrated approaches.	DUCAT, L. <i>et al.</i> A review of the mental health issues of diabetes conference. Diabetes Care, vol. 38, no. 2, p. 333–338 (2015).
The Mental Health Comorbidities of Diabetes	Lee Ducat, Louis H. Philipson, Barbara J. Anderson	2014	English	Mental health	Review	Major depressive disorder (MDD) affects 6.7% of U.S. adults ages 18 and older, and is more frequent in diabetics.	DUCAT, L., PHILIPSON, L. H., ANDERSON, B. J. The mental health comorbidities of diabetes. Jama, v. 312, n. 7, p. 691-692, 2014.
Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis	Barbara Buchberger <i>et al.</i>	2016	English	Mental health	Systematic review	Symptoms of anxiety were reported by up to 32% of diabetic patients.	BUCHBERGER, B. <i>et al.</i> Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. Psychoneuroendocrinology. v. 70, p. 70–84, 2016
The impact of type 1 diabetes mellitus on patients	Victoria Smaniotto, Gilberto Pascolat	2022	Portuguese	Mental health	Research	The drawings of diabetic children, in general,	SMANIOTTO, V.; PASCOLAT, G. The Impact of type 1 diabetes mellitus on

Paediatric Medicine: Analysis by Design					revolved around deprivation and daily procedures.	pediatric patients: Analysis through drawings. SciELO Preprints, 2022.
The effect of multiprofessional health teams in Brazil on diabetes care activities	Daniel Leonardo Ferreira, <i>et al.</i>	2018	Portuguese	Mental health	Systematic review Thirty-five articles were collected that corroborate the importance of multidisciplinary teams in the treatment of diabetes, aiming to highlight the relevance of these professionals in the treatment of diabetes.	FERREIRA, D. L <i>et al.</i> The effect of multiprofessional health teams in Brazil on diabetes care activities. Revista Eletrônica Acervo Saúde, n. 17, ,2018.

Source: Autoral, 2025

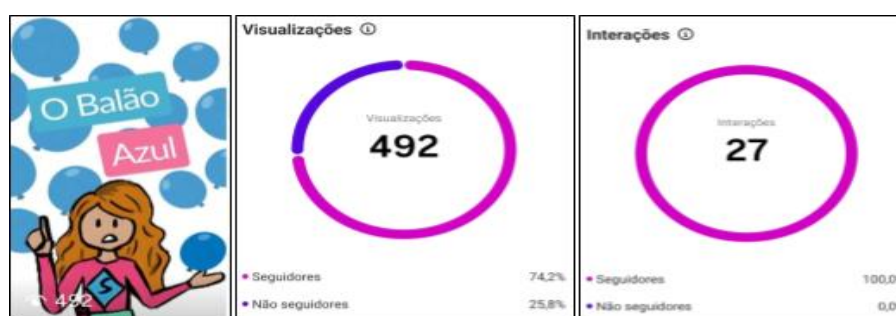
3.2 SOCIAL NETWORKING AND NETNOGRAPHIC ANALYSIS

In total, 7 posts were prepared, one of which was the reel "The blue balloon" and the other six in booklet format, presenting the following themes: Diabetes Distress, DM1 and depression, DM1 and anxiety, DM1 and stress, Tips on how to maintain good Mental Health and DM1 and sleep. Next, each educational material will be analyzed, as described in the methodology section. It is worth mentioning that all information regarding the first six posts, published between January and October 2025, was collected on October 27, 2025.

The reel "The blue balloon" (Figure 3), registered 492 views and 27 interactions, with 25.8% of reach coming from non-followers. The video used a visual metaphor to represent the maintenance of glycemic balance, addressing social support and empathy in the management of DM1. However, the lower number of views, compared to other publications about mental health, and the low engagement can be explained by technical and algorithmic factors: the content was reposted, which tends to reduce reach due to Instagram's prioritization rules, and the video format was outside the recommended vertical standard, which may have compromised the viewing. Despite this, the video maintains symbolic and educational value, reinforcing the importance of empathy in the daily lives of people with DM1.

Figure 3

Cover of the video "The blue balloon" and insights

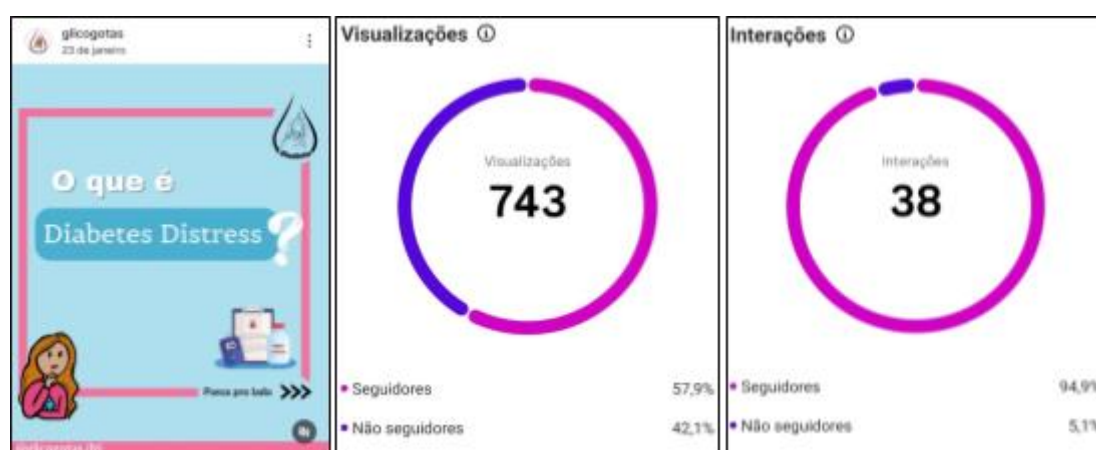


Source: Autoral, 2025

The post about diabetes distress (Figure 4) reached 743 views and 38 interactions, of which 42.1% were non-followers. In relation to the other publications on the subject, this one presented an intermediate level of reach and engagement, which may be related to the lack of knowledge of the term on the part of the public, since the concept is still little disseminated outside academic spaces. Thus, although the content was relevant to the most engaged followers, the use of the technical term "distress" may have made it difficult to identify immediately, reducing the number of likes and comments. Even so, the fact that the publication has reached new audiences demonstrates the growing interest in topics related to emotional health in diabetes.

Figure 4

Cover of the post "What is Diabetes distress?" and insights



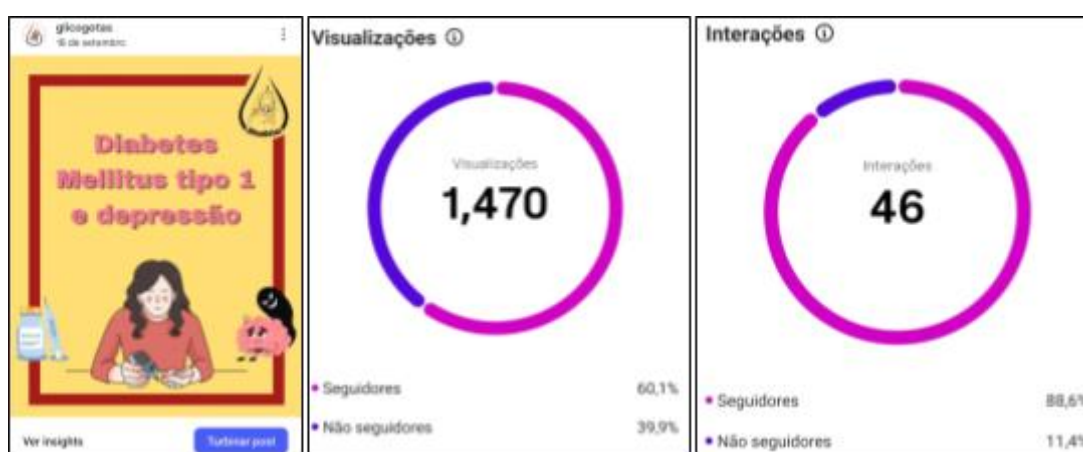
Source: Autoral, 2025

The publication on depression in DM1 (Figure 5) recorded the highest reach and engagement among all the posts evaluated, with 1,470 views and 46 interactions, including 11.4% of non-followers. The high engagement can be attributed to the emotional identification of followers with the theme, the use of accessible language and the emphasis

on sensitive aspects, such as child suffering and the importance of psychological support. Content that addresses the emotional impact of the condition tends to arouse greater empathy, allowing users to recognize themselves in the situations presented. This type of engagement, according to Santos *et al.* (2023), is essential to transform the virtual space into an environment of affective and humanized education, bringing the public closer to scientific discourse.

Figure 5

Cover of the post "Type 1 Diabetes Mellitus and depression" and insights

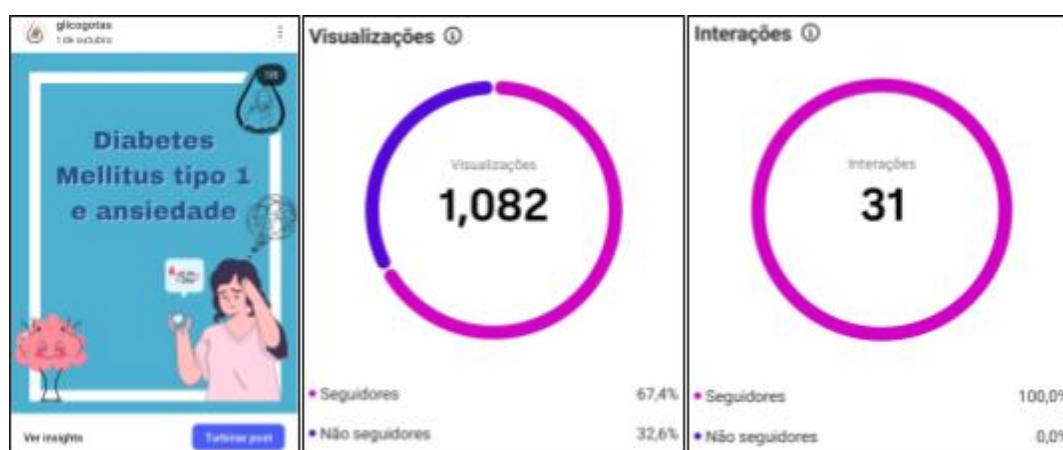


Source: Autoral, 2025

The post about anxiety in DM1 (Figure 6) also had a good reach (1,082 views), but the 31 interactions were carried out exclusively by followers. This pattern suggests that the public is interested in the topic, but consumes it in a more reflective and silent way, without necessarily expressing public reactions. This behavior is common in content that addresses personal and subjective experiences, indicating that qualitative reach (views, dwell time, shares) may be more significant than the number of explicit interactions.

Figure 6

Cover of the post "Type 1 Diabetes Mellitus and anxiety" and insights

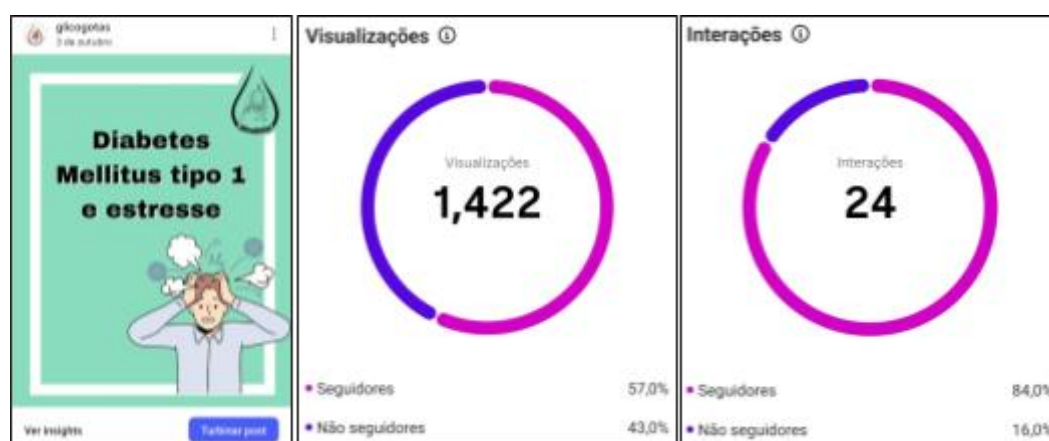


Source: Aural, 2025

Similarly, the post about stress in DM1 (Figure 7) reached 1,422 views and 24 interactions, with 43% of the audience made up of non-followers. The good reach reflects the fact that the term "stress" is widely recognized and easily associated with the emotional demands of the treatment, making it easier for the public to identify. However, the lower number of likes and comments may indicate a passive consumption of information, in which the public reads and internalizes the content without necessarily reacting publicly, a common behavior in topics related to mental health.

Figure 7

Cover of the post "Type 1 Diabetes Mellitus and stress" and insights



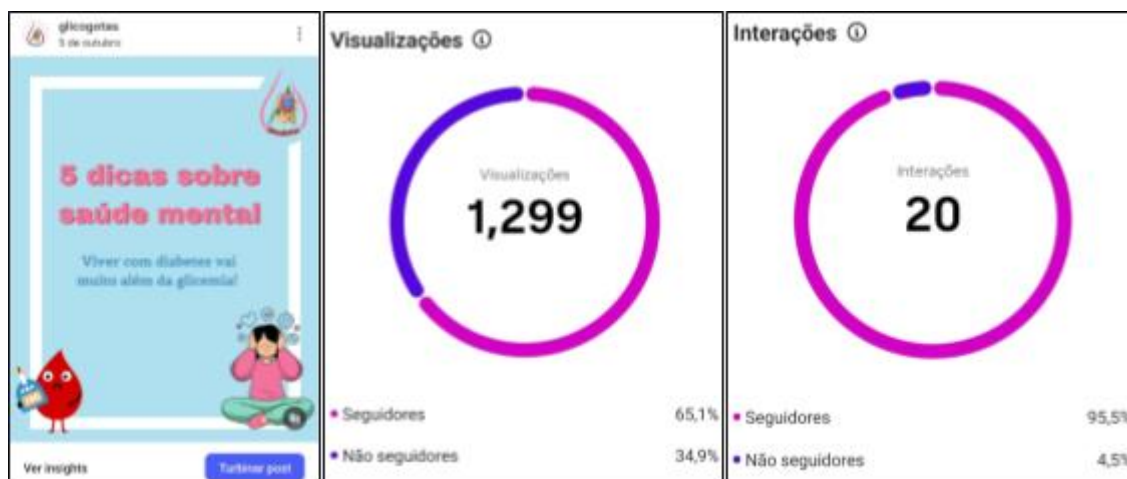
Source: Aural, 2025

The publication with tips on how to manage DM1 (Figure 8) maintained good reach and engagement (1,299 views and 20 interactions), with a balance between followers and non-followers. The lightness of the theme and the practical nature of the recommendations, such as avoiding self-pressure and maintaining pleasurable habits, may have favored

dissemination and interest, especially among people in search of daily guidance. The inclusion of partner profiles and support communities also contributed to strengthening the sense of belonging and the community character of the project.

Figure 8

Cover of the post "5 tips on mental health" and insights

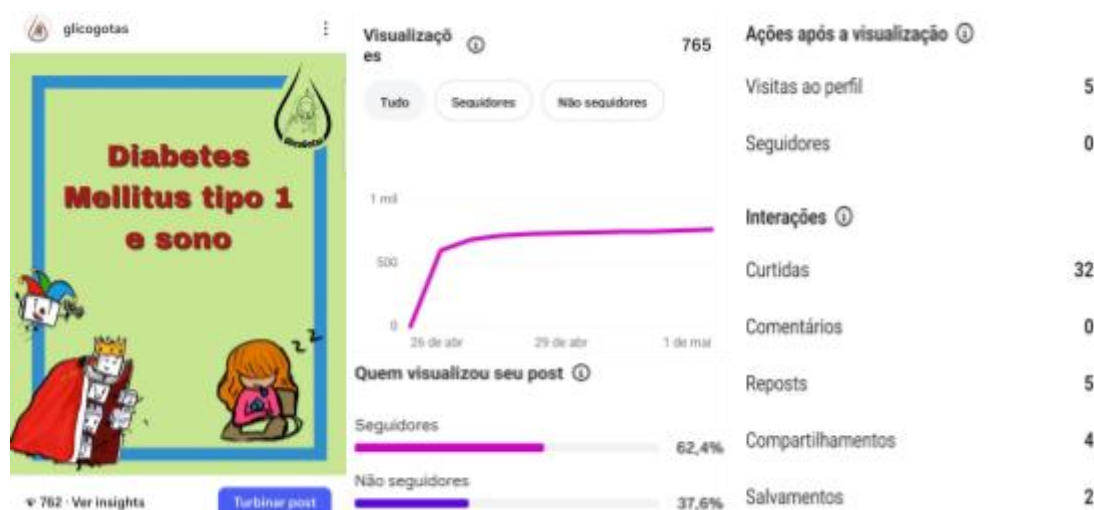


Source: Autoral, 2025

Finally, the most recent publication, referring to the theme "diabetes and sleep" (Figure 9), posted on April 26, 2026, with data collected on May 1, 2026, reached 765 views and 43 interactions in total. It is observed that the insights made available by Instagram have undergone changes in their way of presentation; However, such changes did not compromise the analysis of the data, given that they are recurrent on the platform. It is verified that most of the views came from followers (62.4%), which shows the public's loyalty in relation to the posts. In addition, the expressive reach in a short period of time reinforces this behavior and indicates that the topic addressed remains relevant for both followers and non-followers. Despite this, the number of interactions is still reduced when compared to the total number of views, suggesting the predominance of a pattern of passive engagement on the part of the public.

Figure 9

Cover of the post "Type 1 Diabetes Mellitus and sleep" and insights



Source: Autoral, 2026

The use of Instagram metrics configures a netnographic investigation in health education, which goes beyond quantitative data by capturing symbolic and emotional dimensions of interactions (Soares and Stengel, 2021). Social networks, because they are continuous and timeless, expand the educational reach of content, which remains accessible and relevant over time. Thus, the engagement observed reflects not only numbers, but identification and psychosocial impact, evidencing the potential of these platforms in promoting mental health and supporting self-care in DM1.

4 CONCLUSION

The analysis showed that the management of DM1 involves not only glycemic management, but also important psychological demands, such as stress, anxiety, depression, and diabetes distress, which impact treatment adherence and quality of life. The relevance of scientific dissemination materials, including content on social networks, as tools to support self-care and emotional awareness was highlighted, reinforcing the need for a holistic approach that integrates physical, emotional, and social aspects. Finally, the authors thank the National Council for Scientific and Technological Development (CNPq), the Research Support Foundation of the Federal District (FAPDF), the Federal Institute of Rio de Janeiro (IFRJ) and the Federal Institute of Brasília (IFB) for their institutional, scientific and financial support, which were fundamental for the realization of this work.

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SEX AND ASA CLASSIFICATION, NOT FASTING TIME, ARE ASSOCIATED WITH THE LIKELIHOOD OF COMPLICATIONS IN THE POSTOPERATIVE PERIOD

O SEXO E A CLASSIFICAÇÃO ASA E NÃO O TEMPO DE JEJUM, ESTÃO ASSOCIADOS À PROBABILIDADE DE COMPLICAÇÕES NO PÓS-OPERATÓRIO

EL SEXO Y LA CLASIFICACIÓN ASA, Y NO EL TIEMPO DE AYUNO, ESTÁN ASOCIADOS CON LA PROBABILIDAD DE COMPLICACIONES EN EL POSTOPERATORIO



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ABSTRACT

Background: According to the literature, some factors are associated with the development of postoperative complications including surgical approach, smoking, comorbidities, nutritional status, classification of the American Society of Anesthesiologists (ASA), fasting time period, and others. In the case of surgical patients, some factors are important for the assessment of the outcomes.

Aims: To investigate the factors associated with the likelihood of postoperative complications in surgical patients.

Methods: A prospective observational study was conducted with patients who were admitted to hospital more than 24 h. The following variables were investigated: nutritional risk screening, body mass index, ASA classification, fasting time, length of hospital stay, and postoperative complications. For statistical analysis, the Chi-square, Fisher's exact, and Mann-Whitney tests were used. To investigate the risk factors associated with postoperative complications, simple and multiple Cox regression analyses were used.

Results: In the total group of patients, there was an association between postoperative complications and men ($p=0.0197$), surgical risk (ASA) ($p=0.0397$) and length of hospital stay ($p<0.0001$); men showed a risk 2.2 times greater than women for some kind of postoperative complication ($p=0.0456$; $PR=2.167$; $95\%CI$ 1.015–4.624). In patients undergoing gastrointestinal surgery, there was an association between postoperative complications and length of hospital stay ($p<0.0001$). In patients undergoing other surgeries, there was an association between postoperative complications and length of hospital stay ($p<0.0001$) and ASA classification ($p=0.0160$); ASA classification was considered a factor

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associated with the probability of postoperative complications ($p=0.0335$; $PR=4.125$; $95\%CI$ 1.117–15.237).

Conclusions: Men in the total group of patients and the ASA 3 or 4 criteria in the group of patients undergoing other surgeries were considered factors associated with the occurrence of complications in the postoperative period.

Keywords: Postoperative Complications. Nutritional Status. Fasting. Risk Factors.

RESUMO

Racional: A literatura tem mostrado que alguns fatores estão associados ao desenvolvimento de complicações pós-operatórias incluindo abordagem cirúrgica, tabagismo, comorbidades, estado nutricional, classificação da Sociedade Americana de Anestesiologistas (ASA), tempo de jejum e outros fatores. No caso de pacientes cirúrgicos, alguns fatores são importantes para a avaliação dos resultados.

Objetivos: Investigar os fatores associados à probabilidade de complicações pós-operatórias em pacientes cirúrgicos.

Métodos: Foi realizado um estudo observacional prospectivo com pacientes que ficaram internados por mais de 24 horas. Foram investigadas as seguintes variáveis: triagem de risco nutricional, índice de massa corporal, classificação ASA, tempo de jejum, tempo de internação e complicações pós-operatórias. Para análise estatística foram utilizados os testes Qui-quadrado, Exato de Fisher e Mann-Whitney. Para investigar os fatores de risco associados às complicações pós-operatórias foram utilizadas análises de regressão de Cox simples e múltipla.

Resultados: No grupo total de pacientes houve associação entre complicações pós-operatórias e sexo masculino ($p=0,0197$), risco cirúrgico (ASA) ($p=0,0397$) e tempo de internação ($p<0001$) e os homens apresentaram risco 2.2 vezes maior do que as mulheres de sofrer algum tipo de complicação pós-operatória ($p=0.0456$; $RP=2.167$; $IC95\%$ 1.015–4.624). Nos pacientes submetidos a cirurgias gastrointestinais houve associação entre complicações pós-operatórias e tempo de internação ($p<0001$). Nos pacientes submetidos a outras cirurgias houve associação entre complicações pós-operatórias e tempo de internação ($p<0001$) e classificação ASA ($p=0,0160$); e a classificação ASA foi considerada fator associado à probabilidade de complicações pós-operatórias ($p=0,0335$; $RP=4,125$; $IC95\%$ 1,117–15,237).

Conclusões: O sexo masculino no grupo total de pacientes e o critério ASA 3 ou 4 no grupo de pacientes submetidos a outras cirurgias são fatores associados à presença de complicações no período pós-operatório.

Palavras-chave: Complicações Pós-Operatórias. Estado Nutricional. Jejum. Fatores de Risco.

RESUMEN

Racional: La literatura ha demostrado que algunos factores están asociados con el desarrollo de complicaciones postoperatorias, incluyendo el abordaje quirúrgico, el tabaquismo, las comorbilidades, el estado nutricional, la clasificación de la Sociedad Americana de Anestesiólogos (ASA), el tiempo de ayuno y otros factores. En el caso de los pacientes quirúrgicos, algunos de estos factores son importantes para la evaluación de los resultados.

Objetivos: Investigar los factores asociados con la probabilidad de complicaciones postoperatorias en pacientes quirúrgicos.

Métodos: Se realizó un estudio observacional prospectivo con pacientes que permanecieron hospitalizados durante más de 24 horas. Se investigaron las siguientes variables: cribado de riesgo nutricional, índice de masa corporal, clasificación ASA, tiempo de ayuno, duración de la hospitalización y complicaciones postoperatorias. Para el análisis estadístico se utilizaron las pruebas de Chi-cuadrado, Exacta de Fisher y Mann-Whitney. Para investigar los factores de riesgo asociados con las complicaciones postoperatorias se realizaron análisis de regresión de Cox simple y múltiple.

Resultados: En el grupo total de pacientes se observó asociación entre las complicaciones postoperatorias y el sexo masculino ($p=0,0197$), el riesgo quirúrgico (ASA) ($p=0,0397$) y la duración de la hospitalización ($p<0,0001$), y los hombres presentaron un riesgo 2,2 veces mayor que las mujeres de sufrir algún tipo de complicación postoperatoria ($p=0,0456$; $RP=2,167$; $IC95\%: 1,015-4,624$). En los pacientes sometidos a cirugías gastrointestinales se observó asociación entre las complicaciones postoperatorias y la duración de la hospitalización ($p<0,0001$). En los pacientes sometidos a otras cirugías se observó asociación entre las complicaciones postoperatorias y la duración de la hospitalización ($p<0,0001$) y la clasificación ASA ($p=0,0160$); además, la clasificación ASA fue considerada un factor asociado con la probabilidad de complicaciones postoperatorias ($p=0,0335$; $RP=4,125$; $IC95\%: 1,117-15,237$).

Conclusiones: El sexo masculino en el grupo total de pacientes y el criterio ASA 3 o 4 en el grupo de pacientes sometidos a otras cirugías son factores asociados con la presencia de complicaciones en el período postoperatorio.

Palabras clave: Complicaciones Postoperatorias. Estado Nutricional. Ayuno. Factores de Riesgo.

1 INTRODUCTION

Some factors associated with the development of postoperative complications had already been addressed by the relevant literature, including surgical approach, smoking, comorbidities, nutritional status, classification of the American Society of Anesthesiologists (ASA), fasting time period, and others^{17,27,30,31,35}. Some risk factors have recently been reported in colorectal resection patients such as complex surgical procedures, postoperative albumin infusion, perioperative surgical events, and others²². In the case of surgical patients, some factors are important for the assessment of the outcomes, in such a way that it is crucial to understand these factors. Among them, for example, reducing length of hospital stay is one of the objectives of the enhanced recovery after surgery (ERAS) protocol^{25,41}. Early postoperative ambulation and distant tumor metastases were also reported as protective factors²². Other reports in the literature have already demonstrated that the application of perioperative measures can achieve rapid postoperative recovery, reduce length of hospital stay, and reduce hospital costs^{9,14,38}.

The guidelines based on the Acceleration of Total Postoperative Recovery (ACERTO) project and supported by evidence associated with perioperative nutritional care in elective General Surgery procedures, indicate that the ACERTO recommendations can accelerate the postoperative recovery of patients undergoing elective general surgery, with a reduction in morbidity, length of stay and readmission and, consequently, costs^{1,2,6,10,11}. Hence, the application of multimodal protocols to support clinical practices in the perioperative assessment and the investigation of the factors that may influence the surgical outcomes, justify carrying out this investigation.

The objective of this study is to investigate the factors associated with the likelihood of postoperative complications in surgical patients.

2 METHODS

2.1 STUDY DESIGN AND LOCATION

This is a prospective observational cohort study, conducted in a university hospital with patients admitted under regular follow-up in clinical-surgical wards and intensive care units. For this study, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed³⁹.

This study was approved by the institution's Research Ethics Committee (number 5.973.659). All participants in this investigation received detailed information about the study and signed the Informed Consent Form. All procedures were carried out in accordance with the relevant guidelines and regulations.

Participants, inclusion and exclusion criteria and sample size The study inclusion criteria were: adult patients, with indication and submitted to surgery during hospital stay. Patients under the age of 18 years were excluded as well as those with incomplete data in their medical records and those who had to suspend the surgical procedure. After reviewing the inclusion and exclusion criteria, a population of 154 patients of both sexes, who were on hospital follow-up in the perioperative period, were considered eligible to participate in the study, based on the calculation of surgical procedures performed in the year prior to the research.

2.2 DATA COLLECTION AND METHODOLOGICAL PROCEDURES

Data were collected in the pre-and postoperative periods, initially surveying demographic data and then other variables. Data were collected directly from the patients' medical records and during attendance of the inpatients who were under regular follow-up, by the actual study investigator.

2.3 STUDY VARIABLES

- a) Nutritional Risk Screening (NRS-2002): to assess nutritional risk, the Nutritional Risk Screening (NRS-2002) was used; this instrument has been internationally recommended for the early detection of nutritional risk in hospitalized patients and, in particular, in surgical patients^{19,20,29}. This instrument allows rating nutritional risk by a numerical score, namely=3 (with nutritional risk) and <3 (without nutritional risk) scores^{19,20}, after reviewing weight loss, body mass index, reduction in food intake, and disease severity.
- b) Body mass index (BMI): body weight and height data were collected to determine the body mass index, according to the criteria standardized by the World Health Organization⁴² for adult patients up to 60 years of age (less than 18.5 kg/m²=below the normal weight; 18.5–24.9 kg/m²=normal weight; 25.0–29.9 kg/m²=overweight; 30.0 kg/m²=obesity). For patients over 60 years of age, the cutoff points recommended by Lipschitz²⁴ were considered (<22.0 kg/m²=thinness; 22.0–27.0 kg/m²=adequate weight; >27.0 kg/m²=excess weight).
- c) American Society of Anesthesiologists (ASA) Classification: to investigate the patient's profile during the perioperative period, the ASA classification was considered (ASA I: normal health; ASA II: mild systemic disease; ASA III: severe non-disabling systemic disease; ASA IV: severe systemic disease, disabling, with serious threat to life; ASA V: moribund patient, with minimal survival expectation; ASA VI: brain-dead,

organ donor patient)¹³. In this study, patients with classification up to ASA IV were included.

- d) Fasting time indicated (prescribed) preoperatively: to evaluate the fasting time indicated in the preoperative period, the medical prescription for fasting was reviewed, following the standard description used in the hospital institution, that is, fasting after 10 pm or fasting after 12 am (midnight).
- e) Total fasting time: to investigate the total preoperative fasting time, the time from the start of fasting to the point in time of the surgical procedure initiation was calculated, comparing the total fasting time with the recommendations of multimodal protocols (ACERTO)^{1,6,10,11}.
- f) Fasting abbreviation: to evaluate the abbreviation of fasting, the prescription of a carbohydrate-rich component (CHO) during preoperative fasting was investigated, as recommended by multimodal protocols (ACERTO)^{1,6,10,11}.
- g) Complications in the postoperative period: to investigate the evolution of patients in the postoperative period, the occurrence of clinical complications in the postoperative period was evaluated such as surgical wound (evaluation of the surgical incision healing process), gastrointestinal signs (weight loss and vomiting in the postoperative period), infectious signs (presence of abscesses and changes in body temperature), cardiovascular changes (bleeding, edema and blood pressure changes), and length of hospital stay (days)^{4,32,33}.

2.4 STATISTICAL ANALYSIS

An initial descriptive analysis was carried out to characterize the population under study; frequency tables for the categorical variables, with absolute frequency (n) and percentage (%) values and for the quantitative variables were developed and descriptive measures were obtained (mean, standard deviation, and median). Subsequently, to compare proportions between two groups, the χ^2 test or Fisher's exact test were used, when necessary; for the comparison of continuous or orderable measurements, the Mann-Whitney test was employed.

Subsequently, to evaluate the factors associated with the presence of complications in the postoperative period, the univariate and multiple Cox regression analyses were used, with the Stepwise variable selection process. The level of significance adopted for all statistical tests was 5% ($p < 0.05$). Data were reviewed using the computer program SAS System for Windows^{8,34,40}.

3 RESULTS

In this investigation, a total of 154 patients ($n=154$) were evaluated; they had been admitted for regular follow-up for surgical procedures in clinical-surgical wards and intensive care units, during the period between September 2022 and April 2023. In Table 1 we illustrate the characteristics of the assessed population, observing that 57.1% ($n=88$) of the investigation participants were men; out of the total investigation participants, 47.4% ($n=73$) underwent gastrointestinal tract surgery; 44.2% ($n=68$) were classified as ASA 2 and 42.2% ($n=65$), as ASA 3. Nutritional risk according to the NRS-2002 was assessed in 66.4% ($n=77$) of patients (Table 1). For analysis purposes, fasting time was stratified into $>8h$ and $>10h$. Considering this classification, the total fasting time $>8h$ was performed by 96.8% ($n=149$) patients and $>10h$ by 85.1% ($n=131$). Regarding the abbreviation of fasting, 98.1% ($n=153$) did not ingest a carbohydrate-rich component during preoperative fasting (Table 1). We verified that 22.7% ($n=35$) of patients presented postoperative complications, most of them being cardiovascular (57.1%; $n=20$) (Table 1).

3.1 THE AVERAGE AGE OF THE INVESTIGATION PARTICIPANTS WAS

57.74 years (± 17.72 ; median=62.72 years), body weight 73.85 kg (± 16.61 ; median=72 kg); BMI 26.80 kg/m² (± 5.99 ; median=26.04 kg/m²); fasting time 18.32 hours (± 9.23 ; median=15.58 hours); and hospitalization time 11.82 days (± 14.54 ; median=7 days).

In Table 2 we compared the study variables with the occurrence or not of postoperative complications. In this analysis, we found statistical significance ($p<0.05$) for the variable sex ($p=0.0197$), with a higher proportion for men; patients with surgical risk (ASA) ($p=0.0397$) were classified into two groups: ASA 1 and 2 (healthy patients or with mild systemic disease) and ASA 3 and 4 (patients with severe, life-threatening systemic disease) and length of hospitalization ($p<0.0001$). We observed that patients who presented complications were hospitalized for a period longer than 21.49 days (± 17.58). We found no significant differences in the other comparisons of the reviewed variables (Table 2).

In the comparison between all the study variables (age, sex, BMI, NRS-2002, type of surgery, length of hospital stay, and surgical risk-ASA) and preoperative fasting time equal to or greater than 8 h and equal to or greater than 10h, we found no statistical difference when expanding the analysis to prolonged fasting. In the comparison between the study variables and the patients' sex, we observed a statistical difference only for the length of hospital stay ($p=0.0195$) variable. The other variables did not present statistically significant differences.

Table 1*Characteristics of the population assessed (n=154)*

Variables	Classification	n (154)	%
Sex	Women	66	42.9
	Men	88	57.1
Surgical risk	ASA 1	17	10.9
	ASA 2	68	44.2
	ASA 3	65	42.2
	ASA 4	4	2.6
Type of surgery	Gastrointestinal	73	47.4
	Urological	21	13.6
	Orthopedic	20	13
	Neurological	14	9.1
	Vascular	14	9.1
	Thoracic	12	7.8
Nutritional Risk Screening (NRS-2002)	At risk	77	66.4
	Without risk	39	33.6
Fasting time (8 h)	=8 h	5	3.2
	>8 h	149	96.8
Fasting time (10 h)	=10 h	23	14.9
	>10 h	131	85.1
Fasting Abbreviation (CHO feeding)	No	151	98.1
	Yes	3	1.9
Postoperative complications	No	119	77.3
	Yes	35	22.7
Complication	Cardiovascular	20	57.1
	Gastrointestinal	14	40.0
	Infectious	14	40.0

ASA: American Society of Anesthesiologists; CHO: carbohydrate-rich component.

In Table 3 we show the factors associated with complications in the postoperative period, investigated by simple and multiple Cox regression analysis. We verified that only sex remained a factor associated with complications, with men having a times higher risk than women of suffering some type of complication in the postoperative period ($p=0.0456$; $PR=2.167$; $95\%CI$ 1.015–4.624).

Subsequently, the study variables were analyzed and compared with the type of surgery (gastrointestinal tract-GIT surgeries and other surgeries) to which the patients had been submitted. There was a statistical difference in relation to age ($p=0.0297$), postoperative complications ($p=0.0136$), and fasting time >10 h ($p=0.0264$). We found no significant difference in the other study variables in relation to the type of surgery. In the comparison between the study variables and the classified fasting time ($=10$ h and >10 h) in the two groups of surgeries (GIT surgeries and other surgeries), no statistical difference was evident.

When comparing the reviewed variables and the presence of complications in the postoperative period in the group of patients undergoing GIT surgeries, we found a statistical difference only for length of hospital stay ($p<0001$). The patients who presented complications in the postoperative period were those who remained hospitalized for the longest time (in patients who underwent GIT surgeries). In the comparison between the reviewed variables and the presence of complications in the postoperative period, in the

group of patients undergoing other surgeries, we verified a statistical difference for the length of hospital stay ($p<0001$) and the ASA classification ($p=0.0160$). Patients who presented complications in the postoperative period were those who remained hospitalized for the longest time and who had been classified as ASA 3 and 4 (these are patients who underwent other surgeries).

In Tables 4 and 5 we illustrate the factors associated with postoperative complications investigated by simple and multiple Cox regression analysis, in patients undergoing GIT surgeries and other surgeries. There was no association between the variables in the group of patients undergoing GIT surgeries and no variable was significant at the 5% level (Table 4).

In the group of patients undergoing other surgeries, the ASA classification was considered a factor associated with the probability of complications in the postoperative period; patients classified in categories 3 and 4 had a fourfold higher risk when compared to those classified in categories 1 and 2 ($p=0.0335$; $PR=4.125$; $95\%CI$ 1.117–15.237) (Table 5).

In Figures 1 and 2 we illustrate the percentile rank (PR) and respective 95% confidence interval (LI95–LS95%) for men, compared to women, and for ASA criteria 3 or 4, compared to criteria 1 or 2, estimated by the Cox regression analysis, in the assessment of factors associated with the presence of complications in the postoperative period, considering the total group and the group of other surgeries, respectively. For the GIT surgery group, no variable was significant at the 5% level.

4 DISCUSSION

Most patients were men, with a profile similar to that described by Madan et al.²⁶ and different from the profile of the population studied by Coeckelberghs et al.⁷, who evaluated 740 older adult patients, the majority of whom were women.

The fasting time observed in the participants of this study was mostly prolonged, that is, the application of the intervention and time management did not follow the multimodal protocols^{1,6,10,11}. Denkyi¹², found that anesthesiologists in general have greater knowledge of preoperative fasting compared to other professionals and that the actual fasting time found in the evaluated patients was longer than the prescribed time; data similar to the findings of our study. GIT surgeries were prevalent in patients in our study; similar data were observed in a multicenter study conducted by Coeckelberghs et al.⁷, evaluating colectomy procedures.

The nutritional risk according to the NRS-2002 was verified in the majority of patients; these are relevant data of this investigation, although no statistical difference was observed in the comparison of nutritional risk between those who did or did not present complications in the postoperative period. Another relevant information was the identification of overweight patients, the majority of whom was measured by BMI. This discrepancy shows that the NRS instrument was more sensitive than BMI in identifying patients at nutritional risk. Masoudkabar et al.²⁸, in a cohort study with patients with the same profile found in the present study, demonstrated that overweight and normal weight patients presented similar postoperative results, but patients with a BMI greater than 30 kg/m² presented a significantly higher risk for mortality. Authors of another study, in which the perioperative risks associated with BMI were reviewed, showed that patients with a BMI=40 kg/m² presented statistical significance for cardiac complications, and those with a BMI<18.5 kg/m² had lower short- and long-term survival³.

Table 2

Descriptive analysis of the study variables and comparison with the presence or absence of postoperative complications

Variables	Category	Postoperative complications		n	p-value
		No (%)	Yes (%)		
Age (years)	Mean±SD	n=119 57.15±18.19	n=35 59.73±16.11	n=154 57.60±17.69	0.4102*
	Median	62.73	62.72	62.72	
BMI (kg/m ²)	Mean±SD	n=112 27.01±5.97	n=35 26.57±6.13	n=147 26.90±5.99	0.5067*
	Median	26.23	25.35	26.04	
Total fasting (h)	Mean±SD	n=119 18.47±9.24	n=35 17.83±9.21	n=154 18.32±9.23	0.7140*
	Median	15.67	15.50	15.58	
Sex	Women	n=119 57 (47.9)	n=35 9 (25.7)	n=154 66 (42.9)	0.0197†
	Men	62 (52.1)	26 (74.3)	88 (57.1)	
Fasting time=8 h	Yes	n=119 3 (2.5)	n=35 2 (5.7)	n=154 5 (3.2)	0.3187‡
	No	116 (97.5)	33 (94.3)	149 (96.8)	
Fasting time=10 h	Yes	n=119 16 (13.4)	n=35 7 (20)	n=154 23 (14.9)	0.3389†
	No	103 (86.6)	28 (80)	131 (85.1)	
NRS-2002	At risk	n=83 53 (63.9)	n=33 24 (72.7)	n=116 77 (66.4)	0.3615†
	Without risk	30 (36.1)	9 (27.3)	39 (33.6)	
Surgical risk	ASA 1 and 2	n=119 71 (59.7)	n=35 14 (40)	n=154 85 (55.2)	0.0397†
	ASA 3 and 4	48 (40.3)	21 (60)	69 (44.8)	
Type of surgery	GIT	n=119 50 (42)	n=35 23 (65.7)	n=154 73 (47.4)	0.0688‡
	URO	19 (16)	2 (5.7)	21 (13.6)	
	ORTOP	17 (14.3)	3 (8.6)	20 (13)	
	NEURO	13 (10.9)	1 (2.9)	14 (9.1)	
	VASC	9 (7.6)	5 (14.3)	14 (9.1)	
	TORAX	11 (9.2)	1 (2.9)	12 (7.8)	
Length of hospital stay (days)	Mean±SD	n=119 8.98±12.22	n=35 21.49±17.58	n=154 11.82±14.54	<0.0001*
	Median	6.00	15.00	7.00	

*Mann-Whitney Test; †χ² test; ‡Fisher's exact test. SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists; NRS-2002: Nutritional Risk Screening; GIT: gastrointestinal tract; URO: urological; ORTOP: orthopedic; NEURO: neurological; VASC: vascular; TORAX: thoracic.

Table 3

Study on factors associated with postoperative complications using simple and multiple Cox regression analysis

Variables	Category	p-value	PR	95%CI	
Cox simple analysis					
Sex	Men x Women	0.0456	2.167	1.015	4.624
Age		0.5056	1.007	0.987	1.027
Body mass index		0.7404	0.990	0.935	1.049
Fasting time		0.7504	0.994	0.958	1.032
ASA	(1 and 2) x (3 and 4)	0.0750	1.849	0.940	3.635
NRS-2002	At risk x Without risk	0.4420	1.351	0.628	2.905
Type of surgery	ORTOP x NEURO	0.5205	2.100	0.218	20.188
	GIT x NEURO	0.1463	4.411	0.596	32.662
	TORAX x NEURO	0.9132	1.167	0.073	18.652
	URO x NEURO	0.8143	1.333	0.121	14.704
	VASC x NEURO	0.1418	5.000	0.584	42.797
Fasting time 10 h	=10h x >10h	0.4030	0.702	0.307	1.608
Multiple analysis*					
Sex	Men x Women	0.0456	2.167	1.015	4.624

*Modeling the probability of the presence of complications. PR: percentile rank; CI: confidence interval; ASA: American Society of Anesthesiologists; NRS-2002: Nutritional Risk Screening; ORTOP: orthopedic; NEURO: neurological; GIT: gastrointestinal tract; TORAX: thoracic; URO: urological; VASC: vascular.

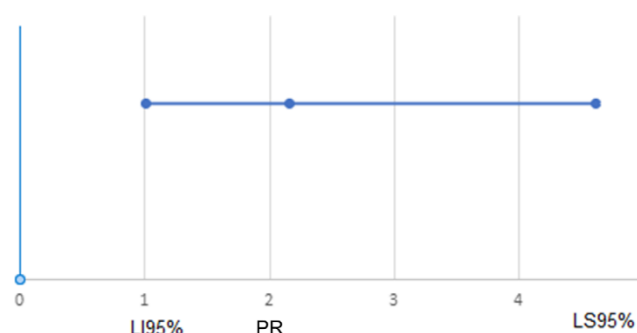
In the present study, the majority of participants were classified as having an ASA 2 or ASA 3 risk, a similar profile found in the study conducted by Madan et al.²⁶; observing that many patients had serious systemic diseases, requiring alertness for health care planning. A statistical difference was observed for surgical risk in patients classified under ASA 3 and 4; in other words the presence of serious systemic diseases may have resulted in postoperative complications. Madan et al.²⁶, in a randomized study with ASA-1 and 2-profile patients undergoing coloproctological surgery, compared the application of the ERAS protocol, obtaining no statistical difference associated with postoperative complications. Thus, it is clear that patients with a more critical classification (ASA 3 and 4) may be at greater risk of postoperative complications; these data corroborate our findings.

A statistical difference was observed regarding sex, suggesting that postoperative complications could occur more frequently in men. Although there was no statistical difference, most of the complications found were related to the cardiovascular system (bleeding, edema, and changes in blood pressure levels). Another relevant finding was the association between prolonged length of hospital stay and the presence of postoperative complications. In the study conducted by Lindemann et al.²³, comparing the application of the ERAS guidelines, the group submitted to this protocol (ERAS) presented a statistically significant reduction in the length of hospital stay. In our investigation, we observed no statistical difference related to preoperative fasting time; however, the study conducted by Lindemann et al.²³, corroborates the findings of the present study with regard to the relation between the hospitalization period and the application of the ERAS guidelines, and may raise

future hypotheses about the association between the length of hospitalization time and prolonged fasting. The preoperative period should be rigorously evaluated, considering noncompliance with these guidelines in the clinical practice despite the existence of current protocols; thus, this is a factor that could be modified to prevent complications^{14,16,37}. In a cohort study conducted by Sinha et al.³⁶, the postoperative evolution of liquid and solid food intake, passage of flatus, catheter removal, ambulation, pain, and length of hospital stay in two groups of patients were investigated; all these variables occurred statistically less in the group that had undergone ERAS interventions, confirming one of the findings of this study in relation to length of hospital stay and its association with postoperative complications.

Figure 1

Percentile rank and respective 95% confidence interval (LI95%–LS95%) for men compared to women, estimated by Cox regression analysis, in the study on factors associated with the presence of complications in the postoperative period, considering the total group



LI: Light interception; PR: percentile rank; LS: longitudinal study.

Table 4

Study on factors associated with postoperative complications, in the group of patients undergoing gastrointestinal tract surgeries, using simple and multiple Cox regression analysis (modeling the probability of presence of complications)

Variables	Category	p-value	PR	95%CI	
Cox simple analysis					
Sex	Men x Women	0.1618	1.885	0.776	4.582
Age		0.7578	1.004	0.979	1.029
Body mass index		0.6328	0.982	0.912	1.057
Fasting time		0.8689	0.996	0.950	1.045
ASA	(3 and 4) x (1 and 2)	0.5912	1.251	0.552	2.836
NRS-2002	At risk x Without risk	0.8280	1.109	0.437	2.812
Fasting time 10h	=10 h x >10 h	0.4048	0.597	0.177	2.009
Multiple analysis*					
No variables significant at the 5% level were selected (n=71)					

*Stepwise variable selection process. PR: percentile rank; CI: confidence interval; ASA: American Society of Anesthesiologists; NRS-2002: Nutritional Risk Screening. The NRS variable was excluded from the multiple analysis due to the reduced number of patients in this analysis.

Table 5

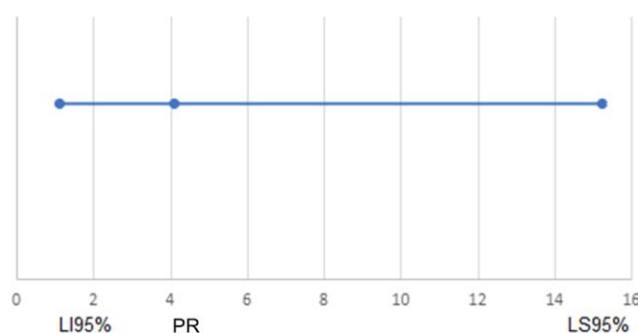
Study on factors associated with postoperative complications in the group of patients undergoing other surgeries, using simple and multiple Cox regression analysis (modeling the probability of presence of complications).

Variables	Category	p-value	PR	95%CI	
Cox simple analysis					
Sex	Men x Women	0.1109	3.437	0.753	15.686
Age		0.8801	1.002	0.971	1.035
Body mass index		0.8919	1.006	0.918	1.103
Fasting time		0.5809	0.981	0.918	1.049
ASA	(3 and 4) x (1 and 2)	0.0396	3.943	1.067	14.564
NRS-2002	At risk x Without risk	0.5071	1.580	0.409	6.111
Fasting time 10h	=10 h x >10 h	0.3016	0.531	0.160	1.764
Multiple analysis*					
ASA	(3 and 4) x (1 and 2)	0.0335	4.125	1.117	15.237

*Stepwise variable selection process. PR: Percentile rank; CI: confidence interval; ASA: American Society of Anesthesiologists; NRS-2002: Nutritional Risk Screening. The NRS variable was excluded from the multiple analysis due to the reduced number of patients in this analysis.

Figure 2

Percentile rank and respective 95% confidence interval (LI95%–LS95%) for American Society of Anesthesiologists criteria 3 or 4 compared to 1 or 2, estimated by Cox regression analysis, in the study of factors associated with the presence of complications in the postoperative period, considering the group of other surgeries. For the gastrointestinal tract surgery group, no variable was significant at the 5% level



LI: Light interception; PR: percentile rank; LS: longitudinal study.

The findings of our investigation indicated that men were at greater risk than women for some type of complication in the postoperative period. The variables studied here were also compared among patients undergoing GIT surgeries and other surgeries; they indicated an association with older age, more postoperative complications, and fasting time >10 hours in patients with GIT surgeries. When comparing the variables with the occurrence of complications in the two groups of surgeries, patients hospitalized for longer periods presented more complications in the group of patients undergoing GIT surgeries. Those who remained hospitalized for longer periods and who had been classified as ASA 3 and 4

presented more complications in the group of patients undergoing other surgeries. Although we found no statistical difference between the variables in this study and the fasting time classified as 10 hours, we observed that, in both groups of surgeries, the majority of patients undergoing fasting time >10 hours presented nutritional risk according to the NRS, indicating the need for future studies to delve deeper into this issue. The difficulty in accessing the patients' records in their entirety due to the fact that they were not fully computerized, especially in relation to complications, as well as the loss of some nutritional indicators, were the main limiting factors of this study.

Another finding was that, using regression analysis in the group of patients undergoing GIT surgeries, we found no association between the variables assessed in relation to complications. In the group of patients undergoing other surgeries, the ASA classification was considered a factor associated with the probability of complications in the postoperative period; patients classified in categories 3 and 4 presented a fourfold higher risk when compared to those classified in categories 1 and 2. In patients classified as ASA 3 and undergoing gastrointestinal, urogenital, or orthopedic surgeries, a similar profile as in our investigation was found; a prospective multicenter study conducted by Bartha et al.⁵, evaluated the ASA classification and surgical severity and showed that both classifications can be used to identify a high-risk surgical population in relation to postoperative morbidity and mortality for gastrointestinal and orthopedic surgery.

The findings of the present investigation are in line with the findings reported by Bartha et al.⁵, with regard to the application of the ASA classification in the preoperative assessment; the results constitute a guidance for the prevention of perioperative complications. There are also reports of an association between malnutrition and postoperative complications and longer hospitalization periods in older adult patients, showing that advanced age and low BMI were considered risk factors for malnutrition¹⁵. As in patients undergoing sleeve gastrectomy, there was a significantly shorter length of hospital stay in the group of patients in which the ERAS protocol was applied and there was no increase in the rate of perioperative morbidity²¹. Other findings reported in the literature indicate a reduction of hospital stay in patients undergoing surgical procedures to whom the ERAS protocol had been applied^{18,21,23}. Such reports suggest the application of multimodal protocols in surgical practice.

The hypothesis raised at the beginning of this study that preoperative fasting time could influence the occurrence of postoperative complications was not confirmed in our investigation. However, relevant findings were observed, such as a prolonged preoperative fasting period, nutritional risk according to the NRS in most patients, more postoperative

complications in those patients with longer length of hospital stay, longer length of hospital stay among male patients, more general postoperative complications, greater occurrence of postoperative complications in male patients, in older age patients and fasting time >10 hours in patients undergoing gastrointestinal tract surgery, association between longer length of hospital stay and postoperative complications in patients with gastrointestinal tract surgery and other surgeries. Using the Cox regression, criteria 3 and 4 in the ASA classification were considered factors associated with the probability of postoperative complications in patients undergoing other surgeries. Considering the total group of patients, men were also considered a factor associated with the probability of postoperative complications.

5 CONCLUSIONS

According to our findings, men in the total group of patients and the ASA 3 or 4 criteria in the group of patients undergoing other surgeries were considered factors associated with the occurrence of complications in the postoperative period.

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FAST, ACCURATE, AND COST-EFFECTIVE: E-FAST'S BREAKTHROUGH IN OPTIMIZING THORACIC TRAUMA MANAGEMENT

RÁPIDO, PRECISO E ECONÔMICO: O AVANÇO DO E-FAST NA OTIMIZAÇÃO DO MANEJO DO TRAUMA TORÁCICO

RÁPIDO, PRECISO Y RENTABLE: EL AVANCE DEL E-FAST EN LA OPTIMIZACIÓN DEL MANEJO DEL TRAUMA TORÁCICO



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ABSTRACT

Objective: Evaluating the diagnostic accuracy of extended focused assessment with sonography for trauma (E-FAST) for detecting pneumothorax, hemothorax, and pulmonary contusions using thoracic computed tomography (CT) as the reference standard.

Material and Methods: Retrospective analysis of 202 adult thoracic trauma patients (2016-2021). E-FAST diagnostic accuracy was calculated using CT as reference standard.

Results: E-FAST was performed in 149 patients (74%), who presented with significantly higher injury severity (injury severity score: 25 vs. 17; $p=0.018$) and hemodynamic instability. E-FAST demonstrated 90% sensitivity for pneumothorax, 86% for hemothorax, and 95% specificity for both conditions. Positive predictive values were 92% for pneumothorax and 89% for hemothorax. E-FAST was superior to chest radiography for detecting pleural complications and facilitated immediate thoracic drainage in 39.1% of cases. Cost analysis revealed four-fold reduction compared to CT.

Conclusion: E-FAST demonstrated high diagnostic accuracy for pneumothorax and hemothorax compared to CT, while also showing superior performance to conventional radiography. E-FAST facilitates rapid bedside assessment and immediate surgical decision-making in critically injured patients. However, the significant selection bias toward critically injured patients limits the conclusions regarding the independent impact on clinical outcomes.

Keywords: Thoracic Injuries. Ultrasonography. Focused Assessment with Sonography for Trauma. Emergency Medicine. Decision Making.

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RESUMO

Objetivo: Avaliar a acurácia diagnóstica do exame estendido de ultrassonografia focada em trauma (E-FAST) para detecção de pneumotórax, hemotórax e contusões pulmonares, utilizando a tomografia computadorizada (TC) de tórax como padrão-ouro.

Material e Métodos: Análise retrospectiva de 202 pacientes adultos com trauma torácico (2016–2021). A acurácia diagnóstica do E-FAST foi calculada utilizando a TC como padrão de referência.

Resultados: O E-FAST foi realizado em 149 pacientes (74%), que apresentaram gravidade de lesão significativamente maior (escore de gravidade da lesão: 25 vs. 17; $p=0,018$) e instabilidade hemodinâmica. O E-FAST demonstrou sensibilidade de 90% para pneumotórax, 86% para hemotórax e especificidade de 95% para ambas as condições. Os valores preditivos positivos foram de 92% para pneumotórax e 89% para hemotórax. O E-FAST foi superior à radiografia de tórax na detecção de complicações pleurais e permitiu drenagem torácica imediata em 39,1% dos casos. A análise de custos revelou redução de quatro vezes em comparação com a TC.

Conclusão: O E-FAST demonstrou alta acurácia diagnóstica para pneumotórax e hemotórax em comparação à TC, além de desempenho superior à radiografia convencional. O E-FAST facilita a avaliação rápida à beira-leito e a tomada de decisão cirúrgica imediata em pacientes gravemente traumatizados. No entanto, o viés significativo de seleção para pacientes mais graves limita as conclusões quanto ao impacto independente nos desfechos clínicos.

Palavras-chave: Lesões Torácicas. Ultrassonografia. Avaliação Focada com Ultrassom em Trauma. Medicina de Emergência. Tomada de Decisão.

RESUMEN

Objetivo: Evaluar la precisión diagnóstica del examen extendido de ultrasonografía enfocada en trauma (E-FAST) para la detección de neumotórax, hemotórax y contusiones pulmonares, utilizando la tomografía computarizada (TC) de tórax como estándar de referencia.

Material y Métodos: Análisis retrospectivo de 202 pacientes adultos con trauma torácico (2016–2021). La precisión diagnóstica del E-FAST se calculó utilizando la TC como estándar de referencia.

Resultados: El E-FAST se realizó en 149 pacientes (74%), quienes presentaron una gravedad de lesión significativamente mayor (índice de gravedad de la lesión: 25 vs. 17; $p=0,018$) e inestabilidad hemodinámica. El E-FAST demostró una sensibilidad del 90% para neumotórax, 86% para hemotórax y una especificidad del 95% para ambas condiciones. Los valores predictivos positivos fueron del 92% para neumotórax y 89% para hemotórax. El E-FAST fue superior a la radiografía de tórax en la detección de complicaciones pleurales y permitió el drenaje torácico inmediato en el 39,1% de los casos. El análisis de costos reveló una reducción de cuatro veces en comparación con la TC.

Conclusión: El E-FAST demostró una alta precisión diagnóstica para neumotórax y hemotórax en comparación con la TC, además de un rendimiento superior a la radiografía convencional. El E-FAST facilita la evaluación rápida a pie de cama y la toma de decisiones quirúrgicas inmediatas en pacientes gravemente traumatizados. Sin embargo, el importante sesgo de selección hacia pacientes más graves limita las conclusiones sobre su impacto independiente en los resultados clínicos.



Palabras clave: Lesiones Torácicas. Ultrasonografía. Evaluación Focalizada con Ultrasonido en Trauma. Medicina de Emergencia. Toma de Decisiones.

1 INTRODUCTION

Thoracic trauma is the second most frequent unintentional injury and the third most common cause of death in polytrauma patients, after abdominal injury and head trauma (1). Among patients with severe trauma, thoracic injuries account for 25% of fatalities (2). Patients with severe injuries and critical thoracic trauma present with the highest rates of prehospital intubation, cardiopulmonary resuscitation, emergency chest tube placement, blood transfusion, and urgent surgical intervention. Prompt recognition, diagnosis, and appropriate management are mandatory to improve outcomes, particularly in tertiary hospitals that manage complex cases. Traditional diagnostic modalities, including chest radiography (CXR) and computed tomography (CT), are clinically effective but constrained by radiation exposure, logistical limitations, and substantial costs, particularly in resource-limited healthcare settings. This highlights the need to explore diagnostic alternatives such as thoracic ultrasonography.

The extended focused assessment with sonography for trauma (E-FAST) has emerged as a rapid, reproducible, noninvasive, and cost-effective bedside tool for thoracic trauma evaluation, demonstrating high sensitivity and specificity for detecting pulmonary contusions, pneumothorax, and hemothorax, and doing so without exposing patients to ionizing radiation (3).

Despite the growing global adoption of E-FAST, data on the diagnostic accuracy, clinical impact, and economic benefits of E-FAST in tertiary hospitals in Brazil remain limited.

This retrospective study evaluated E-FAST utilization in 202 patients with thoracic trauma at a regional trauma center, with the primary objective of determining the diagnostic accuracy of E-FAST for detecting pneumothorax, hemothorax, and pulmonary contusions, using thoracic CT as the reference standard. The secondary objectives included comparing the diagnostic performance of E-FAST with that of conventional CXR, assessing the impact of E-FAST on surgical decision-making and immediate treatment, evaluating the cost-effectiveness of E-FAST implementation, and determining the influence of E-FAST on clinical outcomes. This study aimed to validate the E-FAST as an effective tool for optimizing thoracic trauma management in high-volume tertiary settings.

2 MATERIAL AND METHODS

This retrospective study reviewed the medical records of 476 patients treated at the Emergency and Trauma Surgery Service at University Hospital of Pontifícia Católica de Campinas, a tertiary referral center with 31 years' experience in complex trauma management, between January 2016 and December 2021. Adults (aged ≥ 18 years) with

confirmed thoracic trauma were included in the study. Patients were excluded if patients aged <18 years, died upon trauma bay admission, or had incomplete medical records, resulting in a final sample size of 202. Incomplete records that were not imputed were excluded to ensure data reliability.

The primary outcome was length of hospital stay (days), with secondary outcomes including the need for mechanical ventilation, the use of vasoactive drugs, and mortality. Data extracted from electronic medical records included demographic variables (age and sex), epidemiological variables (trauma mechanism and time from event to admission), clinical variables [revised trauma score (RTS), thoracic trauma severity score (TTSS), injury severity score (ISS), injury burden, and initial management], and diagnostic and treatment variables. The E-FAST, CXR, and CT findings were systematically compared.

E-FAST examinations were performed at the discretion of attending trauma surgeons, emergency physicians, or general surgery residents (second- and third-year) with variable levels of ultrasound experience, following standardized institutional protocols. The decision to perform E-FAST was not randomized and instead followed institutional protocols that prioritized unstable or high-risk patients, typically those presenting with clinical signs of thoracic injury.

Pneumothorax evaluation involved assessing the anterior chest wall (2nd-6th intercostal spaces, clavicular line) with a linear probe. Normal lung sliding appears as a “marching ants” or “sandy beach” pattern. The absence of pleural sliding combined with a “stratosphere” or “barcode” sign on M-mode served as the diagnostic criterion for pneumothorax. The presence of a lung point is considered pathognomonic of pneumothorax. Hemothorax detection employs two complementary approaches: Curvilinear probe placement in the lower intercostal spaces (6th-8th, posterior axillary line) to detect pleural fluid, which appears as anechoic or hypoechoic areas; and identification of the spinal stripe superior to the diaphragm in bilateral upper- quadrant views. All examinations were performed during the primary survey to guide definitive management.

2.1 STATISTICAL ANALYSIS

The diagnostic accuracy of e-FAST was assessed by calculating sensitivity and specificity for detecting pulmonary contusions, pneumothorax, and hemothorax, using thoracic CT as the reference standard.

To address potential selection bias, we performed stratified analyses based on the ISSs and hemodynamic status. Propensity score analysis was conducted to balance the baseline characteristics between patients who underwent E-FAST and those who did not.

Chi-square tests were used for categorical variables and Mann-Whitney U tests for continuous variables. Multiple logistic regression was performed to identify independent predictors of E-FAST utilization while controlling for potential confounders, including age, injury mechanism, hemodynamic status, and ISSs. The diagnostic performance was estimated with 95% confidence intervals (CI). A sensitivity analysis was performed to assess the robustness of our findings across different patient subgroups. Statistical significance was set at $p < 0.05$, and analyses were performed using SPSS v26, Minitab 21.2, and Excel 2010.

Direct costs were calculated using institutional billing data from the Brazilian Sistema Único de Saúde (SUS). Indirect costs, including personnel time, equipment maintenance, training requirements, and potential costs associated with false-positive results, were not included in this analysis, which represents a limitation of the economic evaluation.

This retrospective, single-center study introduces several potential sources of bias, including selection bias (preferential use of E-FAST in critically ill patients), information bias (variable documentation quality and single-center analysis), and temporal bias (evolving protocols over the 5-year study period). The non-randomized nature of E-FAST utilization and the variable experience of operators represent additional limitations that may affect the generalizability of our findings to other institutions.

3 RESULTS

Of the 476 medical records reviewed, 202 adults with thoracic trauma were included in the final analysis after excluding 274 cases. The study population demonstrated a significant male predominance (77.9; $n=156$), with a mean age of 43.6 ± 2.9 years (95% CI).

Emergency medical service transport was used in 69% of cases ($n=138$), with SAMU 192 representing the most frequent prehospital response system (35.5%). Notably, 79% of patients were admitted within two hours of the traumatic event; prehospital response times were <30 min. The mean hospital length of stay was 8.5 ± 3.6 days, and the mean RTS was 6.29 ± 0.16 .

Among the 202 patients, blunt trauma predominated in 172 cases (85.1%), whereas penetrating injuries occurred in 30 patients (14.9%). Road traffic injuries (RTI) were the most common mechanism of injury (41.3%), followed by interpersonal violence (31.8%) and falls (25.4%). Accidental falls occur predominantly from a standing height and are more prevalent among older patients (90%). Within the RTI category, two-wheeled vehicle accidents represented the largest subset (19.2% of the total cases), followed by motor vehicle collisions and rollovers (16.7%). The mechanisms of trauma included penetrating injuries (gunshot

wounds in 28 cases, 13.8%; stab wounds, 9.9%) and assaults with blunt objects (11.3%) (Table 1).

Most patients (n=148; 72.9%) were hemodynamically and respiratorily stable on admission to the intensive care unit. Hemodynamic instability (SBP <90 mmHg, base excess >-5, or lactate >3.5 milimol/L) was observed in 30 patients. Regarding injury distribution, 107 patients presented with multisystem trauma involving regions beyond the thorax, whereas only 11.8% of patients sustained isolated thoracic trauma.

Specific thoracic lesions included rib fractures in 141 patients (84 with displacement), simple pneumothorax in 63 patients, simple hemothorax in 38 patients, hemopneumothorax in 17 patients, pulmonary contusion in 15 patients, massive hemothorax in 7 patients, and tension pneumothorax in 4 patients. The TTSS distribution indicated injuries ranging from moderate to severe, with a mean TTSS of 10.2 ± 6.8 .

Associated injuries were frequent. Orthopedic fractures occurred in 80 patients, of whom 60% had fractures involving the lower extremities and 27% had pelvic fractures. Traumatic brain injury was present in 70 patients (34.7%), and abdominal and facial trauma affected 46 patients (22.8%). Among the intra- abdominal injuries, splenic trauma was the most common (n=28), followed by hepatic laceration (n=19), diaphragmatic injury (n=10), renal trauma (n=8), and mesenteric injury (n=5). Spinal cord trauma and soft-tissue injuries occurred in 25 and 22 patients, respectively. The mean ISS was 18 ± 4.5 ; 65% of patients had an ISS >15 (Tables 2 and 3).

Non-operative management with clinical observation was implemented in 66% of cases, whereas 30% required immediate thoracic drainage. Digital thoracostomy followed by tube drainage was necessary in 3% of patients, and an emergency department thoracotomy for resuscitation was performed in 1% of patients. Forty patients required thoracic reintervention, with repeat thoracic drainage the most common procedure, followed by thoracoscopy; there were also two delayed thoracotomies for empyema or retained hemothorax.

Table 1

Trauma mechanisms in 202 patients

Mechanism	Number	Percentage	Category
Motorcycle	39	19.3	Blunt
Falls	36	17.8	Blunt
Motor	32	15.8	Blunt
Gunshot	28	13.9	Penetrating
Assault	23	11.4	Blunt
Stab	20	9.9	Penetrating

Falls	14	6.9	Blunt
Pedestrian	6	3	Blunt
Bicycle	2	1	Blunt
Horse	2	1	Blunt
Total	202	100	
Blunt trauma: 172 patients (85.1%), Penetrating trauma: 30 patients (14.9%).			

Table 2

Thoracic injury patterns

Injury	Number	Percentage	Severity
Rib	141	69.8	84
Simple	63	31.2	-
Simple	38	18.8	-
Hemopneumothorax	17	8.4	-
Pulmonary	15	7.4	-
Massive	7	3.5	-
Tension	4	2	-
Mean thoracic trauma severity score: 10.2±6.8 (moderate to severe injuries). Patients may have multiple thoracic injuries.			

Table 3

Associated extra-thoracic injuries

Injury	Patients	Prevalence	Specific
Orthopedic	80	39.6	Lower Pelvis Upper
Traumatic	70	34.7	All
Abdominal trauma	46	22.8	Splenic Hepatic Diaphragmatic Renal: 8 (17.4%) Mesenteric
Spinal	25	12.4	All
Soft	22	10.9	-
Mean ISS: 18±4.5 (65% of patients with ISS >15) ISS: Injury severity score, Note: Patients may have multiple associated injuries.			

E-FAST was performed in 149 patients (74%) during the admission evaluation. CT was performed in 153 patients (78%), and CXR was performed in 115 (59%).

Significant differences were observed between patients who underwent E-FAST and those who did not. Patients selected for the E-FAST examination presented with a higher mean (ISS: 25 vs. 17; $p=0.018$), increased hemodynamic instability (50% vs. 32.1%; $p=0.014$), greater requirement for mechanical ventilation (43.4% vs. 15.5%; $p<0.001$), and more frequent vasoactive drug support (33.8% vs. 8.8%; $p<0.001$).

Among the patients who underwent E-FAST, immediate thoracic drainage was performed in 39.1% (n=59) based on the ultrasound findings. In 83% of the cases requiring thoracic decompression, the procedure was performed in the emergency department.

CT imaging identified a mean of 2.54 thoracic lesions per patient, compared with 2.18 per patient among patients without CT evaluation ($p=0.025$). E-FAST demonstrated superior performance compared with radiography for early assessment of severity ($p<0.001$ for hemodynamic instability). The diagnostic performance of E-FAST and comparative results are presented in (Tables 4 and 5).

E-FAST utilization was associated with increased morbidity, as 19% of patients were discharged with thoracic sequelae compared with 7.6% of patients without E-FAST ($p=0.021$). Patients who underwent E-FAST had higher mean values for (RTS: 6.46 vs. 6.00), (ISS: 25 vs. 17), and (TTSS: 17 vs. 7) ($p=0.018$).

E-FAST guided immediate surgical decision-making and facilitated prompt thoracic drainage in 39.1% of cases (n=59; odds ratio: 0.61, 95%; CI: 0.30-1.25). Diagnostic time was reduced by 20-50 minutes in patients who underwent E-FAST compared with those who underwent conventional imaging workflows.

The overall mortality rate was 9.2% (n=17), with multi-organ failure being the primary cause of death.

Table 4

E-FAST diagnostic performance (using CT as reference standard)

Condition	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI
Pneumothorax	90%	95%	92%	94%	93%	86-97%
Hemothorax	86%	95%	89%	93%	92%	86-97%
Pulmonary	75%	95%	88%	89%	88%	81-94%

E-FAST vs. chest radiography performance
 • Pneumothorax detection : E-FAST 90% vs. CXR 65% sensitivity ($p<0.001$)
 • Hemothorax detection : E-FAST 86% vs. CXR 71% sensitivity ($p<0.05$)
 PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, CT: Computed tomography, E-FAST: Extended focused assessment with sonography for trauma.

Table 5

CT vs. E-FAST comparative diagnostic performance

Parameter	CT imaging	E-FAST	Statistical
Total	153 (75.7%)	149 (73.8%)	-
Mean	2.54±1.2	2.18±1.0	$p=0.025^*$
Comprehensive	153/153 (100%)	142/149 (95.3%)	$p<0.001^*$
Complex	High	Limited	-
Associated	98/153 (64.1%)	45/149 (30.2%)	$p<0.001^*$

Clinical decision impact:

- CT- guided management changes : 89/153 (58.2%)
- E-FAST- guided immediate interventions: 59/149 (39.6%)
- Diagnostic concordance (when both performed): 127/134 (94.8%)
- Diagnostic role definition:
 - CT: Gold standard for comprehensive injury assessment and surgical planning
 - E-FAST: Rapid screening tool for immediate life-threatening injuries
- *: Statistically significant difference ($p < 0.05$), CT: Computed tomography, E-FAST: Extended focused assessment with sonography for trauma.

4 DISCUSSION

Thoracic trauma represents a significant global health burden, contributing to approximately 25% of all direct trauma-related deaths (4). Our epidemiological findings are consistent with established patterns: Young males (18-40 years) accounted for 77.9% of cases, and RTI were the leading mechanism (41.3%). This disproportionate incidence among young adults emphasizes the critical need for targeted prevention strategies, including enhanced road safety education programs, particularly in middle-income countries (5,6). The high ISS and TTSS scores in our series underscored the complexity of the injuries, with 65% of patients having ISS >15 and frequent multisystem involvement.

The predominance of prehospital transport via SAMU 192 (69% of cases) and the high proportion of patients arriving within two hours (79%) reflect Brazil's improved emergency infrastructure and align with the critical "golden hour" concept

(7). This improvement can be attributed to three key factors: Effective triage protocols, consistently trained first responders, and streamlined communication systems

That facilitate rapid transport to definitive trauma care facilities in the United States. However, motorcycle-related trauma (19.2%) and interpersonal violence (31.8%) remained significant concerns in urban settings. Penetrating injuries are often more severe (8). Although blunt trauma is typically associated with higher overall mortality rates, most penetrating thoracic injuries in our series progressed to hemodynamic instability, requiring massive transfusion protocols and immediate surgical interventions.

Multiple studies have validated the diagnostic superiority of E-FAST over conventional imaging. Ding et al.'s (9) meta-analysis reported a pooled sensitivity of 88-99% for ultrasound-based diagnosis of pneumothorax, whereas contemporary literature reports 81-95% sensitivity for hemothorax detection (10-15). Our findings align with this evidence, demonstrating 90% and 86% sensitivity for pneumothorax and hemothorax, respectively, with 95% specificity for both conditions.

Its superior performance compared with supine CXR (sensitivities of 90% vs. 65% for pneumothorax; $p < 0.001$) supports current trauma guidelines that recommend ultrasound as the preferred initial imaging modality for unstable patients. This superior performance is

particularly relevant because small- and medium-sized pneumothoraces and hemothoraces may be missed on supine CXR; this is especially important in our setting, where 79% of patients arrive within two hours of injury, and underscores the need for rapid diagnostic capabilities during the critical initial assessment period.

CT remains the gold standard for comprehensive thoracic trauma evaluation, providing definitive diagnostic information and injury characterization that E-FAST cannot fully replace. Our finding that CT identified a mean of 2.54 thoracic lesions per patient, compared with 2.18 lesions in patients without CT evaluation ($p=0.025$), reinforces CT's superior comprehensive diagnostic capability. Our institutional protocol appropriately positions E-FAST as a rapid screening tool that complements, rather than replaces, CT imaging. However, the diagnostic limitations of this technique must be considered. Operator variability and patient-related factors, such as subcutaneous emphysema, pleural adhesions, and chronic obstructive pulmonary disease, can compromise diagnostic accuracy and potentially lead to confusion with trauma-related changes.

E-FAST facilitated immediate thoracic drainage decisions in 39.1% of cases, with 83% of decompressions performed in the emergency department, demonstrating its value in rapid therapeutic decision-making. This capability aligns with contemporary management, which favors nonoperative approaches (66% of our cases), while enabling prompt intervention when indicated (16,17). The integration of E-FAST with institutional protocols emphasizing image-based criteria for thoracic drainage (30% of cases) supports evidence-based decision-making. Our implementation of the "35-mm rule" for pneumothorax observation and of the >300 mL threshold for hemothorax drainage aligns with the current literature supporting selective management approaches (18-23).

Another common dilemma faced by trauma surgeons is managing hypotensive patients with penetrating thoracoabdominal injuries, particularly in determining which cavities require surgical exploration. Therefore, bedside ultrasonography is mandatory in such situations. Matsushima et al. (24) demonstrated that pericardial FAST examination was highly sensitive and could reliably determine the need for pericardial exploration, whereas positive abdominal FAST findings warranted exploratory laparotomy.

4.1 STUDY LIMITATIONS

The most significant limitation of our study was the substantial selection bias in E-FAST utilization. Patients who underwent E-FAST presented with significantly higher (ISS: 25 vs. 17; $p=0.018$) greater hemodynamic instability (50% vs. 32.1%; $p=0.014$), and increased requirements for intensive interventions, including mechanical ventilation (43.4%

vs. 15.5%; $p < 0.001$) and vasoactive drug support (33.8% vs. 8.8%; $p < 0.001$). This selection pattern, while clinically appropriate for prioritizing critically ill patients, creates a fundamental bias that precludes valid conclusions about the independent impact of E-FAST on clinical outcomes, such as mortality, length of stay, or morbidity. The observed association between E-FAST utilization and increased morbidity (thoracic sequelae: 19% vs. 7.6%; $p = 0.021$) likely reflects the underlying severity of illness rather than the causal effect of the diagnostic modality.

The retrospective, single-center design of our study introduces important limitations that must be considered when interpreting our findings. Data from a single Brazilian tertiary trauma center may not be generalizable to other healthcare systems with different resources, protocols, or patient populations. The retrospective nature of the study introduces potential documentation bias and limits our ability to control for confounding variables that could influence diagnostic accuracy or clinical outcomes. Furthermore, our institutional protocols and operator experience may differ from those of other centers, potentially affecting the reproducibility of our results.

A significant limitation of this study is the lack of a systematic assessment of the operator's experience and training levels. Ultrasound is inherently operator-dependent, and variations in physicians' expertise, training, and experience with E-FAST can significantly affect diagnostic accuracy. This limitation is well-documented in the recent literature and represents a persistent challenge in E-FAST implementation. Tan et al. (25) demonstrated that general surgery residency programs have non-standardized E-FAST training approaches, with some relying solely on Advanced trauma life support protocols, while others employ mixed methods, leading to significantly lower sensitivity rates (35.6%). A positive resident-performed E-FAST was generally accurate (85.6%), but its sensitivity was considerably lower than reported in the literature. Similarly, our institution did not maintain formal records of individual operator competency assessments or standardized training during the study period.

The impact of operator variability is further illustrated by Khosravian et al. (26), who found that 29.8% of E-FAST examinations at a level-1 trauma center were undocumented, technically limited, or incomplete, with the thoracic portion of the E-FAST among the most common sources of diagnostic error. While structured training programs have shown promise, with Cevik et al. (27) reporting an 88% pass rate after standardized 1-hour didactic sessions plus a 4-hour practical training for medical students, the absence of universal competency standards across institutions limits the reproducibility and generalizability of E-FAST diagnostic accuracy studies, including our findings. Furthermore, inadequate

documentation practices are highlighted by Shwe et al. (28), who found that 78% of E-FASTs lacked any documentation in the patient's chart, even though an E-FAST was recorded and reviewed during ultrasound quality assurance. These findings underscore the critical need for standardized training protocols and competency-based assessment programs to optimize E-FAST reliability and ensure consistent diagnostic performance across different healthcare settings.

Additional limitations include temporal bias during the five- year study period due to evolving protocols, and a cost analysis limited to direct examination costs that did not capture indirect costs, training requirements, or potential costs associated with false-positive results that may lead to unnecessary interventions.

A fourfold reduction in the cost of E-FAST compared with CT (USD 15 vs. USD 60) represents substantial potential savings for high-volume trauma centers. However, this analysis considered only the direct examination costs and did not account for training requirements, equipment maintenance, or potential costs associated with false-positive results. In addition to economic considerations, E-FAST offers significant radiation safety advantages. Patients in our institution receive 5-10 mSv of radiation exposure per thoracic CT examination, which is approximately ten times that of CXR. E-FAST provides a radiation-free diagnostic alternative, which is particularly important in trauma settings where multiple imaging studies may be required.

Despite limitations due to selection bias, our findings support the integration of E-FAST into trauma protocols for rapid initial assessment, particularly in resource-limited settings where CT availability may be restricted. The Brazilian healthcare system faces substantial challenges in the management of trauma victims, with Campinas facing obstacles such as hospital overcrowding and limited resources. In this context, optimizing CT utilization through selective application is critically important to avoid diagnostic overutilization and reduce healthcare costs.

The utility of E-FAST in mass casualty scenarios was demonstrated during the 2023 earthquakes in Türkiye. Taşkın et al. (29) reported that blunt thoracic trauma was observed in 95.5% of earthquake victims, with 103 patients (57.5%) undergoing E-FAST evaluation in the emergency department. Their study highlighted how E-FAST enabled rapid and accurate clinical decision-making in resource-constrained disaster settings, reinforcing the critical role of point-of-care ultrasound in the assessment of thoracic injuries during mass-casualty events.

When combined with CT for detailed injury characterization, as implemented in our institutional protocol, this approach is consistent with established clinical guidelines. CT

should not be replaced when comprehensive diagnosis is required; however, E-FAST serves as a useful adjunct to CT (30). Our institutional protocol demonstrated that the bedside E-FAST application significantly reduced diagnostic time by 20-50 minutes compared with conventional imaging workflows, facilitating rapid surgical decision-making.

Future research should prioritize several key areas to address the limitations of our study. Prospective multicenter randomized controlled trials are needed to eliminate selection bias and determine the true impact of E-FAST on clinical outcomes.

Comprehensive cost-effectiveness analyses should include indirect costs, costs associated with avoided complications, training requirements and associated costs, and costs of false-positive interventions. The development of structured training programs with competency assessments is essential to address operator variability and improve reproducibility across institutions.

5 CONCLUSION

E-FAST demonstrated high diagnostic accuracy for pneumothorax (90% sensitivity, 95% specificity) and hemothorax (86% sensitivity, 95% specificity) with CT as the reference standard, and it outperformed conventional radiography. E-FAST facilitates rapid bedside assessment and immediate surgical decision-making in critically injured patients. However, the significant selection bias toward critically injured patients limits the conclusions regarding the independent impact on clinical outcomes. These findings support the integration of E-FAST as a complementary diagnostic tool in thoracic trauma protocols.

5.1 ETHICS

Ethics Committee Approval: The study received approval from the University Hospital of Pontifícia Católica de Campinas-Campinas Research Ethics Committee (CAAE: 58584822.0.0000.5481, number: 466/12, date: April 27, 2022).

Informed Consent: Informed consent was obtained from the parents of all patients or their guardians.

5.2 FOOTNOTES

Author Contributions

Surgical and Medical Practices - G.P.M., J.L.B.A.; Concept - G.P.M., V.F.K., E.S.H., J.L.B.A.; Design - H.H.F.M., V.A.L.M.; Data Collection or Processing - V.F.K., H.H.F.M.; Analysis or Interpretation - G.P.M., V.F.K., V.A.L.M.; Literature Search - G.P.M., E.S.H., V.F.K.; Writing - G.P.M., V.F.K., J.L.B.A.

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DOES ULTRASOUND DETECT JOINT AND INTESTINAL CHANGES IN PSORIATIC ARTHRITIS AND ULCERATIVE COLITIS AFTER IMMUNOBIOLOGICAL TREATMENT: A CASE REPORT

O ULTRASSOM DETECTA ALTERAÇÕES ARTICULARES E INTESTINAIS NA ARTRITE PSORIÁSICA E NA COLITE ULCERATIVA APÓS TRATAMENTO COM IMUNOBIOLOGICOS: UM RELATO DE CASO

¿PUEDE LA ECOGRAFÍA DETECTAR CAMBIOS ARTICULARES E INTESTINALES EN LA ARTRITIS PSORIÁSICA Y LA COLITIS ULCEROSA TRAS EL TRATAMIENTO CON INMUNOBIOLOGICOS? UN INFORME DE CASO



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ABSTRACT

Background: Ultrasound (US) can be a valuable tool for assessing arthritis associated with inflammatory bowel disease (IBD), especially in cases of psoriatic disease. The clinical case reviewed in this article addresses an exploratory finding that evaluates the effects of immunobiological treatments on dactylitis and IBD with the use of US techniques.

Case summary: A 40-year-old Caucasian woman with psoriatic arthritis (PsA) and ulcerative colitis (UC) reported experiencing finger pain, knee arthritis, and bloody diarrhea. She showed a high Disease Activity index for PsA score and a severe Mayo score. She began treatment with adalimumab. Over the course of six months, the 18 MHz US procedure was performed on her joints and a 3.5 MHz US on her in-testines. The joint US indicated dactylitis and swelling in her finger joints, while the intestinal US revealed 6.6 mm swelling in the sigmoid colon, increased abdominal fat, and high Doppler signal. Her fecal calprotectin level was 5984 mg/kg, and a colonoscopy showed that UC extended to the hepatic flexure, along with mild narrowing of the transverse colon. After six months treatment, all parameters showed improvement, including a remission of the Mayo score, better colonoscopy results, and Limberg score of 0.

Conclusion: More research is needed to find out the importance of using US in patients with PsA and UC as this could improve treatment strategies.

Keywords: Ultrasonography. Psoriatic Arthritis. Ulcerative Colitis. Tumor Necrosis Factor. Case Report.

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RESUMO

Contexto: O ultrassom (US) pode ser uma ferramenta valiosa para a avaliação da artrite associada à doença inflamatória intestinal (DII), especialmente em casos de doença psoriásica. O caso clínico revisado neste artigo aborda um achado exploratório que avalia os efeitos dos tratamentos imunobiológicos na dactilite e na DII por meio do uso de técnicas de ultrassonografia.

Resumo do caso: Uma mulher caucasiana de 40 anos, com artrite psoriásica (APs) e colite ulcerativa (CU), relatou dor nos dedos, artrite no joelho e diarreia sanguinolenta. Ela apresentava alto índice de atividade da doença para APs e escore de Mayo grave. Iniciou tratamento com adalimumabe. Ao longo de seis meses, foi realizada ultrassonografia de 18 MHz nas articulações e de 3,5 MHz no intestino. O US articular indicou dactilite e edema nas articulações dos dedos, enquanto o US intestinal revelou espessamento de 6,6 mm no cólon sigmoide, aumento da gordura abdominal e sinal Doppler elevado. A calprotectina fecal foi de 5984 mg/kg, e a colonoscopia mostrou extensão da CU até a flexura hepática, além de leve estreitamento do cólon transverso. Após seis meses de tratamento, todos os parâmetros apresentaram melhora, incluindo remissão do escore de Mayo, melhora dos achados colonoscópicos e escore de Limberg 0.

Conclusão: São necessários mais estudos para determinar a importância do uso do ultrassom em pacientes com APs e CU, pois isso pode contribuir para a melhoria das estratégias terapêuticas.

Palavras-chave: Ultrassonografia. Artrite Psoriásica. Colite Ulcerativa. Fator de Necrose Tumoral. Relato de Caso.

RESUMEN

Contexto: La ecografía (US) puede ser una herramienta valiosa para la evaluación de la artritis asociada a la enfermedad inflamatoria intestinal (EII), especialmente en casos de enfermedad psoriásica. El caso clínico revisado en este artículo aborda un hallazgo exploratorio que evalúa los efectos de los tratamientos inmunobiológicos en la dactilitis y la EII mediante el uso de técnicas de ecografía.

Resumen del caso: Una mujer caucásica de 40 años con artritis psoriásica (APs) y colitis ulcerosa (CU) refirió dolor en los dedos, artritis de rodilla y diarrea sanguinolenta. Presentaba un alto índice de actividad de la enfermedad para APs y un score de Mayo severo. Inició tratamiento con adalimumab. Durante seis meses, se realizó ecografía de 18 MHz en las articulaciones y de 3,5 MHz en el intestino. La ecografía articular indicó dactilitis e inflamación en las articulaciones de los dedos, mientras que la ecografía intestinal reveló un engrosamiento de 6,6 mm en el colon sigmoide, aumento de la grasa abdominal y señal Doppler elevada. La calprotectina fecal fue de 5984 mg/kg y la colonoscopia mostró extensión de la CU hasta la flexura hepática, además de un leve estrechamiento del colon transverso. Tras seis meses de tratamiento, todos los parámetros mostraron mejoría, incluyendo remisión del score de Mayo, mejoría en la colonoscopia y un score de Limberg de 0.

Conclusión: Se necesitan más investigaciones para determinar la importancia del uso de la ecografía en pacientes con APs y CU, ya que esto podría mejorar las estrategias de tratamiento.

Palabras clave: Ecografía. Artritis Psoriásica. Colitis Ulcerosa. Factor de Necrosis Tumoral. Informe de Caso.

1 INTRODUCTION

Psoriasis (PsO) is associated with several manifestations, including joint involvement and systemic conditions such as uveitis and inflammatory bowel disease (IBD). Patients with PsO, psoriatic arthritis (PsA), and spondyloarthritis have a 1-4 times higher risk and a 1-6 times higher risk of developing IBD compared to the general population. IBD includes primarily two main forms: (1) Crohn's disease (CD); and (2) Ulcerative colitis (UC). Both CD and UC are chronic disorders characterized by intermittent remission phases and periods of active inflammation, with symptoms such as abdominal pain, diarrhea, and rectal bleeding. The risk of developing PsO, PsA, ankylosing spondylitis (AS), and IBD is polygenic and often these disorders overlap, which may explain the clustering of immune-mediated chronic inflammatory diseases with various phenotypes across generations[1]. IBD encompasses two conditions: (1) CD, which can affect any part of the gastrointestinal tract in a discontinuous manner and impact the intestinal wall transmurally; and (2) UC, which affects the mucosa continuum and concentrates primarily in the rectum [1-3]. Notably, the prevalence of IBD does not reflect the significant rates of subclinical intestinal involvement detected by endoscopic examinations or biopsies; actually, this condition rate can be as high as 65%-70%. A connection between joint manifestations and IBD may also be observed.

The pathophysiology underlying the hypothesis of "arthritogenic bowel" involves genetic factors. A significant cause is the high prevalence of the human leukocyte antigen (HLA)-B27 antigen, found in approximately 25% of individuals with spondyloarthritis and 78% of those with IBD. Other genetic factors, such as HLA-DRB1 and HLA-B44, have also been identified, along with non-histocompatibility factors like variations in the CARD15 gene, which increases the risk of sacroiliitis in CD[4,5]. These conditions are supported by transcriptomic analysis, which identifies CD 64+ myeloid cells as a source of interleukin (IL)-23 stimulation in the intestine. The situation is exacerbated by epigenetic alterations thought to occur due to microbial dysbiosis, triggering the transcription of several interleukins, including IL-17 and tumor necrosis factor (TNF). This process leads to the differentiation of Th17 Lymphocytes, mediated by autoreactive T and B lymphocytes. Consequently, locally recruited macrophages and lymphocytes that express intestinal markers, along with cytokines IL-17 and IL-23, can migrate through the intestinal vasculature. This movement is facilitated by increased vascular permeability associated with inflammation, allowing those cells to reach the synovial vessels. While substantial evidence supports such hypothesis, further research is necessary for its validation.[5,6].

Regarding AS, few reports detailing this disorder association with IBD are available. However, one study indicates a significant reduction in microbiota among AS patients,

demonstrating dysbiosis similar to that seen in IBD patients, with a comparable bacterial profile. Nevertheless, stronger evidence is needed to provide more evidence for this association[7]. In recent years, high-resolution ultrasound (US), particularly Doppler technology in US, has proven beneficial in diagnosing and monitoring rheumatological diseases helping to evaluate synovitis and enthesopathies, especially in cases of subclinical disease activity. Advances in understanding intestinal imaging using US techniques have also allowed for the demonstration of pathological changes associated with IBD[8,9]. US can help characterize intestinal inflammation by highlighting hypoechogenicity and thickening of the inflamed intestinal wall, while Doppler assesses vascular changes due to intense neovascularization, inflammatory infiltration, small artery thrombosis, and dilation of arteries and veins that are manifestations of IBD[9,10].

2 CASE PRESENTATION

2.1 CHIEF COMPLAINTS

This clinical case emphasizes the importance of US for assessing joint ill manifestations as well as detecting intestinal inflammation and helping monitoring treatments.

2.2 HISTORY OF PRESENT ILLNESS

Two patients, 51 ± 11 years of age, were diagnosed with PsA and UC through colonoscopy. The intestinal US examinations performed revealed signs of inflammation while remaining blinded to their clinical conditions. One patient was female and the other was male. The female patient, a businesswoman, completed US treatment and follow-up, allowing her to be included in the study. In contrast, the male patient was excluded due to lack of follow-up on his intestinal US procedure.

2.3 HISTORY OF PAST ILLNESS

The female patient had been diagnosed with PsO on her scalp and elbows eight years before.

2.4 PERSONAL AND FAMILY HISTORY

After experiencing skin lesions for four years, she began to develop inflammatory joint pain while opening and closing her fingers, along with arthritis in her left knee. Three years after these joint complaints started, she experienced over 20 episodes of bloody diarrhea

and was subsequently diagnosed with UC. Her father had been diagnosed with PsA 20 years earlier.

2.5 PHYSICAL EXAMINATION

Before starting the adalimumab treatment, the patient's exams indicated she had: (1) Mild PsO according to the Psoriasis Area and Severity Index (PASI); (2) High score on the Disease Activity Index for PsA (DAPSA); and (3) Severe Mayo score (Table 1). The clinical evaluation was conducted using the PASI, which measures the severity of PsO based on four criteria: (1) Crythema; (2) Induration; (3) Scaling; and (4) The extent of the affected area. The severity of skin involvement is categorized based on the surface area affected (BSA) as follows: (1) No PsO (0 BSA); (2) Mild (< 10 BSA); (3) Moderate (10-20 BSA); and (4) Severe (> 20 BSA)[11].

To assess arthritis, the DAPSA score was used. This score includes the number of painful and swollen joints (28 in total), the patient's visual analogue pain scale (ranging from 0 to 10), the physician's assessment, and the inflammatory marker C-reactive protein. Disease activity is classified into four categories: (1) High (≥ 28); (2) Moderate (15-28); (3) Low (5-14); and (4) In remission (≤ 4)[12-14].

2.6 LABORATORY EXAMINATIONS

The patient's laboratory exams showed a negative rheumatoid factor, a fecal calprotectin level of 5984 mg/kg[15], serology testing for hepatitis B, C, human immunodeficiency virus, and syphilis, a negative Mantoux test, and no anomalies on the chest X-ray.

2.7 IMAGING EXAMINATIONS

The patient gave her consent by signing the Informed Consent Form for the US evaluation and other procedures conducted at the Rheumatology Clinic. This evaluation was performed by a single rheumatologist with 17 years' experience in general and articular US examinations, specifically for rheumatology and immune-mediated diseases, as part of the University's postgraduate program and the Hospital's US service. The assessment followed established protocols, using all appropriate equipment configurations for monitoring the treatment, and all images were recorded on an external hard drive. For the evaluation, the MyLab Gold 25 US system (Esaote SpA, São Paulo, Brazil) was used. It was equipped with an 18 MHz high-frequency linear probe for use in the joint assessment and a 3.5 MHz convex probe for intestinal examination. The Doppler specifications were standardized, featuring a

frequency range of 2.5-8.0 MHz and pulse repetition frequencies of 0.7-1.0 kHz. The joints US assessment covered all the fingers, evaluating both dorsal and palmar recesses[9,16]. The intestinal US evaluation was conducted with the patient fasting and positioned supine to preserve the intestines' physiological state, minimizing interference from luminal contents and vascular changes. A comprehensive assessment of both the small intestine and colon was performed, scanning all segments in both the long and short axes, paying particular attention to any abnormal areas. The intestinal loops in the sigmoid colon region, including assessments of mesenteric fat thickening were specifically measured. Doppler signal evaluations were carried out to monitor the treatment parameters. Importantly, oral contrast was not used, as US allows dynamic, real-time observation of intestinal movements and caliber while the patient is at rest. The evaluation focused on the five concentric, compressible layers with varying echogenicities, assessing increased wall thickness greater than 3 mm, depending on the specific location. Additionally, the mesenteric fat and Doppler signal were graded from 0 to 3 to semi-quantify the severity of the inflammatory process[9,17].

3 MULTIDISCIPLINARY EXPERT CONSULTATION

When there is a link between arthritis and IBD, the concept of an arthritogenic bowel becomes particularly important.

Table 1

Clinical, ultrasound, laboratory, and colonoscopy parameters before and after treatment

	Before	After
Psoriasis Area and Severity Index	8.3	2.0
Disease Activity Index for Psoriatic Arthritis	29.16	0
Mayo score	12	0
Paratenonitis	Present	Absent
Fecal calprotectin	5984 mg/kg	600 mg/kg
Colonoscopy	Intense inflammation	Remission
Intestinal wall thickness	6.6 mm	2.8 mm
Degree of thickening of perienteric fat	2	0
Doppler degree in the intestinal wall	3	0

This connection emphasizes the need for a multidisciplinary approach, which is associated with better clinical outcomes. These outcomes include higher rates of sustained remission, reduced hospitalizations stay and reduced surgical procedures, as well as an

overall improved quality of life as reported by patients. Additionally, a multidisciplinary approach encourages collaborative clinical decision-making, humanizes patient care, and enhances the integration of support, education, and research within specialized centers. Therefore, it is crucial to promote and incorporate multidisciplinary consultations as a standard practice for managing patients with UC, especially in complex clinical situations within tertiary care centers and IBD referral units[18,19].

4 FINAL DIAGNOSIS

The fingers' joints examination revealed findings consistent with dactylitis, which was attributed to significant paratenonitis in the second and third proximal interphalangeal joints of the right hand, characterized by effusion. A bowel US showed 6.6 mm edema in the sigmoid colon wall and indicated grade 2 mesenteric fat and grade 3 Doppler signal on the Limberg scale. Additionally, a colonoscopy revealed severe UC extending to the hepatic flexure and mild stenosis of the transverse colon, with a Mayo score 3 and 7 UC Disease Activity Index Score.

4.1 TREATMENT

The treatment consisted of 100 mg adalimumab and azathioprine during six months.

4.2 OUTCOME AND FOLLOW-UP

All clinical, US, laboratory, and colonoscopy parameters showed improvement, indicating preserved mucosa with a distinct vascular pattern, with no edema, erosions, or ulcerations, and no signs of inflammatory activity (Table 1, Figures 1, 2 and 3).

5 DISCUSSION

High-resolution B-mode and Doppler ultrasonography effectively translate clinical and often subclinical dactylitis into observable conditions such as synovitis, tenosynovitis, enthesitis, and inflammation of both the subcutaneous tissue and the periextensor tendon. Recently, a dactylitis score scale has been developed for patients with PsA, as this condition can be challenging to detect during clinical examinations. Patients frequently exhibit US abnormalities without accompanying inflammatory signs. The clinical significance of dactylitis is highlighted by its role as a marker of disease aggressiveness and poor prognosis in affected patients. An US study found that 35.7% of PsO patients exhibited subclinical dactylitis compared to a control group, along with a 30% occurrence of moderate peritendinitis of the fingers' extensor tendon[18, 20,21].

The use of US in UC has proven beneficial as it helps to identify structural damage to the large intestine a damage which is an indication of an active inflammatory process in the bowel. Accuracy of US in assessing the bowel inflammation extent and severity, as well as in monitoring therapeutic responses has been evidenced[19].

Figure 1

Follow-up treatment after the use of adalimumab. A: It shows the presence of effusion as indicated by the color map in B-mode; B: It shows the absence of effusion (arrows). They illustrate the longitudinal dorsal recess of the second proximal interphalangeal joint with peritendinitis

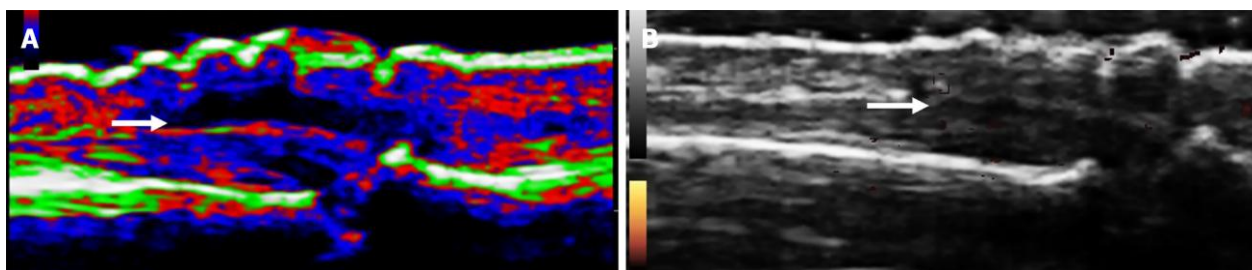


Figure 2

Monitoring intestinal inflammatory activity: Improvement after adalimumab treatment. A and B: Reduced intestinal wall thickening (arrows) and perienteric fat (star) (short axis images of the sigmoid colon); C and D: Decreased Doppler signal per the Limberg scale (arrows).

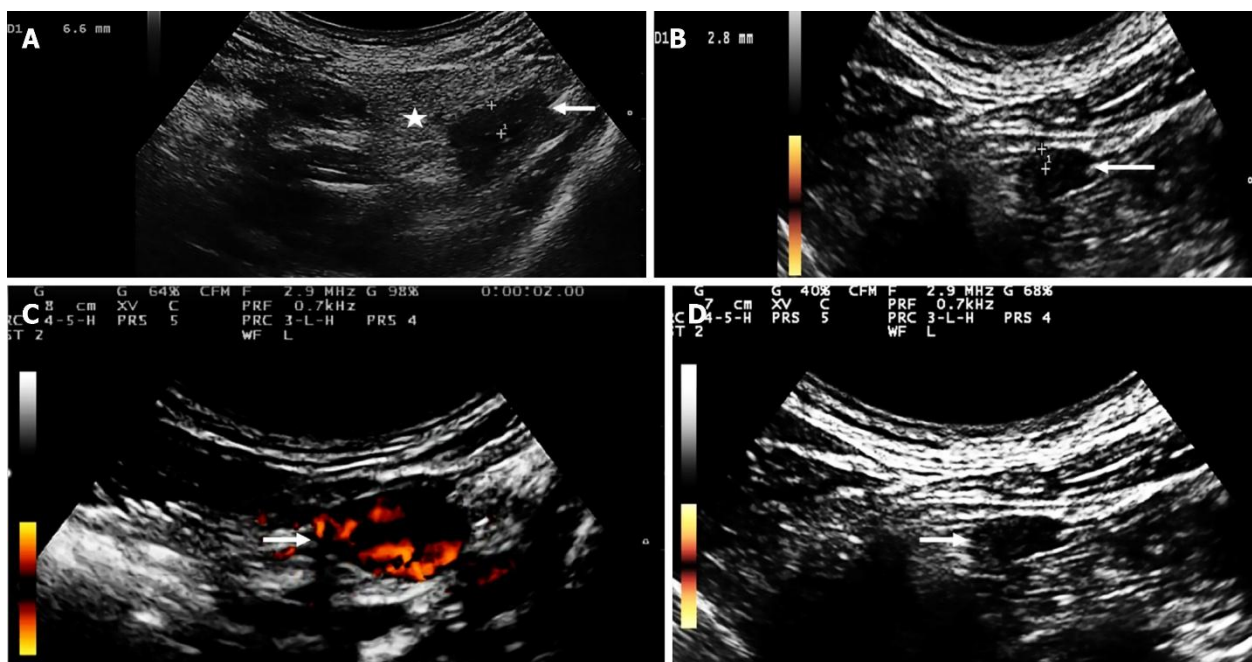
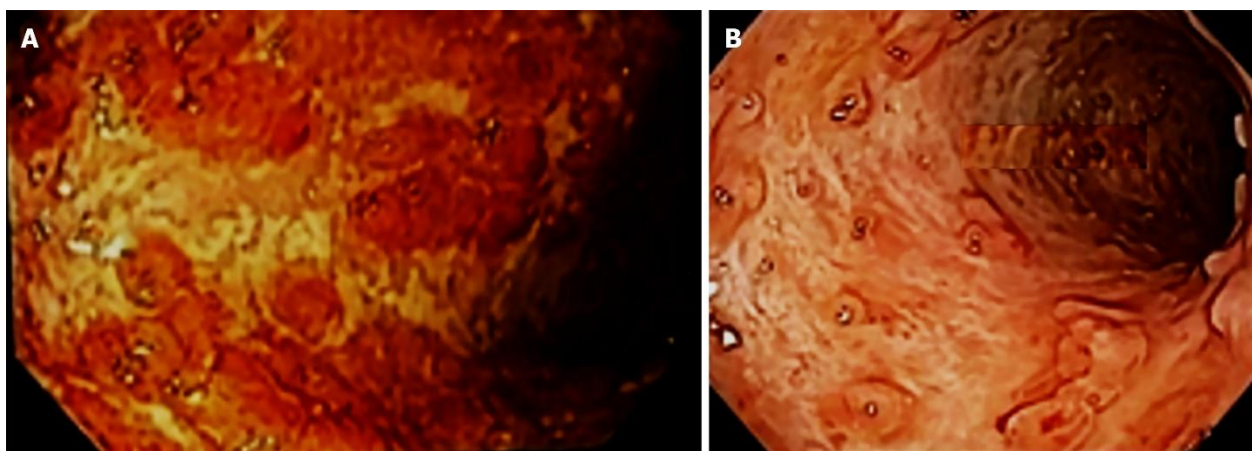


Figure 3

Treatment follow-up after adalimumab use. A: Colonoscopy show intense proctocolitis; B: Remission, respectively.



The TNF plays a crucial role in the pathogenesis of immune-mediated inflammatory diseases; hence, inhibiting TNF is vital for managing severe and progressive inflammatory conditions. This intervention can lead to rapid and sustained clinical remission, enhance quality of life, and prevent damage to other target organs. Adalimumab, the first fully human monoclonal antibody targeting TNF, has demonstrated efficacy and tolerability in patients with various extensive inflammatory diseases, including PsA, plaque PsO, and IBD such as CD and UC. Accurate mapping of intestinal manifestations in patients with PsA is crucial, as it allows for more precise treatment approaches. Adjustments in the therapeutic classes and the potential increase of the anti-TNF drug dosage may be necessary for effectively managing intestinal inflammation, since differences in dosing requirements compared to arthritis treatment exist. Research indicates that a higher dosage of adalimumab achieves sustained efficacy in inducing remission of intestinal inflammation, reporting a 25% success rate in moderate to severe cases over four years[22,23].

However, the limitations of US in UC affect its effectiveness in the assessments, as inflammation primarily affects the mucosa. The technique is better suited for identifying changes in deeper bowel layers, as seen in CD. Visualizing the rectum can be challenging, and mild or microscopic inflammation may not be detected, the tissues often appearing normal. In cases of remission, the bowel wall thickness typically returns to normal, further decreasing US sensitivity. Factors such as flatulence, obesity, and operator's skill can also impact image quality. Therefore, while US may have some use, it cannot replace colonoscopy for confirming remission or for monitoring[19].

6 CONCLUSION

Our study emphasizes the importance of joint and intestinal mapping when treating patients with a humanized monoclonal anti-TNF agent. Further research is needed to determine the necessity of US monitoring in patients with PsA and IBD. This could improve the selection of safer and more appropriate treatment options for these patients.

6.1 FOOTNOTES

Author contributions: Mendonça JA did the ultrasound exams; Mendonça JA and de Aquino JLB contributed equally, with the writing and the method description of this article as the co-corresponding authors; all authors read and approved the final manuscript.

Informed consent statement: Informed consent for publication was obtained for this case report.

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COVID-19 VACCINATION AND INFODEMIC: CHALLENGES FOR NURSING IN PROMOTING HEALTH LITERACY

VACINAÇÃO COVID-19 E INFODEMIA: DESAFIOS PARA A ENFERMAGEM NA PROMOÇÃO DA LITERACIA EM SAÚDE

VACUNACIÓN COVID-19 E INFODEMIA: DESAFÍOS PARA LA ENFERMERÍA EN LA PROMOCIÓN DE LA ALFABETIZACIÓN EN SALUD



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ABSTRACT

This study analyses how health literacy influences attitudes of acceptance and hesitancy towards COVID-19 vaccination in adult populations, within a context marked by the infodemic and the spread of misinformation. Through a narrative review and thematic analysis of nine international studies, the results show that sufficient or high levels of health literacy are consistent predictors of greater vaccine acceptance. Conversely, exposure to false information, conspiracy theories and unreliable sources emerges as a negative predictor of vaccine confidence and of adherence to vaccination campaigns. The results of the studies analysed further showed that sociodemographic factors, trust in health institutions and governments, as well as the type of information sources consulted, modulate the combined impact of health literacy and the infodemic on vaccination decisions. This supports the urgent need for public policies that promote critical health literacy, integrating multisectoral strategies in school, community and clinical settings. It reinforces the fundamental role of nursing in health education, acting to simplify communication and to empower citizens to make informed and conscious decisions.

Keywords: Health Literacy. Health Education. Infodemic. Vaccine Hesitancy. COVID-19 Vaccination. Nursing.

RESUMO

Este trabalho analisa de que forma a literacia em saúde influencia as atitudes de aceitação e hesitação face à vacinação contra a COVID-19 em populações adultas, num contexto marcado pela infodemia e pela disseminação de desinformação. Através de uma revisão narrativa e análise temática de nove estudos internacionais, os resultados demonstram que níveis suficientes ou elevados de literacia em saúde são preditores consistentes de uma maior aceitação vacinal. Inversamente, a exposição a informação falsa, teorias da conspiração e fontes pouco credíveis surgem como preditores negativos da confiança nas vacinas e da adesão às campanhas de vacinação. Os resultados dos estudos analisados evidenciaram ainda que fatores sociodemográficos, a confiança em instituições de saúde e governos, bem como o tipo de fontes de informação consultadas, modulam o impacto combinado da literacia em saúde e da infodemia nas decisões vacinais. Sustenta-se, assim

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a necessidade urgente de políticas públicas que promovam a literacia em saúde crítica, integrando estratégias multissetoriais em contextos escolares, comunitários e clínicos. Reforça-se o papel fundamental da enfermagem na educação para a saúde, atuando na simplificação da comunicação e na capacitação dos cidadãos para decisões informadas e conscientes.

Palavras-chave: Literacia em Saúde. Educação em Saúde. Infodemia. Hesitação Vacinal. Vacinação COVID-19. Enfermagem.

RESUMEN

Este trabajo analiza de qué forma la alfabetización en salud influye en las actitudes de aceptación y vacilación frente a la vacunación contra la COVID-19 en poblaciones adultas, en un contexto marcado por la infodemia y por la difusión de desinformación. A través de una revisión narrativa y un análisis temático de nueve estudios internacionales, los resultados demuestran que niveles suficientes o elevados de alfabetización en salud son predictores consistentes de una mayor aceptación de la vacuna. Inversamente, la exposición a información falsa, teorías de la conspiración y fuentes poco fiables surgen como predictores negativos de la confianza en las vacunas y de la adhesión a las campañas de vacunación. Los resultados de los estudios analizados evidenciaron además que factores sociodemográficos, la confianza en instituciones de salud y gobiernos, así como el tipo de fuentes de información consultadas, modulan el impacto combinado de la alfabetización en salud y de la infodemia en las decisiones de vacunación. Se sostiene, así, la necesidad urgente de políticas públicas que promuevan la alfabetización en salud crítica, integrando estrategias multisectoriales en contextos escolares, comunitarios y clínicos. Se refuerza el papel fundamental de la enfermería en la educación para la salud, actuando en la simplificación de la comunicación y en la capacitación de los ciudadanos para decisiones informadas y conscientes.

Palabras clave: Alfabetización en Salud. Educación en Salud. Infodemia. Vacilación ante la Vacuna. Vacunación COVID-19. Enfermería.

1 INTRODUCTION

The global emergence of Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, began in 2020 as a public health crisis of unprecedented proportions (Bilhim, 2021). Owing to its rapid and extensive spread, combined with its morbidity and mortality, it imposed unique challenges worldwide, exerting constant pressure on health systems and societies across the globe.

In the face of this threat, the highest priority became the development and implementation of safe and effective vaccines, regarded as the fundamental strategy for mitigating the impact of the pandemic and controlling the spread of the disease (Reiter et al., 2020; Thanh Le et al., 2020). However, the success of vaccination campaigns depended not only on biotechnological innovation but, above all, on the rate of population adherence to vaccination. Achieving herd immunity and preventing the collapse of health systems required, and continues to require, large-scale vaccination coverage (Wang et al., 2020).

Along these lines, vaccine acceptance is regarded as a decisive factor for the effectiveness of public health policies. The study of citizens' attitudes towards vaccination has become a research priority, underscoring the need to understand the various factors that promote the intention to vaccinate (Arriaga et al., 2021). When discussing vaccination, one cannot overlook an important concept, Health Literacy, which, according to the World Health Organization, as cited in Almeida et al. (2019, p. 9), consists of the degree to which individuals have the capacity to obtain, process and understand basic health information in order to use health services and make appropriate health decisions.

At the same time, the pandemic scenario was characterised by a phenomenon of enormous complexity, which became known as the “infodemic”, that is, an excess of information, not always reliable, that hindered the public's access to trustworthy sources. This information overload, marked by the dissemination of misinformation through social media and other channels, proved to be a strong driver of vaccine hesitancy, generating confusion, insecurity and distrust (Cinelli et al., 2020; Coelho et al., 2023; Massarani et al., 2021).

The present study aims to analyse the role of health literacy in modulating attitudes towards vaccination, taking into account the impact of the infodemic. Such an approach is essential in order to underpin public health policies and educational strategies capable of promoting informed decisions and positive vaccination behaviours, investing in health promotion and in education for self-care within the community.

2 THEORETICAL BACKGROUND

2.1 THE PHENOMENON OF VACCINE HESITANCY

Although the success of immunisation programmes depends on high rates of acceptance and coverage (Bendau et al., 2021; Marzo et al., 2022), and although the epidemiological benefits are widely recognised, debate over vaccine hesitancy has increased considerably worldwide (Oliveira et al., 2021). According to MacDonald et al. (2015), as referenced by Ebrahimi et al. (2024, p. 184), vaccine hesitancy, a phenomenon that emerged and evolved alongside the practice of vaccination, constitutes an important barrier to the potential benefits afforded by this measure, and has been recognised by the World Health Organization, according to Muralidharan et al. (2025), as “the delay in acceptance or refusal of vaccines despite their availability in health services” (p. 528).

2.2 THE INFODEMIC AND MISINFORMATION

The COVID-19 outbreak and the response that followed were accompanied by an intense infodemic. As stated by the World Health Organization, this phenomenon is characterised by an excess of information, some accurate and some not, which makes it difficult to find reliable sources and trustworthy guidance. The exponential increase in information, amplified by social media, is where misinformation thrives (Pan American Health Organization, 2020).

According to the Pan American Health Organization (2020), misinformation is defined as “false or inaccurate information with the deliberate intention to deceive” (p. 2), and it can profoundly affect every aspect of life, particularly people’s mental health. The rapid absorption of misinformation, grounded in conspiracy theories, can lead to behavioural change, exposing people to greater health risks.

Misinformation constitutes a significant threat to public health (Ebrahimi et al., 2024); according to Pian et al. (2021), as referenced in Ebrahimi et al. (2024, p. 185), this excess of information, frequently contradictory and from unauthorised sources, may compromise governmental efforts, lead to inappropriate health behaviours and contribute to the loss of public trust in health authorities and systems.

The mass media, according to Bendau et al. (2020), Kennedy (2020) and Wilson & Wiysonge (2020), as referenced in Bendau et al. (2021, p. 1), played a crucial role in the transmission of information to the population, having been associated with fears and apprehensions, conspiracy theories, and also with vaccine hesitancy in the context of the pandemic.

In this way, the rise in vaccine hesitancy is associated with a lack of credibility in governmental vaccination campaigns and with the belief that the data provided are not adequate to dispel existing concerns within the population (Bendau et al., 2021).

2.3 HEALTH LITERACY AS A PROTECTIVE FACTOR

According to Kickbusch (2008), as referenced in Almeida et al. (2019, p. 12), health literacy goes beyond the mere ability to read, constituting an essential protective factor, especially in a crisis context such as COVID-19, where the infodemic amplified vaccine hesitancy. The study of health literacy requires the analysis of conceptual models that classify the different competences required of citizens.

2.4 LITERACY MODELS AND THE RESPONSE TO THE INFODEMIC

Although most models comprise individual and community factors, the classification system is useful for identifying the capacities required to resist misinformation and to form positive attitudes towards vaccination.

The original model by Nutbeam (2000), as cited in Almeida et al. (2019), established three different foundational levels of competence:

Table 1

Original Health Literacy Model

Level	Description	Relevance to Vaccination
Functional	Basic reading and writing skills necessary to function effectively in a health context.	Enables reading of the vaccine information leaflet.
Interactive	More advanced cognitive literacy and social skills for active participation in health care.	Enables the individual to question the health professional about the vaccine.
Critical	The capacity to critically analyse and use information in order to take part in actions that overcome structural barriers to health.	Crucial for assessing the credibility of sources and for opposing conspiracy theories.

Source: Almeida et al. (2019).

In the context of COVID-19 and the infodemic, the level of health literacy and the new classification proposals added by other authors, Zarcadoolas (2005) and Manganello (2008), as cited in Almeida et al. (2019, p. 12), became the focus of intervention, since they enable citizens to filter misinformation.

Table 2*Modified Health Literacy Model*

Level	Description	Relevance to Vaccination
Scientific	Levels of competence with science and with the technology of numbers.	Assists in understanding concepts such as mRNA technology, clinical trials and efficacy rates.
Media	The capacity to critically evaluate media messages.	It is the primary shield against misinformation, making it possible to distinguish fake articles from credible news.
Civic	Competences that enable citizens to become aware of public issues and to engage in the decision-making process.	Facilitates the understanding of vaccination as an act of collective responsibility and public health.

Source: Almeida et al. (2019).

Misinformation, frequently disseminated in digital format, requires the citizen to possess both high scientific and high media literacy simultaneously. The lack of these specific competences, when combined with the perception that official information is insufficient, gives rise to the possibility of an opening for the phenomenon of vaccine hesitancy (Bendau et al., 2021).

In this way, health literacy acts as a protective factor by providing a set of cognitive tools that enable the citizen to understand the complexity of the health crisis, to critically analyse information sources, and to form a proactive attitude towards COVID-19 vaccination.

2.5 THE ROLE OF NURSING IN HEALTH EDUCATION

Several authors, such as Bendau et al. (2021), Cénat et al. (2024), Ebrahimi et al. (2024), Köse et al. (2023) and Muralidharan et al. (2025), demonstrate that health literacy is a crucial element for the acceptance of COVID-19 vaccination, requiring explicit integration both into educational policies and into clinical nursing practice. According to Smith (2021), although nursing is the largest group of health professionals in the world, the concept of Health Literacy has received little attention in the literature of the discipline, even though nurses were urged, during the pandemic, to provide accurate and comprehensible information to service users. The study by Fenta et al. (2023) reinforces that adults “with higher Health Literacy better understand the benefits of vaccines” (p. 7), which validates Smith’s (2021) thesis that health literacy “has broadened its original focus on elementary literacy skills to also include the ability to critically analyse and use health information, thereby providing better engagement with health systems” (p. 1).

Within this logic of continuous learning, the articulation between curricular policies and community strategies is the basis for resilience in the face of infodemics (Arriaga et al., 2023). However, the effectiveness of these strategies depends on the capacity of nurses to adapt

their communication. As demonstrated by Sayar et al. (2023), “health literacy plays a relevant role in the interpretation of information about vaccination, with individuals at lower levels presenting greater difficulties in distinguishing correct information from misinformation about COVID-19” (p. 2). This role of the nurse as educator and ‘advocate for service users’ (Smith, 2021) is fundamental for transforming health education that is merely informative into a tool for critical empowerment, enabling more conscious decisions regarding vaccination (WHO & UNESCO, 2021).

Health education has evolved significantly, especially from the twenty-first century onwards, where the need for more complex and integrated approaches is recognised. Bonito (2008) emphasises that promoting health implies “not only including so-called educational actions, but also enabling the acquisition or the development of competences (...) empowering and making the person responsible for their own choices” (p. 72).

2.6 IMPLICATIONS FOR PUBLIC HEALTH AND FUTURE POLICIES

The evolution of the COVID-19 pandemic made unequivocally evident the strategic role of Health Literacy as a sound investment and a central axis in future public policies. Inadequate levels of health literacy, which affect a considerable proportion of the Portuguese population, as some studies show (Arriaga et al., 2020; Cruz et al., 2023), are associated with direct and indirect negative consequences, both for the individual and for the health system.

Possessing low Health Literacy has negative repercussions for the public health landscape, translating into:

- **Poorer health status and worse health outcomes:** the complexity of accessing, understanding and applying health information results in less adoption of protective and disease-prevention behaviours (Cruz et al., 2023).
- **Increased use of, and costs in, health services:** the absence of knowledge about therapeutics and failures in adherence to therapeutic regimens lead to medication errors and to higher rates of hospitalisation and re-hospitalisation (Cruz et al., 2023). Consequently, inadequate health literacy is directly linked to increased costs for the National Health Service, calling into question its long-term sustainability (Arriaga et al., 2023).
- **Compromised effectiveness of risk communication:** in emergency scenarios, such as the pandemic, health literacy determines the population’s capacity to understand and comply with public health guidance. The coexistence of misinformation/infodemic

and low health literacy weakens risk communication, preventing the timely and correct adoption of essential preventive measures (Espanha, 2020).

Health Literacy is understood as a relevant factor in the context of public health, being described as “a determinant of health (...) determined by a set of factors related to individual characteristics (...) and to social, cultural and health-system factors” (Arriaga et al., 2023, p. 15).

The National Plan for Health Literacy and Behavioural Sciences 2023–2030, issued by the Directorate-General for Health, gives substance to this vision, focusing on health-promoting ecosystems and on the sustainability of the system (Arriaga et al., 2023).

Accordingly, in order to achieve this objective and to confront the challenges of public health, future policies should focus on three fundamental axes:

- **Simplification and adequacy of communication:** health organisations and the professionals who are part of them should simplify communication, verifying service users’ understanding, so as to make ‘navigability’ within the National Health Service clearer and accessible to all (Lopes & Vaz de Almeida, 2022). It is necessary to create informational materials that are easy to read and understand, as well as to use a variety of communication channels (Espanha, 2020).
- **Development of critical competences:** rather than developing functional health literacy, policies should promote critical health literacy, equipping citizens with advanced cognitive competences to critically analyse information, actively combating misinformation and enabling them to exercise greater control over their health decisions (Cruz et al., 2023).
- **A multisectoral and proximity-based approach:** Health Literacy should not be seen as the exclusive responsibility of the health sector. It is essential to promote a multidisciplinary and multisectoral approach, integrating the promotion of health literacy across various settings: school, occupational and community. By integrating these settings, real conditions are created that enable citizens to apply health knowledge in their daily lives (Borges, 2025). It also becomes essential that policies prioritise the empowerment of vulnerable groups, namely older adults, individuals with low levels of schooling and people from less favoured social classes, given that they present the most inadequate levels of health literacy (Cruz et al., 2023).

By recognising Health Literacy as an investment in human resources, and not merely as a cost (Cruz et al., 2023), future public health policies in Portugal may strengthen the population’s resilience in the face of crises, promote well-being and also ensure the sustainability of the National Health Service.

3 METHODOLOGY

With the aim of systematising current knowledge on the importance of Health Literacy in the formation of attitudes towards COVID-19 vaccination, a qualitative study was undertaken, developed from a narrative review and thematic analysis of previous studies on the subject under examination. According to Rother (2007), “the narrative review is a comprehensive mode of investigation and publication, proving pertinent for describing and discussing the development or the ‘state of the art’ of a specific subject, from a theoretical or contextual point of view” (p. 1).

This being so, the present study aims to analyse the role of Health Literacy in modulating attitudes of acceptance and hesitancy towards COVID-19 vaccination in adult populations, taking into account the influence of exposure to the infodemic, so as to inform the design of nursing interventions in a community context.

To guide this research, and to ensure a systematic and focused approach, the PIO method was used to formulate the research question. This method, widely used in the formulation of research questions in health, allows the essential elements involved in the phenomenon under study to be structured clearly, ensuring greater rigour in the definition of the problem and in the identification of the variables to be analysed. Thus, the following research question was formulated:

- in adult populations (P), what is the impact of levels of health literacy and of exposure to the infodemic/misinformation (I) on attitudes of acceptance and hesitancy towards COVID-19 vaccination (O)?

The search strategy adopted for the identification of the primary studies aimed at gathering relevant literature available in open access, through the careful exploration of online resources and search engines of a generalist and scientific nature.

4 RESULTS AND DISCUSSION

The main results of the analysis of the selected studies are presented below; they were grouped and organised in a table in order to answer the research question. In this way, the table summarises the characteristics and dimensions of the studies, making it possible to understand them and to compare them, namely with regard to the objective, participants and main established evidence.

Table 3*Characteristics and dimensions of the studies*

Study 1	Bendau, A., Plag, J., Petzold, M. B., & Ströhle, A. (2021). COVID-19 vaccine hesitancy and related fears and anxiety. <i>International Immunopharmacology</i>, 97, 107724.
Objective	To identify the predictive factors of willingness to be vaccinated, and to investigate acceptance in the general population and its relationship with fears, media use and sociodemographic factors shortly after the start of vaccination in Germany.
Participants	1,779 adults (1,380 women, 389 men and 10 individuals of different ethnicities); the mean age was 41.33 years.
Established evidence	Vaccine acceptance in the sample studied was relatively high: 78.3% of the sample stated that they would accept vaccination (64.5% stated they would accept vaccination without hesitation and 13.8% would prefer to accept it), 10.4% were undecided, 5.2% preferred not to be vaccinated and 6% firmly refused. The authors established the need to differentiate between types of fear, as these showed opposing associations with willingness to vaccinate. Specifically, COVID-19-related anxiety and health-related fears (fear of infection and of health consequences for oneself or loved ones) correlated significantly and positively with greater vaccine acceptance. By contrast, fear of social consequences and fear of economic consequences showed significant negative associations with willingness to vaccinate. Regarding sociodemographic factors, age and educational level correlated positively and significantly with vaccine acceptance. The use of media to obtain information about the pandemic was also significantly associated with acceptance. The group that reported using both official websites and social media to obtain information had the highest acceptance scores, while the group that used neither source reported the lowest level of acceptance.
Study 2	Oliveira, B. L. C. A. de, Campos, M. A. G., Queiroz, R. C. de S., Britto e Alves, M. T. S. S. de, Souza, B. F. de, Santos, A. M. dos, & Silva, A. A. M. da. (2021). Prevalência e fatores associados à hesitação vacinal contra a covid-19 no Maranhão, Brasil. <i>Revista de Saúde Pública</i>, 55, 12.
Objective	To estimate the prevalence and the factors associated with hesitancy in receiving the vaccine against SARS-CoV-2 in Maranhão, Brazil.
Participants	5,001 individuals: 872 in Stratum 1 (four municipalities); 1,236 in Stratum 2 (122 municipalities); 612 in Stratum 3 (85 municipalities); 1,022 in Stratum 4 (five municipalities); and 1,021 in Stratum 5 (one municipality).
Established evidence	The prevalence of hesitancy regarding the COVID-19 vaccine was 17.5%. Hesitancy was higher among women (19.8%), older adults (22.8%) and evangelicals (24.1%). Hesitancy varied significantly according to the geographical stratum of residence: residents of Imperatriz showed a greater probability of vaccine hesitancy, and those of the greater Island of São Luís also had a greater probability of hesitancy. The most relevant clinical factor associated with hesitancy was the subjective experience of the disease (absence of symptoms); individuals who did not report having had symptoms possibly related to COVID-19 were more prone to vaccine hesitancy.
Study 3	Muralidharan, D., Paul, A., Panangadanakath, S., Nandakumar, S. T., Poothotill, S. S., MoiduKunhi, R. A., & Ameen, Z. (2025). COVID-19 vaccine acceptance and hesitancy: Perceptions in Kerala, the Indian state with the highest literacy. <i>Journal of Preventive Medicine & Public Health</i>, 58, 527–537.
Objective	To assess acceptance, hesitancy and the determinants associated with the COVID-19 vaccine in the general population of Kerala, India, after the vaccine became available.
Participants	1,078 individuals: 650 female and 428 male. More than half of the sample belonged to the 18–29 age group, most with a high level of schooling, the majority having completed an undergraduate degree (48.3%).

Established evidence	Of the 1,078 participants, 85.0% (n=916) accepted the COVID-19 vaccine and 15.0% (n=162) were hesitant about it. Male sex was associated with a greater probability of hesitancy. Younger age (18–29 years) was a significant predictor of hesitancy. A lower level of schooling (school level) increased the probability of hesitancy. Uncertainty about the efficacy and safety of the vaccine emerged as a significant determinant of hesitancy towards the COVID-19 vaccine. Trust in the government significantly influences public acceptance of vaccines. Individuals who follow the preventive measures recommended by the government against COVID-19 tend to strongly accept vaccination. Health professionals are trusted sources of information about vaccination and influence decision-making processes regarding vaccines.
Study 4	Köse, S., Mandiracioglu, A., Özbel, Y., Zeyrek, S., Dereli Akdeniz, D., & Kafil, H. S. (2023). COVID-19 vaccination acceptance and hesitancy among the Turkish adult population. GMS Hyg Infect Control, 18.
Objective	To determine acceptance of COVID-19 vaccination in the Turkish adult population.
Participants	2,023 individuals, mean age 39.22; the majority female (51.5%), and 63.4% of the sample held a university degree.
Established evidence	The intention to be vaccinated against COVID-19 was 68.7% among the participants surveyed. The individuals most likely to accept vaccination were in the 50–59 age group, health professionals, and those who had previously been vaccinated against other diseases. Participants who hesitated to be vaccinated presented various reasons for their attitude, namely: concern that the vaccine might have side effects, lack of confidence in the vaccine, above all because it was new, lack of belief that the vaccine would work, confidence in their own immune system, and not feeling a need to be vaccinated either because they felt protected from the disease or because they were not afraid of becoming ill.
Study 5	Ebrahimi, F., Torkian, S., Rashti, R., Emami, M., Shahnazi, H., & Maracy, M. R. (2024). Exploring the Relation Between Health Literacy, Infodemic, and Acceptance of COVID-19 Vaccination in Iran: A Cross-Sectional Study. HLRP: Health Literacy Research and Practice, 8(4), e184–e193.
Objective	To measure the acceptability of the COVID-19 vaccine, health literacy regarding COVID-19 and the COVID-19 infodemic, as well as their predictors, in the Iranian population.
Participants	2,168 individuals from five provinces of Iran, mean age 31.26 years. Most participants were aged between 18 and 29 years, 58.9% were female and 80.1% held a university qualification.
Established evidence	68.6% of participants expressed willingness to accept the COVID-19 vaccine; only 45% of participants had sufficient knowledge (health literacy) about COVID-19. 52.2% of participants felt confused by false or differing information during the pandemic; in fact, 13.2% were “very confused” and 39.0% were “somewhat confused”. Having sufficient Health Literacy about COVID-19 was significantly associated with greater vaccine acceptance. Acceptance of the COVID-19 vaccine was higher in people with adequate levels of health literacy. This study demonstrates that improving knowledge about COVID-19 is an important target for public health interventions, given its potential to increase vaccine acceptance.
Study 6	Malik, A. A., McFadden, S. M., Elharake, J., & Omer, S. B. (2020). Determinants of COVID-19 vaccine acceptance in the US. EClinicalMedicine, 26, 100495.
Objective	To understand risk perceptions regarding the COVID-19 pandemic, acceptance of a COVID-19 vaccine and trust in information sources, in the adult population of the USA.
Participants	672 individuals took part in this study, 57% of the sample being women and 38% aged 55 or over. 52% held a university qualification.
Established evidence	Of the 672 participants surveyed, 450 (67%) stated that they would accept a COVID-19 vaccine if it were recommended to them. As for demographic characteristics, men (72%) were more likely to accept the vaccine if it were

	recommended, as were younger adults (relative to those aged 55 or over). The relationship between adherence to the influenza vaccine and acceptance of the COVID-19 vaccine was significant. For example, participants who had not completed secondary education showed very low adherence to the influenza vaccine. Participants reported greater trust in health professionals, and also indicated health professionals (n = 503; 75%) and health authorities (n = 470; 70%) as the most trusted sources of information about COVID-19. By comparison, 144 participants (21%) indicated social media as a trusted source of information about COVID-19. This study shows that acceptance of the COVID-19 vaccine can be predicted with relative accuracy through demographic characteristics. Acceptance of the COVID-19 vaccine also varies according to education and employment; as years of schooling increase, reported acceptance of the COVID-19 vaccine also increases. The study concludes that it is essential for health authorities and policymakers to prioritise the development of effective, evidence-based messaging to promote acceptance of the COVID-19 vaccine among all Americans, especially in the most vulnerable groups. The need to involve health professionals and health authorities in community communication is crucial for increasing trust and adherence.
Study 7	Cao, A., Ueta, M., Uchibori, M., Murakami, M., Kunishima, H., Kumar, R. S., Prommas, P., Tomoi, H., Gilmour, S., Sakamoto, H., Hashizume, M., Naito, W., Yasutaka, T., Maruyama-Sakurai, K., Miyata, H., & Nomura, S. (2024). Trust in governments, public health institutions, and other information sources as determinants of COVID-19 vaccine uptake behavior in Japan. Vaccine, 42, 3684–3692.
Objective	To elucidate the determinants of adherence to COVID-19 vaccination and to assess the relationship between trust in different information sources and COVID-19 vaccination behaviour in Japan.
Participants	19,174 individuals answered a questionnaire, with a mean age of 54.7 years, mostly female (50.4%). The most common level of schooling was higher education, with married marital status most prevalent at 63%.
Established evidence	The study's finding lies in the robust relationship between trust and vaccination behaviour; that is, aggregated trust in vaccine approval systems and institutions (which includes trust in scientists in the field of vaccine development, public authorities for approval and health-care providers) was identified as a consistently powerful predictor of adherence to COVID-19 vaccination. Trust in information about the COVID-19 pandemic from governmental sources emerged as the strongest determinant of vaccine adherence among the information sources analysed. Greater trust in traditional media (television, newspapers and radio) was also a strong determinant of vaccine adherence. Trust in internet information sources had a significant negative effect on vaccination adherence. The vaccination decision was classified as a multifactorial process interacting with psychosocial determinants, with the following determinants being statistically significant predictors of adherence: descriptive social norm, perceived impact of COVID-19, Health Literacy, belief in anxiety relief, and perception of benefits and disadvantages. Lower levels of schooling were negatively associated with adherence. Occupations in the medical and health field were selected as the reference group as they had a higher adherence rate, while several other occupations showed negative associations. Trust in the government and in public health institutions is a powerful determinant of vaccination adherence.
Study 8	Marzo, R. R., Ahmad, A., Abid, K., Khatiwada, A. P., Ahmed, A., Kyaw, T. M., Abidin, I. B. Z., Srithar, M., Sinnathamby, S., Sarvasundram, A. P., & Shrestha, S. (2022). Factors influencing the acceptability of COVID-19 vaccination: A cross-sectional study from Malaysia. Vacunas, 23(S1), S33–S40.
Objective	To determine the acceptance, preferences and impact factors of future COVID-19 vaccines in Malaysia and the factors that influence acceptance of COVID-19 vaccination among vaccination candidates.
Participants	1,282 participants, the majority male (71.1%), with 898 of them aged under 24. 72.7% of participants held higher education.

Established evidence	The vast majority of the 1,282 respondents considered that vaccination would be an effective way to prevent and control COVID-19, totalling 95.9%. Around 96% of respondents indicated that they would accept vaccination if the COVID-19 vaccine were successfully developed and approved for inclusion in the list of available medicines in the future. Only 38.2% of the respondents who would accept the vaccine stated that they would receive it as quickly as possible once available. The most important factors influencing respondents' vaccination decisions were: medical recommendation (97.3%), convenience of the vaccine (95.7%) and the price of the vaccine (91.3%). People aged 25–34 were less likely to accept the vaccine compared with the reference group (age < 24). Students were twice as likely to accept the vaccine compared with those in employment. In this study, people with a higher level of education were more likely to consider vaccination than those with a lower level of schooling. Vaccine acceptance was higher in individuals with postgraduate education, which highlights that health departments should design educational programmes to raise awareness about COVID-19 vaccination among people with less schooling, leading to an overall improvement in acceptance.
Study 9	Cénat, J. M., Moshirian Farahi, S. M. M., Broussard, C., & Dalexis, R. D. (2024). The state of COVID-19 vaccine confidence and need in Black individuals in Canada: Understanding the role of sociodemographic factors, health literacy, conspiracy theories, traumatic stressors and racial discrimination. Vaccine, 42, 960–968.
Objective	To investigate the factors associated with vaccine confidence in Black individuals in Canada.
Participants	2,002 participants, 51.55% female, the majority aged between 14 and 24. 39.59% of participants held university education.
Established evidence	The results showed that the mean confidence in, and need for, the COVID-19 vaccine was higher in unemployed participants than in employed participants. The results showed significant differences in confidence in, and need for, the COVID-19 vaccine between age groups, where participants aged 55 or over, as well as those aged between 45 and 54, presented higher means of confidence in, and need to receive, the COVID-19 vaccine, compared with those aged between 14 and 24 and between 25 and 34. Comparisons showed that participants with a post-secondary certificate or diploma below the bachelor's level reported a lower mean confidence in, and need for, the COVID-19 vaccine compared with participants without a secondary school diploma, without a post-secondary certificate or diploma but who had attended a higher-education institution, and with a university certificate, diploma or degree above the bachelor's level. The results showed that health literacy and COVID-19-related traumatic stressors were associated with increased confidence in, and need for, the COVID-19 vaccine. This study demonstrates the positive role that health literacy can play in fostering confidence in vaccines. This study also demonstrated the importance of increasing health knowledge in Black communities and of reducing conspiracy theories in order to increase confidence in, and the need for, vaccination.

Source: Prepared by the authors (2025).

The aim is to interconnect the evidence found across the various studies analysed, focusing on the central research question previously defined. Reading the articles made it possible to identify that health literacy and exposure to the infodemic/misinformation are significant predictors of attitudes of acceptance of, and hesitancy towards, COVID-19 vaccination.

The interconnection of the results demonstrates that Health Literacy stands as a protective factor, whereas the infodemic/misinformation functions as a barrier that conditions confidence, with effects that differ according to literacy levels and information sources.

Health Literacy was shown to be a consistently positive predictor of acceptance of COVID-19 vaccination (Ebrahimi et al., 2024). The study by Ebrahimi et al. (2024) revealed that individuals with “high levels of COVID-19 health literacy presented a significantly greater probability of accepting the vaccine” (p. 188). This finding corroborates the perspective that a greater understanding of health information enables individuals to engage in more positive and adaptive behaviours in the face of the pandemic, such as vaccination (Li et al., 2020, as cited in Ebrahimi et al., 2024).

Similarly, Cénat et al. (2024), in analysing vaccine confidence in Black communities in Canada, identified that health literacy “positively predicted confidence in the vaccine and the perceived need to receive it” (p. 963). Health Literacy is a crucial factor in building confidence and reducing hesitancy (Cénat et al., 2024; Ebrahimi et al., 2024).

Level of schooling, frequently used as an indicator of Health Literacy, and age also emerged as a significant factor (Bendau et al., 2021). In the study in Kerala, India (Muralidharan et al., 2025), vaccine hesitancy was more associated with a lower educational level. However, the relationship between education/income and acceptance is not linear in all contexts, as demonstrated in a study by Oliveira et al. (2021) in Maranhão, Brazil, where level of instruction and income were not statistically significantly associated with hesitancy (Oliveira et al., 2021).

The disparity in insufficient Health Literacy was observed in specific demographic groups in Iran, being more prevalent in individuals with a lower level of schooling and lower income, which reinforces the idea that these populations require particular attention in public health strategies to promote literacy. According to the study by Ebrahimi et al. (2024), high Health Literacy was, at times, more common “in women in Iran, potentially owing to greater access to the internet and to following news about COVID-19” (p. 189).

The COVID-19 pandemic was accompanied by an infodemic/misinformation, characterised by the rapid and extensive dissemination of accurate and inaccurate information about the virus and the vaccines (Ebrahimi et al., 2024; Köse et al., 2023; Oliveira et al., 2021).

The studies confirm that exposure to misinformation/infodemic and to conspiracy theories is a powerful negative predictor of vaccine acceptance (Ebrahimi et al., 2024). In Canada, Cénat et al. (2024) observed that beliefs in conspiracy theories were negatively associated with vaccine confidence. Similar results were found in Turkey, where vaccine hesitancy was motivated by distrust of vaccine manufacturers and by concerns about side effects, often fuelled by negative information conveyed on social media (Köse et al., 2023).

The infodemic leads to a state of confusion in the population, where individuals are unable to discern which data to believe. In Iran, 52.2% of respondents reported being “very confused” or “somewhat confused” owing to contradictory information. Confusion about vaccine information, in turn, was positively associated with hesitancy (Ebrahimi et al., 2024).

The interconnection between health literacy and exposure to misinformation is complex and not always intuitive. Although it would be expected that high Health Literacy would protect against confusion and misinformation, the study by Ebrahimi et al. (2024) in Iran found a paradoxical result: “higher scores of COVID-19 health literacy were associated with a higher adjusted probability of confusion by false information” (p. 190). A plausible explanation for this phenomenon lies in the fact that, as the participants in this study were younger and had greater access to the internet, their greater health literacy may result from continuous and active following of news about the pandemic. However, in doing so, they inevitably expose themselves to the vast volume of contradictory and false information circulating on social media, intensifying their perception of confusion.

The source of exposure to information functions as a decisive mediator between misinformation and vaccine attitudes. Depending on the credibility and quality of the sources consulted, the information received may reinforce confidence in vaccination or foster doubts, fears and distorted perceptions of risk. The analysis of the impact of these information sources reveals a clear dichotomy, which can be categorised as follows:

1. **Official and Traditional Media vs. Acceptance:** trust in official and credible information sources (such as health professionals, health authorities and governmental websites) is positively associated with acceptance (Bendau et al., 2021; Cao et al., 2024; Malik et al., 2020). In Japan, aggregated trust in vaccine approval systems and institutions (including scientists and health-care providers) was a powerful predictor of vaccination adherence. Trust in traditional media (television, radio, newspapers) was also shown to be a significant determinant of adherence in Japan (Cao et al., 2024).
2. **Social Media and the Internet vs. Hesitancy:** by contrast, social media and other unofficial sources are frequently channels for the spread of misinformation and conspiracy theories (Bendau et al., 2021; Köse et al., 2023). While in the USA the use of official websites and social media together appeared to have the highest level of acceptance, the use of social media alone resulted in a level of acceptance slightly higher than using no source, but lower than using official websites alone (Bendau et al., 2021). In Japan, however, trust in internet sources (including social media) and in

celebrity blogs had an opposite, negative effect on vaccination adherence (Cao et al., 2024).

The studies analysed emphasise that attitudes of acceptance and hesitancy vary significantly according to the sociocultural, demographic and geographical context (Oliveira et al., 2021; Ebrahimi et al., 2024; Muralidharan et al., 2025).

Vaccine hesitancy was influenced by a range of sociodemographic factors, including:

- **Age and Gender:** Younger individuals and women tended to show greater hesitancy in several studies (Malik et al., 2020; Marzo et al., 2022; Muralidharan et al., 2025). However, the correlation between age and acceptance is inconsistent globally, with older adults in Maranhão, Brazil, being more prone to hesitancy, which may be explained by lower functional literacy and greater exposure to conflicting political discourse (Oliveira et al., 2021).
- **Socioeconomic and Educational Status:** hesitancy was associated with low levels of schooling and income (Malik et al., 2020; Muralidharan et al., 2025). The perception that the vaccination process was complicated and inconvenient, particularly owing to digitalisation, reinforced hesitancy in groups with lower incomes and low levels of schooling (Muralidharan et al., 2025).

Trust in governmental entities and in public health institutions acts as a powerful moderator of exposure to the infodemic (Cao et al., 2024). However, in historically marginalised populations, such as the Black communities in Canada, racial discrimination and systemic distrust of health institutions contribute negatively to confidence and acceptance (Cao et al., 2024; Cénat et al., 2024; Malik et al., 2020). In addition, the perception of individual risk influenced acceptance; fears directly related to physical health (infection and consequences for one's own health or that of loved ones) correlated positively with greater acceptance (Bendau et al., 2021; Oliveira et al., 2021). On the other hand, fear of social and economic consequences associated with the pandemic had a negative correlation with vaccine acceptance (Bendau et al., 2021). Interestingly, individuals who did not experience COVID-19 symptoms were more prone to hesitancy, suggesting a lower perception of risk (Oliveira et al., 2021).

5 CONCLUSION

The present study sought to determine the impact of levels of health literacy and of exposure to the infodemic/misinformation on attitudes of acceptance of, and hesitancy towards, COVID-19 vaccination in adult populations, comparing the effects between different

levels of literacy and of exposure to information. The overall results demonstrate an intrinsic, and at times paradoxical, relationship between these factors.

In general, sufficient or high levels of health literacy are significantly and positively associated with acceptance of the COVID-19 vaccine. Health literacy facilitates the capacity of individuals to access, understand and use information related to COVID-19 in order to make informed decisions about their health, such as vaccination. Conversely, vaccine hesitancy was associated with lower levels of schooling and income, which are predictors of low health literacy.

Exposure to the infodemic, in particular to conspiracy theories and misinformation, is a consistently negative predictor of vaccine acceptance. It is concluded that overcoming vaccine hesitancy in adult populations requires a dual approach: the strengthening of Health Literacy, aimed at refining the discernment of information, and the rigorous management of the infodemic, with the objective of restoring institutional trust and reducing confusion. However, in order to become effective, the enhancement of Health Literacy requires credible and coherent information sources, since the individuals most active in seeking information are more susceptible to the confusion generated by the infodemic.

Future strategies should focus on robust curricular integration, ensuring that health education is a cross-cutting and continuous component from the school setting through to the community; on adapted communication within health services, through health professionals, towards more transparent communication about the safety and efficacy of vaccination; and on the development of community intervention strategies. In this context, the role of nursing proves fundamental, since nurses constitute the largest group of care providers globally and are essential in the provision of reliable and comprehensible information to service users.

As Smith (2021) notes, “nurses occupy a privileged position to help and support those with limited health literacy” (p. 2), and it is important that they lead the transition from basic literacy skills to a capacity for critical analysis that empowers the individual in the face of the complexity of the infodemic. This direct intervention is vital for mitigating informational confusion and for promoting conscious adherence to public health measures through the implementation of educational programmes that reinforce the importance of health literacy.

Health Literacy is a protective factor when supported by curricular policies and intervention strategies that ensure access to credible and coherent information sources, empowering the population for the critical discernment of information. The response to the infodemic is not solely a matter of literacy at the individual level, but rather of systemic responsibility in education and public health.

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ANTINEOPLASTIC POTENTIAL OF PSEUDOBOMBAX MILLEI: PHYTOCHEMICAL, GENOMIC AND MOLECULAR INTEGRATION IN UTERINE LEIOMYOMAS

POTENCIAL ANTINEOPLÁSICO DE PSEUDOBOMBAX MILLEI: INTEGRAÇÃO FITOQUÍMICA, GENÔMICA E MOLECULAR EM LEIOMIOMAS UTERINOS

POTENCIAL ANTINEOPLÁSICO DE PSEUDOBOMBAX MILLEI: INTEGRACIÓN FITOQUÍMICA, GENÓMICA Y MOLECULAR EN LEIOMIOMAS UTERINOS



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ABSTRACT

This chapter analyses the antineoplastic potential of *Pseudobombax millei* from an ethnopharmacological, chemotaxonomic and genomic perspective. Evidence on secondary metabolites and their molecular mechanisms in uterine leiomyomas is integrated, highlighting their possible therapeutic application. *Pseudobombax millei* (Standl.) A. Robyns, a species endemic to Ecuador known as "Beldaco", has traditional ethnopharmacological applications in the management of genitourinary disorders. In this context, the present analysis develops a chemotaxonomic and genomic framework aimed at exploring its antineoplastic potential against uterine leiomyomas. In the absence of a reference genome for the species, comparative phylogenetic inference strategies and phytochemical extrapolation based on members of the Bombacoideae subfamily were employed. Likewise, molecular modelling in leiomyoma cell lines (ELT-3 and UtLM), together with bioinformatic analyses using in silico TBLASTN alignments, suggests a phytochemical profile enriched in flavonoids, naphthoquinones and triterpenoids, including compounds such as lupeol. From a mechanistic perspective, these metabolites could exert antiproliferative effects through the antagonism of steroid hormone signalling and the induction of intrinsic apoptosis, via modulation of the p53/Bax pathway and the activation of effector caspases (Caspase-3/7). Consistently, the available comparative evidence points to the evolutionary conservation of flavonoid biosynthetic pathways within the Malvaceae family. Taken together, these findings position *P. millei* as a promising candidate for the development of non-invasive therapeutic strategies in the management of uterine leiomyomas, although its validation requires in vitro and in vivo experimental studies to confirm its efficacy and safety.

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Keywords: Pseudobombax Millei. Uterine Leiomyomas. Phytochemistry. Apoptosis. Ethnopharmacology.

RESUMO

Este capítulo analisa o potencial antineoplásico de *Pseudobombax millei* sob uma perspectiva etnofarmacológica, quimiotaxonômica e genômica. Integram-se evidências sobre metabólitos secundários e seus mecanismos moleculares em leiomiomas uterinos, destacando sua possível aplicação terapêutica. *Pseudobombax millei* (Standl.) A. Robyns, espécie endêmica do Equador conhecida como "Beldaco", possui aplicações etnofarmacológicas tradicionais no manejo de transtornos geniturinários. Nesse contexto, a presente análise desenvolve um marco quimiotaxonômico e genômico orientado a explorar seu potencial antineoplásico frente aos leiomiomas uterinos. Diante da ausência de um genoma de referência para a espécie, empregaram-se estratégias de inferência filogenética comparada e extrapolação fitoquímica baseadas em membros da subfamília Bombacoideae. Da mesma forma, a modelagem molecular em linhagens celulares de leiomioma (ELT-3 e UtLM), junto a análises bioinformáticas mediante alinhamentos TBLASTN in silico, sugere um perfil fitoquímico enriquecido em flavonoides, naftoquinonas e triterpenoides, que inclui compostos como o lupeol. Sob uma perspectiva mecanística, esses metabólitos poderiam exercer efeitos antiproliferativos mediante o antagonismo da sinalização hormonal esteroide e a indução de apoptose intrínseca, através da modulação da via p53/Bax e da ativação de caspases efectoras (Caspase-3/7). De maneira consistente, a evidência comparada disponível aponta para a conservação evolutiva das rotas biossintéticas dos flavonoides dentro da família Malvaceae. Em conjunto, esses achados posicionam *P. millei* como um candidato promissor para o desenvolvimento de estratégias terapêuticas não invasivas no manejo dos leiomiomas uterinos, embora sua validação requeira estudos experimentais in vitro e in vivo que confirmem sua eficácia e segurança.

Palavras-chave: Pseudobombax Millei. Leiomiomas Uterinos. Fitoquímica. Apoptose. Etnofarmacologia.

RESUMEN

Este capítulo analiza el potencial antineoplásico de *Pseudobombax millei* desde una perspectiva etnofarmacológica, quimiotaxonómica y genómica. Se integran evidencias sobre metabolitos secundarios y sus mecanismos moleculares en leiomiomas uterinos, destacando su posible aplicación terapéutica. *Pseudobombax millei* (Standl.) A. Robyns, especie endémica del Ecuador conocida como "Beldaco", posee aplicaciones etnofarmacológicas tradicionales en el manejo de trastornos genitourinarios. En este contexto, el presente análisis desarrolla un marco quimiotaxonómico y genómico orientado a explorar su potencial antineoplásico frente a los leiomiomas uterinos. Ante la ausencia de un genoma de referencia para la especie, se emplearon estrategias de inferencia filogenética comparada y extrapolación fitoquímica basadas en miembros de la subfamilia Bombacoideae. Asimismo, el modelado molecular en líneas celulares de leiomioma (ELT-3 y UtLM), junto con análisis bioinformáticos mediante alineamientos TBLASTN in silico, sugiere un perfil fitoquímico enriquecido en flavonoides, naftoquinonas y triterpenoides, que incluye compuestos como el lupeol. Desde una perspectiva mecanística, estos metabolitos podrían ejercer efectos antiproliferativos mediante el antagonismo de la señalización hormonal esteroidea y la inducción de apoptosis intrínseca, a través de la modulación de la vía p53/Bax y la activación de caspasas efectoras (Caspasa-3/7). De manera consistente, la evidencia comparada disponible apunta a la conservación evolutiva de las rutas biosintéticas de los flavonoides dentro de la familia Malvaceae. En conjunto, estos hallazgos posicionan a *P. millei* como un candidato prometedor para el desarrollo de estrategias terapéuticas no invasivas en el manejo de los leiomiomas uterinos, aunque su validación requiere estudios experimentales in vitro e in vivo que confirmen su eficacia y seguridad.

Palabras clave: Pseudobombax Millei. Leiomiomas Uterinos. Fitoquímica. Apoptosis. Etnofarmacología.

1 INTRODUCTION

Uterine leiomyomas represent the most prevalent benign neoplasm in women of reproductive age. Their pathogenesis involves hormonal, genetic and molecular factors. Given current therapeutic limitations, natural compounds emerge as promising alternatives. Clinically known as uterine fibroids, with a cumulative incidence reaching up to 70–80% in women by the age of 50.¹ Originating from the monoclonal expansion of myometrial smooth muscle stem cells, these hormone-dependent tumours represent a significant clinical, social and economic burden on a global scale.³ In recent decades, their incidence has shown an increasing trend, with a substantial impact on disability-adjusted life years (DALYs), which entails a high demand for medical care.⁷

From a clinical standpoint, leiomyomas display remarkable heterogeneity, both in their location and in their symptomatic expression. Their manifestations range from pelvic pain, abnormal uterine bleeding and anaemia, to severe reproductive complications, including infertility and recurrent pregnancy loss.¹

The pathogenesis of uterine leiomyomas is multifactorial and comprises a complex interaction between steroid hormone signalling, aberrant remodelling of the extracellular matrix (ECM), localised chronic inflammation, oxidative stress and genetic and epigenetic alterations.¹ Genomic profiling studies have identified recurrent mutations, particularly in the MED12 gene, as well as the overexpression of HMGA2 and fumarate hydratase deficiency, as key drivers of tumorigenesis.¹ These alterations, together with early epigenetic events in myometrial stem cells, favour the generation of tumour-initiating cells that are highly dependent on oestrogen and progesterone for their sustained growth.¹⁰

Despite their high prevalence and the associated clinical impact, current therapeutic options remain limited. Surgical interventions, such as hysterectomy and myomectomy, involve inherent risks and, in many cases, compromise fertility. For their part, pharmacological treatments, including gonadotropin-releasing hormone (GnRH) agonists and selective progesterone receptor modulators (SPRMs), are associated with significant adverse effects.¹ The prolonged use of GnRH agonists, for example, induces a state of hypoestrogenism that may cause loss of bone mineral density, vasomotor symptoms and vaginal dryness, which limits their short-term application.¹

In this context, the search for non-invasive, safe and fertility-preserving therapies has driven interest in ethnopharmacology as a source of bioactive compounds.² South America, and particularly Ecuador, harbours an exceptional biodiversity with a vast repertoire of medicinal plants traditionally used in reproductive health.¹ Within this scenario, the

Tumbesian region —recognised as a biodiversity hotspot that extends between south-western Ecuador and north-western Peru— stands out for its high plant endemism.¹⁸

Pseudobombax millei (Standl.) A. Robyns, known locally as "Beldaco", is a deciduous arboreal species endemic to the Tumbes–Guayaquil seasonal dry forests.²² It is morphologically characterised by its tall stature, open crown, palmate leaves and white flowers with prominent stamens.²² It is currently classified as "Data Deficient" (DD) by the IUCN, facing significant threats arising from habitat fragmentation, agricultural expansion and climate change.²²

In traditional Ecuadorian medicine, species of the Malvaceae family, particularly of the Bombacoideae subfamily, have been employed in the treatment of inflammatory processes, genitourinary disorders and uterine conditions empirically described as "cysts".¹ Nevertheless, despite their ancestral use, the phytochemical characterisation and pharmacological validation of *P. millei* are still limited, evidencing an important translational gap in the scientific literature.¹ Likewise, there is a marked taxonomic bias in research, with disproportionate attention given to species such as *Bombax ceiba* and *Ceiba pentandra*, to the detriment of the genus *Pseudobombax*.²⁷

In this context, the present chapter develops an integrative analysis aimed at exploring the antineoplastic potential of *Pseudobombax millei* against uterine leiomyomas. Given the absence of specific genomic and metabolomic data, chemotaxonomic extrapolation and comparative phylogenetic inference strategies are employed to predict its phytochemical profile and its possible mechanisms of action. In particular, secondary metabolites such as flavonoids, naphthoquinones and triterpenoids (including lupeol) are analysed, which could modulate cell proliferation and apoptosis in leiomyoma models.

Additionally, the integration of bioinformatic tools allows the genomic basis of these biosynthetic pathways to be explored, highlighting the role of key enzymes such as chalcone synthase (CHS). Taken together, this multidisciplinary approach lays the foundations for future experimental research aimed at validating the therapeutic potential of this species in the context of translational medicine.

2 ETHNOPHARMACOLOGICAL RELEVANCE OF PSEUDOBOMBAX MILLEI

The traditional use of medicinal plants in Ecuador provides a solid empirical basis. *Pseudobombax millei* has been employed in gynaecological disorders, suggesting relevant biological activity.

2.1 CONTEXT OF TRADITIONAL MEDICINE IN THE ECUADORIAN FLORA

Ecuador is distinguished by a high degree of biological and cultural diversity, reflected in the richness of its ecosystems—from the coastal lowlands to the Andean region and the Amazon basin—and in the wide use of its flora for medicinal purposes.¹⁷ This knowledge is preserved and transmitted by at least 18 indigenous groups, as well as by numerous rural communities, where the use of medicinal plants constitutes a current practice.¹⁷

In many regions, particularly in coastal areas and in the Andean foothills, traditional phytotherapy represents not only a therapeutic alternative, but frequently the main form of health care, especially in contexts with limited access to conventional medical services.¹ Within this framework, various plant parts—including bark, leaves, roots and phloem—are collected and processed by means of decoctions, infusions or macerations for therapeutic use.¹

Within this ethnobotanical system, *Pseudobombax millei*, together with sympatric species such as *Muntingia calabura*, *Brugmansia candida* and *Tessaria integrifolia*, occupies a relevant place.²⁵ Ethnomedical studies have documented the use of "Beldaco" extracts mainly as anti-inflammatory agents, commonly termed "desinflamantes" in traditional medicine.²⁶ More specifically, healers, herbalists and midwives use preparations derived from the bark and the inner phloem of *Bombacoideae* species for the treatment of conditions of the female reproductive tract, described in vernacular terms as "cysts", pelvic inflammation and uterine bleeding alterations.¹

The correspondence between these traditional applications and the clinical symptomatology of uterine leiomyomas suggests a possible underlying biological basis, which confers scientific relevance to their systematic study.

2.2 TRANSLATIONAL GAP AND PHARMACOLOGICAL TRANSLATION OF TRADITIONAL USES

The transition from empirical knowledge towards pharmacological validation requires the establishment of clear links between the effects observed in traditional medicine and the molecular mechanisms that underlie them. In this sense, the use of *P. millei* in conditions described as "internal inflammation" is consistent with the current understanding of the pathogenesis of uterine leiomyomas, where inflammatory processes play a central role.

These tumours are characterised by the dysregulation of inflammatory mediators, including cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor alpha (TNF- α), as well as by the activation of enzymes such as cyclooxygenase-2 (COX-2).¹ In this context, studies carried out on related species of the *Bombacoideae*

subfamily have shown that aqueous and hydroalcoholic bark extracts present significant anti-inflammatory and antinociceptive activities in *in vivo* models, such as carrageenan-induced oedema and experimental peritonitis.³³ These effects are associated with the inhibition of myeloperoxidase (MPO) activity, the reduction of leukocyte migration and the modulation of prostaglandin biosynthesis, which supports the physiological plausibility of their traditional uses.³³

Nevertheless, the study of *Pseudobombax millei* is limited by a marked taxonomic bias in the scientific literature.²⁷ The majority of investigations within the Malvaceae family have concentrated on species such as *Bombax ceiba* and *Ceiba pentandra*, while the genus *Pseudobombax* remains scarcely explored.²⁷ In addition, there is a methodological bias that prioritises the analysis of easily accessible plant structures, such as leaves and bark, to the detriment of tissues such as the inner phloem and roots, which could harbour distinctive metabolic profiles.²⁷

As a result, while some species have reached advanced levels of experimental evidence, the information available for *Pseudobombax* is limited mainly to preliminary studies, generating a significant translational gap, particularly in terms of pharmacokinetics, specific bioactivity and mechanisms of action.²⁷

On the other hand, traditional preparation methods —such as prolonged hydroalcoholic maceration and aqueous decoction— favour the extraction of a broad spectrum of secondary metabolites, both polar and semipolar.¹ The empirical efficacy reported for these preparations suggests that the phloem of *P. millei* could concentrate bioactive compounds capable of modulating the inflammatory and proliferative microenvironment characteristic of uterine leiomyomas.

3 CHEMOTAXONOMY AND PHYTOCHEMICAL EXTRAPOLATION

The Malvaceae family presents metabolites such as flavonoids, triterpenoids and phenolic compounds. These compounds have antioxidant, antiproliferative and anti-inflammatory effects.

Given the limited availability of phytochemical data specific to *Pseudobombax millei*, chemotaxonomic extrapolation constitutes a valid methodological strategy to infer its secondary metabolite profile. This approach is based on the principle that phylogenetically related species share conserved biosynthetic pathways and, therefore, present similarities in their chemical composition.⁴⁰

In this context, the integration of taxonomic, phylogenetic and phytochemical information makes it possible to guide the identification of bioactive compounds in poorly

studied species, facilitating their pharmacological valorisation and their possible therapeutic application.

3.1 CHEMOTAXONOMIC PROFILE OF THE BOMBACOIDEAE SUBFAMILY

Phytochemical studies in the Bombacoideae subfamily —particularly in the genera *Pseudobombax*, *Bombax* and *Pachira*— evidence a relatively conserved secondary metabolome, characterised by the presence of flavonoids, phenolic acids, naphthoquinones, triterpenoids and alkaloids.^{1, 39, 42–44}

This profile constitutes a useful predictive model for inferring the chemical composition of the phloem of *P. millei*, especially in the absence of direct studies.

Table 1

Chemotaxonomic profile of the Bombacoideae subfamily and putative role of secondary metabolites in the modulation of uterine leiomyoma

Phytochemical class	Representative compounds	Bombacoideae source species	Putative role in the modulation of uterine leiomyoma
Flavonoids	Quercetin, Rutin, Catechins, Isovitetxin, Apigenin	<i>P. ellipticum</i> , <i>B. ceiba</i> , <i>P. marginatum</i> , <i>P. simplicifolium</i> ³⁵	Antagonism of ER/PR, inhibition of Wnt/ β -catenin, potent scavenging of ROS, reduction of ECM deposition ²
Triterpenoids	Lupeol, β -sitosterol, Stigmasterol, α -amyrin	<i>Pseudobombax</i> spp., <i>B. ceiba</i> ⁴²	Antiproliferative activity, inhibition of angiogenesis, induction of sub-G1 cell cycle arrest, reduction of hormone-induced hyperplasia ¹
Naphthoquinones	Isohemigossypolone, Aquatidial, Hibiscolactone A	<i>Pachira aquatica</i> , <i>B. ceiba</i> , <i>Varronia</i> spp. ³⁷	Cytotoxic induction, redox cycling leading to localised oxidative stress, ROS-mediated tumour apoptosis ⁵⁴
Phenolic acids	Gallic acid, Caffeic acid, Quinic acid	<i>P. ellipticum</i> , <i>P. simplicifolium</i> , <i>B. ceiba</i> ⁴³	Direct antioxidant defence, neutralisation of stress pathways, downregulation of NF- κ B inflammatory signalling ¹
Alkaloids	Lycorine-type derivatives (predicted)	Extrapolated from Bombacoideae, <i>B. ceiba</i> ¹	Interference in DNA synthesis, activation of proapoptotic caspases, modulation of PI3K/AKT survival pathways ¹

Source: prepared by the authors.

Flavonoids and phenolic compounds. The genus *Pseudobombax* stands out for its richness in polyphenolic compounds. HPLC-MS studies in *P. ellipticum* have identified multiple catechins, procyanidins, quercetin glycosides and organic acids such as malic and quinic acids.⁴⁴ These compounds present a recognised antioxidant activity, acting as modulators of the cellular redox balance.

In the context of uterine leiomyomas, where moderate levels of reactive oxygen species (ROS) favour cell proliferation and angiogenesis, the modulation of this balance by flavonoids could interfere with tumour progression and induce apoptosis mediated by oxidative stress.¹³ Likewise, the anti-inflammatory effects observed in related species such as *P. marginatum* and *P. ellipticum* have been associated with their high phenolic content, supporting their traditional use.³⁹

Triterpenoids. Lupeol, a pentacyclic triterpene widely distributed in the genus *Pseudobombax*, has been isolated in various species, including *P. simplicifolium*.¹ Likewise, phytosterols such as β -sitosterol and stigmasterol—common in *Bombacoideae*—have demonstrated antiproliferative activity in human uterine leiomyoma cells.⁴⁹

In vitro studies indicate that these compounds can reduce smooth muscle proliferation induced by hormonal stimuli, suggesting a possible modulatory effect on tumour growth.⁴⁹

Naphthoquinones. Naphthoquinones represent another relevant class of metabolites in *Bombacoideae*, with compounds such as isohemigossypolone and aquatidial described in *Pachira aquatica*.⁵¹ These molecules present cytotoxic activity through the generation of intracellular oxidative stress via redox cycles.⁵⁴

This mechanism can trigger apoptosis via the intrinsic pathway, which positions naphthoquinones as compounds of interest in the study of solid tumours and hyperproliferative processes.⁵⁴

3.2 METHODOLOGICAL CONSIDERATIONS FOR EXTRACTION AND CHARACTERISATION

The characterisation of the metabolome of *P. millei* requires the application of methodologies that allow the integrity of potentially thermolabile and oxidation-sensitive compounds to be preserved, as well as guaranteeing the representativeness of the extract obtained.

Processing of the plant material. Lyophilisation constitutes a suitable strategy for the conservation of secondary metabolites, since it allows the elimination of water by sublimation at low temperatures, minimising thermal and enzymatic degradation. This method is particularly relevant for phenolic compounds and flavonoids.¹

Hydroalcoholic extraction. The use of hydroalcoholic mixtures (for example, 70% ethanol) allows the simultaneous extraction of compounds with different degrees of polarity, including polyphenols, glycosides and triterpenoids.¹ This approach, moreover, is consistent with the traditional preparation methods employed in folk medicine.³⁹

Metabolomic analysis (HPLC–PDA–MS/MS). Given the absence of previous chemical profiles for *P. millei*, the use of untargeted analytical techniques is fundamental. Liquid chromatography coupled with tandem mass spectrometry (HPLC–MS/MS), together with photodiode array detection (PDA), constitutes a high-sensitivity tool for the tentative identification of metabolites in complex matrices.⁶⁰

The comparison of exact masses, fragmentation patterns and retention times with specialised databases (such as GNPS) makes it possible to construct a reliable preliminary phytochemical profile. This approach has demonstrated usefulness in the characterisation of related species within the genus *Pseudobombax*.⁴⁴

4 MOLECULAR MECHANISMS INVOLVED IN THE ACTION ON UTERINE LEIOMYOMAS

The metabolites act through the induction of apoptosis (Bax/Bcl-2, caspases), inhibition of hormonal signalling and regulation of fibrosis. These actions are key in the control of tumour growth.

4.1 RELEVANCE OF LEIOMYOMA CELL MODELS

The evaluation of the biological activity of phytochemical compounds requires the use of cell models that adequately reproduce the genetic and phenotypic characteristics of uterine leiomyomas.¹

Among the most used models, the following stand out:

ELT-3 line (Eker rat leiomyoma). The ELT-3 cell line (CVCL_4616) is derived from leiomyomas developed in Eker rats, carriers of a germline mutation in the tumour suppressor gene *Tsc2*.⁶⁶ These cells present a high sensitivity to steroid hormones, which makes them a suitable model to study oestrogen- and progesterone-dependent proliferation, as well as the response to antiproliferative agents.¹

UtLM line (human uterine leiomyoma). Due to the limited proliferative capacity of primary leiomyoma cells, the UtLM line (CVCL_9Z19) has been immortalised through the expression of human telomerase reverse transcriptase (hTERT).⁶⁷ This model preserves key molecular characteristics of the original tumour, including the expression of hormonal receptors, and constitutes a reference system for mechanistic studies in human cells.¹

On the basis of the previously described chemotaxonomic profile, it is proposed that the secondary metabolites of *P. millei* could modulate tumorigenesis in these models through multiple molecular axes.

4.2 INDUCTION OF APOPTOSIS AND REGULATION OF THE CELL CYCLE

A central characteristic of uterine leiomyomas is the evasion of apoptosis, associated with the overexpression of antiapoptotic proteins (such as Bcl-2 and Bcl-xL) and the decrease in proapoptotic factors such as Bax.¹

Various secondary metabolites—particularly flavonoids, alkaloids and naphthoquinones—have demonstrated the capacity to restore these apoptotic pathways:

Modulation of the Bax/Bcl-2 ratio. Flavonoids can decrease the expression of Bcl-2 and increase that of Bax, favouring the permeabilisation of the mitochondrial membrane and the release of cytochrome c into the cytosol.¹⁷⁰

Activation of the caspase cascade. The release of cytochrome c promotes the formation of the apoptosome and the activation of caspase-9, followed by the activation of effector caspases (caspase-3/7), leading to apoptosis.¹ Likewise, the activation of p53 reinforces this process by positively regulating the expression of Bax.⁷²

Regulation of the cell cycle. Compounds such as lupeol and other triterpenoids can interfere with the progression of the cell cycle through the inhibition of cyclin-dependent kinases (CDK) and the induction of inhibitors such as p21 and p27, generating arrest in the G0/G1 or G2/M phases.⁷⁹ This effect contributes to limiting the proliferation of leiomyoma cells.

4.3 MODULATION OF HORMONAL SIGNALLING AND SURVIVAL PATHWAYS

Leiomyomas are tumours highly dependent on oestrogen and progesterone signalling. The activation of oestrogen receptors (ER α , ER β) regulates the expression of progesterone receptors (PGR), enhancing cell proliferation through pathways such as PI3K/AKT/mTOR and MAPK/ERK.⁴

In this context, various flavonoids structurally similar to oestradiol (such as quercetin, kaempferol and genistein) act as selective oestrogen receptor modulators (SERM).² These compounds can bind to oestrogen receptors without inducing a complete transcriptional activation, exerting a functional antagonistic effect.

As a consequence, a decrease in the expression of PGR and an attenuation of the survival signalling pathways occurs, particularly the AKT pathway, which increases the susceptibility of tumour cells to apoptosis.¹³

4.4 INHIBITION OF FIBROSIS AND REMODELLING OF THE EXTRACELLULAR MATRIX

Leiomyomas are characterised by an excessive accumulation of extracellular matrix (ECM), especially type I collagen and fibronectin, which contributes to their stiffness and growth.¹⁰ This process is mediated to a large extent by the overexpression of transforming growth factor beta (TGF- β), especially the TGF- β 3 isoform.¹⁰

Mutations in the MED12 gene, present in a high percentage of fibroids, are associated with the activation of these profibrotic pathways.¹⁰

Various phytochemical compounds, particularly flavonoids and alkaloids, have demonstrated antifibrotic activity through the modulation of the TGF- β /Smad and Wnt/ β -catenin pathways.² These compounds can inhibit the expression of genes such as COL1A1 and fibronectin, as well as block the phosphorylation and nuclear translocation of Smad2/3.⁷⁷

Interference in these pathways not only reduces the deposition of extracellular matrix, but also alters the mechanotransduction signals that favour tumour proliferation, potentially contributing to the reduction of leiomyoma volume.¹⁰

5 THE GENOMIC CHALLENGE: PHYLOGENETIC INFERENCE IN PSEUDOBOMBAX MILLEI

Phylogenetic inference makes it possible to approximate the genetic basis of *P. millei*. The conservation of biosynthetic pathways such as that of flavonoids is highlighted. Although the inferred phytochemical profile and the proposed molecular mechanisms support a coherent pharmacological hypothesis, the elucidation of the biosynthetic bases in *Pseudobombax millei* faces a fundamental limitation: the absence of genomic and transcriptomic data available in public repositories.

In this context, the understanding of the biosynthetic capacity of this species depends on the use of comparative genomics and phylogenetic inference approaches, which allow functional information to be extrapolated from related species with characterised genomes.

5.1 PHYLOGENETIC FRAMEWORK AND SELECTION OF PROXY SPECIES

In the absence of a reference genome, it is necessary to employ phylogenetically close species as proxy models. Morphological and phylogenetic studies place the genus *Pseudobombax* within the "core Bombacoideae" clade, in close relationship with genera such as *Ceiba* and *Pachira*.¹

Molecular analyses based on conserved markers, such as *rbcL*, *matK* and the ITS region, have demonstrated a high genetic proximity between these taxa, which supports their use in comparative studies.⁸²

Among them, *Ceiba pentandra* stands out as a reference model, due to the availability of a fully sequenced and annotated genome (NCBI GCA_019963855.1). This resource makes it possible to infer the organisation of key biosynthetic pathways, such as those associated with phenylpropanoids and flavonoids, in *P. millei*.

5.2 IN SILICO INFERENCE OF THE FLAVONOID PATHWAY: FOCUS ON CHALCONE SYNTHASE (CHS)

Chalcone synthase (CHS; EC 2.3.1.74) is a key enzyme in the biosynthesis of flavonoids, by catalysing the formation of naringenin chalcone, the central precursor of multiple flavonoid subclasses.¹ Therefore, the identification of its corresponding gene constitutes an essential step to validate the biosynthetic capacity of a plant species.

In this study, a bioinformatic approach was implemented based on the exploration of the genome of *Ceiba pentandra* as a proxy system. Initially, homology searches at the nucleotide level were carried out using CHS reference sequences from different plant species. However, these analyses did not produce significant alignments, which suggests a high divergence at the sequence level.

Subsequently, the structural annotation of the genome was examined through the analysis of GFF files, identifying genes associated with phenylpropanoid pathways (such as PAL and WRKY-type transcription factors), but without explicit evidence of annotation for CHS.

Finally, protein-level search strategies (TBLASTN) were applied, taking advantage of the greater conservation of functional domains. Nevertheless, these analyses also did not allow a complete coding region corresponding to CHS to be conclusively identified in the reference genome.

5.3 EVOLUTIONARY IMPLICATIONS AND LIMITATIONS OF THE APPROACH

The absence of direct detection of the CHS gene in the proxy genome does not necessarily imply its functional absence. On the contrary, it reflects the structural and evolutionary complexity of the gene families involved in plant secondary metabolism.

The CHS gene family is known for its high plasticity, including events of gene duplication, structural reorganisation, pseudogenisation and variations in the intron-exon architecture.⁸² In the Malvaceae family, these processes can be accentuated by the activity of transposable elements, such as LTR-type retrotransposons, which influence the size and organisation of the genome.⁸²

In this context, it is plausible that the CHS genes in *P. millei* present a high sequence divergence, a fragmented organisation or epigenetic regulation mechanisms that hinder their identification through conventional bioinformatic tools.

Nevertheless, the indirect phytochemical evidence —particularly the presence of flavonoids in related species— supports the functionality of this biosynthetic pathway. Consequently, the definitive validation of these mechanisms will require the development of *de novo* transcriptomic studies (RNA-seq), ideally focused on metabolically active tissues such as the phloem.

6 CLINICAL AND THERAPEUTIC IMPLICATIONS

The derived compounds could contribute to the development of non-invasive therapies for uterine leiomyomas.

The evidence integrated in this chapter —which encompasses ethnopharmacology, chemotaxonomy and genomic inference— suggests that *Pseudobombax millei* constitutes a potentially relevant source of bioactive compounds with applicability in the management of uterine leiomyomas. The traditional use of "Beldaco" in inflammatory and gynaecological conditions provides an empirical foundation which, when reinterpreted under a biomolecular approach, acquires relevance in the context of contemporary pharmacological research.

The chemotaxonomic extrapolation based on the Bombacoideae subfamily, together with modern strategies of metabolomic characterisation, makes it possible to infer the presence of a diverse set of secondary metabolites, including flavonoids, triterpenoids such as lupeol and naphthoquinones. These compounds have been widely associated with antioxidant, anti-inflammatory and antiproliferative activities in various biological models.

From a mechanistic perspective, these metabolites could interfere with key processes in the pathogenesis of uterine leiomyomas. These include the modulation of oestrogen- and progesterone-dependent hormonal signalling, the regulation of cell survival pathways, the induction of apoptosis through the alteration of the Bax/Bcl-2 balance and the activation of caspases, as well as the inhibition of TGF- β -mediated fibrosis and the deposition of extracellular matrix.

These properties position *P. millei* as a potential candidate for the development of non-invasive therapies aimed at the control of tumour growth, particularly in patients in whom the preservation of fertility or the avoidance of surgical interventions is sought. Nevertheless, it is important to highlight that the available evidence is based mainly on theoretical inferences and data derived from related species, so its direct clinical application is not yet viable.

In this sense, the translation of these findings towards therapeutic applications requires the development of stepwise experimental studies, including in vitro assays in specific leiomyoma cell models, in vivo studies that evaluate efficacy and safety, and eventually controlled clinical trials. Likewise, it is fundamental to advance in the pharmacokinetic characterisation, the bioavailability and the toxicological profile of the active compounds.

Finally, the limited availability of genomic information for *P. millei* represents a challenge, but also an opportunity for future research. The implementation of transcriptomic (RNA-seq) and metabolomic studies will allow a more precise understanding of its biosynthetic pathways and will facilitate the identification of biomolecules with therapeutic potential. Taken together, these approaches could contribute to the development of new pharmacological strategies based on natural products, with applications in gynaecological medicine and benign oncology.

7 LIMITATIONS AND FUTURE PERSPECTIVES

Experimental studies are required to validate these findings and allow their clinical application.

Despite the integrative contributions presented in this chapter, there are important limitations that must be considered. In the first place, the available evidence is based predominantly on chemotaxonomic inferences, data from related species and in silico analyses, due to the absence of direct experimental studies in *Pseudobombax millei*. This limitation restricts the capacity to establish definitive conclusions about its biological efficacy and its clinical applicability.

Likewise, the lack of specific genomic and metabolomic information for the species hinders the precise characterisation of its biosynthetic pathways and the identification of active compounds responsible for the proposed effects. This knowledge gap highlights the need to generate primary data that validate the hypotheses raised.

In this context, future lines of research should be oriented towards experimental validation through in vitro studies using relevant cell models, such as the UtLM and ELT-3 lines. These studies would allow key parameters to be evaluated, including cytotoxicity, intracellular oxidative stress and the activation of apoptotic pathways, through techniques such as flow cytometry and protein expression analysis.

In a complementary manner, the development of untargeted metabolomic studies will be fundamental to identify and characterise the bioactive compounds present in the phloem

of *P. millei*. The integration of these approaches with molecular biology and bioinformatic tools will allow progress towards a more complete understanding of its therapeutic potential.

In the medium term, the generation of transcriptomic data (RNA-seq) and in vivo studies will contribute to validating the biological relevance of the findings and to establishing safety and efficacy profiles. These advances will be essential for an eventual translation towards clinical applications.

Finally, the study of *Pseudobombax millei* has not only biomedical implications, but also ecological and cultural ones. As a species classified as data deficient, its research and conservation acquire additional relevance, by integrating with strategies for the sustainable use of biodiversity. In this sense, the articulation between ethnobotanical knowledge, scientific research and environmental conservation represents an integral approach for the development of new therapeutic alternatives in the management of uterine leiomyomas.

8 CONCLUSIONS

Pseudobombax millei constitutes a promising resource in modern pharmacological research, by integrating ethnopharmacological evidence with chemotaxonomic and molecular foundations that support its antineoplastic potential against uterine leiomyomas.

The extrapolation of its phytochemical profile, together with the analysis of cellular mechanisms involved in proliferation, apoptosis and fibrosis, suggests that its secondary metabolites could modulate key processes in the pathogenesis of this disease.

Nevertheless, the absence of direct experimental validation and of specific genomic information limits its immediate clinical application, highlighting the need for in vitro and in vivo studies and omics approaches that allow its efficacy and safety to be confirmed.

Taken together, *P. millei* represents a promising candidate for the development of non-invasive therapies in gynaecology, while underlining the importance of the research and conservation of biodiversity as a source of biomedical innovation.

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INTEGRATIVE APPROACH IN THE REHABILITATION OF FLACCID TETRAPARESIS AFTER CERVICAL HERNIA: A CASE REPORT

ABORDAGEM INTEGRATIVA EM REABILITAÇÃO DE TETRAPARESIA FLÁCIDA APÓS HÉRNIA CERVICAL: RELATO DE CASO

ENFOQUE INTEGRADOR EN LA REHABILITACIÓN DE TETRAPARESIA FLÁCIDA DESPUÉS DE HERNIA CERVICAL: REPORTE DE CASO



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ABSTRACT

This report describes the integrative therapeutic approach applied to a five-year-old, 17.7 kg male beagle patient with cervical disc extrusion at C2-C3, which progressed to flaccid tetraparesis. After performing the ventral slot fenestration surgical technique, the patient presented with oedema around the surgical wound, intense pain, and a neurological condition characterised by tetraparesis and proprioceptive ataxia of the left thoracic and pelvic limbs, and was then referred to the rehabilitation service. Rehabilitation treatment associated with integrative techniques of Traditional Chinese Medicine (TCM) was instituted. The resolution of post-surgical complications occurred immediately, culminating in clinical discharge within a few weeks. The case demonstrates the effectiveness of integrative techniques in the neurological and functional recovery of patients with neurological injuries.

Keywords: Tetraparesis. Integrative Veterinary Medicine. Acupuncture. Veterinary Rehabilitation.

RESUMO

Este relato descreve a abordagem terapêutica integrativa aplicada a um paciente canino da raça beagle, macho, com cinco anos de idade e 17,7 kg, acometido por extrusão discal cervical em C2-C3, com evolução para tetraparesia flácida. Após a realização da técnica cirúrgica de slot ventral para fenestração, o paciente apresentava edema ao redor da ferida cirúrgica, dor intensa e quadro neurológico caracterizado por tetraparesia e ataxia proprioceptiva dos membros torácico e pélvico esquerdos, sendo então encaminhado ao serviço de reabilitação. Foi instituído tratamento em reabilitação associado a técnicas integrativas da Medicina Tradicional Chinesa (MTC). A resolução das complicações pós-cirúrgicas ocorreu de forma imediata, culminando na alta clínica em poucas semanas. O caso evidencia a eficácia das técnicas integrativas na recuperação neurológica e funcional de pacientes com lesões neurológicas.

Palavras-chave: Tetraparesia. Medicina Veterinária Integrativa. Acupuntura. Reabilitação Veterinária.

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RESUMEN

Este informe describe el abordaje terapéutico integrativo aplicado a un paciente canino de raza beagle, macho, de cinco años de edad y 17,7 kg, afectado por extrusión discal cervical en C2-C3, con evolución hacia tetraparesia flácida. Tras la realización de la técnica quirúrgica de slot ventral para fenestración, el paciente presentaba edema alrededor de la herida quirúrgica, dolor intenso y un cuadro neurológico caracterizado por tetraparesia y ataxia propioceptiva de los miembros torácico y pélvico izquierdos, siendo entonces remitido al servicio de rehabilitación. Se instauró tratamiento de rehabilitación asociado a técnicas integrativas de la Medicina Tradicional China (MTC). La resolución de las complicaciones posquirúrgicas ocurrió de forma inmediata, culminando con el alta clínica en pocas semanas. El caso evidencia la eficacia de las técnicas integrativas en la recuperación neurológica y funcional de pacientes con lesiones neurológicas.

Palabras clave: Tetraparesia. Medicina Veterinaria Integrativa. Acupuntura. Rehabilitación Veterinaria.

1 INTRODUCTION

Intervertebral disc disease (IVDD) is one of the most frequent neurological conditions in veterinary clinical practice, characterised by compression of the spinal canal resulting from extrusion or protrusion of disc material. These alterations are classified, respectively, as Hansen type I and Hansen type II, and may occur in ventral, dorsal or lateral directions. In addition to these, there is also the Hansen type III form, generally associated with traumatic lesions (Fernández; Bernardini, 2010; Ramalho *et al.*, 2015; Santos *et al.*, 2015; Santos *et al.*, 2021). According to Fernández; Bernardini (2010), type I herniations, or disc extrusions, result from a degenerative process of the nucleus pulposus, which may begin early, in animals between six and seven months of age. This process generally evolves asymptotically until the nucleus pulposus is progressively replaced by hyaline cartilage, with a consequent reduction in water content. As a result, extrusion of the disc material occurs through a dorsal or dorsolateral fissure in the annulus fibrosus (Fernández; Bernardini, 2010). The main risk factors include racial predisposition and age group, the disease being more common in chondrodystrophic breeds such as dachshund, lhasa apso, shih tzu, pekingese, beagle and basset hound, generally between three and six years of age (Padilha Filho; Selmi, 1999, Fernández; Bernardini, 2010, Cecim, 2019; Borges *et al.*, 2024).

Among cases of intervertebral disc disease (IVDD), approximately 14 to 16% correspond to cervical herniations, which most frequently affect the vertebral space between C2 and C3 (Padilha Filho; Selmi, 1999). In most cases, cervical extrusion occurs in the dorsal direction, manifesting through clinical signs such as ataxia, postural alterations associated with pain, paresis or paralysis of the limbs, and proprioceptive deficits (Padilha Filho; Selmi, 1999; Amorim *et al.*, 2024; Santos *et al.*, 2015). However, the herniation may also occur in the lateral or intraforaminal directions, presenting symptomatology distinct from that observed in the most common cases. In these situations, there may be weight-bearing lameness ipsilateral to the herniation, especially when there is compression of the peripheral nerve roots (Padilha Filho; Selmi, 1999). Clinical signs may appear acutely, evolving within minutes or days (Santos *et al.*, 2021).

The diagnosis is established based on the clinical history, the neurological examination and imaging examinations that allow differentiation of diseases capable of causing similar symptomatology. The main imaging examinations described in the literature are: radiography, myelography, magnetic resonance imaging (MRI) and computed tomography (CT) (Fernández; Bernardini, 2010; Santos *et al.*, 2015; Amorim *et al.*, 2024; Borges *et al.*, 2024). According to Fernández; Bernardini (2010), the radiographic study, plain or contrast-enhanced, frequently provides findings suggestive of spinal cord compression; however, in

these cases, the use of more advanced techniques becomes necessary. Among these, myelography makes it possible to confirm and locate extradural spinal cord compression, whether ventral, dorsoventral, lateralised or dorsal, in addition to identifying contiguous compressions. However, since it is an invasive technique that uses contrast medium, in situations of reduction of the subarachnoid space secondary to pathological processes that prevent the adequate distribution of the contrast, the exact location of the lesion may be impaired. For this reason, the use of more advanced techniques, such as computed tomography and, preferably, magnetic resonance imaging, proves to be more appropriate, as they are non-invasive methods capable of revealing both the disc material and possible haemorrhages. Additionally, performing computed tomography after myelography, while the contrast is still in the subarachnoid space, may improve diagnostic accuracy. It should also be noted that magnetic resonance imaging, in addition to identifying the extruded material and haemorrhages within the vertebral canal, allows the assessment of alterations in the state of the spinal cord, which generally manifest through morphological and signal changes in the examination.

The treatment of intervertebral disc disease may be conducted conservatively, through the use of anti-inflammatory medications, physiotherapy techniques and acupuncture, or, in more severe cases refractory to clinical treatment, through surgical intervention. The choice of surgical technique depends on the location of the lesion and the degree of involvement of the spinal canal (Borges *et al.*, 2024; Guidi *et al.*, 2021; Santos *et al.*, 2015).

In cervical herniations, the most commonly employed surgical techniques include the ventral slot or fenestration, dorsal laminectomy, hemilaminectomy, partial pediclectomy and mini-hemilaminectomy (Padilha Filho; Selmi, 1999; Cecim, 2019; Guidi *et al.*, 2021). In cases of thoracolumbar disc herniation, partial corpectomy is the procedure of choice (Guidi *et al.*, 2021). The choice of the neurosurgical procedure depends on the symptoms manifested. Dorsal fenestration is indicated in patients with pain only, being inadequate for the removal of disc material that invades the spinal cord and nerve roots, and may increase morbidity time in cervical disc disease. Hemilaminectomy and laminectomy, in turn, are indicated in cases showing signs of recurrent and chronic exacerbations of neck pain and especially in those with moderate to severe tetraparesis, being rarely indicated owing to numerous disadvantages (Seim III; Withrow, 1996). Currently, the most indicated technique in cervical extrusions is ventral decompression of the spinal cord through ventral slot neurosurgery, which removes part of the ventral portion of the vertebral body and the intervertebral disc, promoting the removal of the herniated material, minimal manipulation, rapid recovery, few

complications, rapid operative time and permanent relief of signs (Seim III; Withrow, 1996, Rocha, et.al., 2012; Campos, et.al, 2023).

Given that a favourable prognosis occurs in 96.2% of cases submitted to decompression techniques, compared with conservative treatment with rates of 72.8% (Olby, 2010), and that the ventral slot technique may evolve into adverse events in 9.9% of dogs (Rossmeisl, et. al., 2013).

Adequate functional recovery depends on the adoption of complementary strategies, such as physiotherapeutic rehabilitation and the use of integrative therapies. The present study describes a clinical case conducted under a multidisciplinary approach, highlighting the effects of Traditional Chinese Medicine (TCM) associated with modern physiotherapy techniques, aiming at the functional recovery and improvement of the patient's quality of life.

2 CASE REPORT

The clinical case of a canine patient is reported: a male beagle, 5 years old, weighing 17.7 kg, referred for rehabilitation care at a private clinic after corrective surgical treatment of cervical disc extrusion.

The clinical symptomatology began on the twenty-second of March 2025, with a painful condition accompanied by vocalisation, mild ventroflexion of the neck and no gait alterations. After being attended to, he was medicated with dipyrone, methadone and dexamethasone via the subcutaneous route. Laboratory examinations, cervical spine radiography and abdominal ultrasonography were requested, and evaluation and follow-up with a neurologist were required. The radiographic examination of the skull and cervical spine had the following suggestive diagnoses: skull radiography report — differential diagnosis for otitis; mild articular incongruity in the temporomandibular joint; discrete/incipient periodontal disease. And in the cervical spine radiography report — degenerative disease (mineralisation) of the intervertebral disc in the C2-C3 and C4-C5 spaces; secondary to muscular tension/contracture in the intervertebral spaces between C3-C4, C5-C6, C6-C7, C7-T1 and incipient degenerative process (osteoarthritis) in the vertebral bodies at C2-C3, as shown in Figures 1, 2 and 3.

Figure 1

SKULL — Radiographic images in laterolateral projection (right and left)



Source: radiovet.

Figure 2

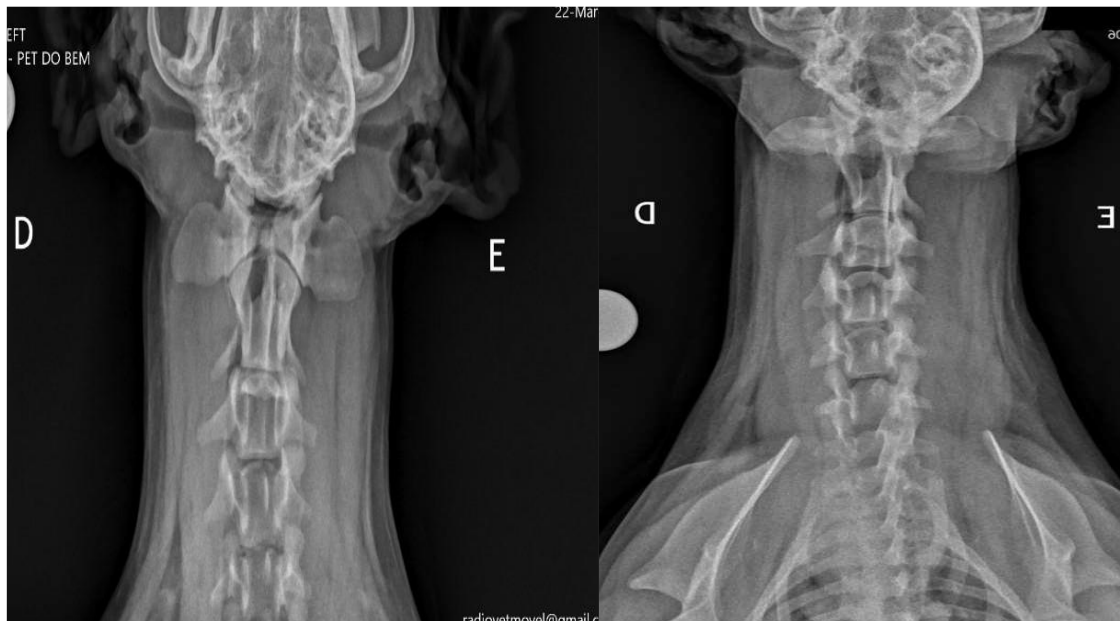
CERVICAL SPINE — Radiographic images in right laterolateral projections



Source: radiovet.

Figure 3

CERVICAL SPINE — Radiographic images in ventrodorsal projections

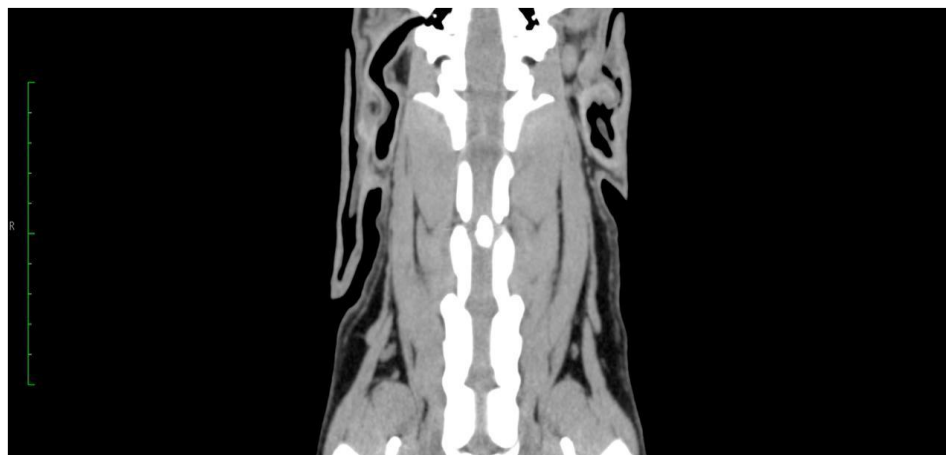


Source: radiovet.

On the twenty-eighth of March, the patient was evaluated by the neurologist, who requested computed tomography (CT) of the upper cervical region to elucidate the radiographic images. However, two days later, he presented clinical worsening with cervicalgia, cervical ventroflexion with deviation to the right, apathy, anorexia, recumbency sometimes lateral sometimes sternal, hyporexia and uncoordinated ambulation. In view of the condition, he was submitted to CT of the cervical spine, which revealed signs of extradural compressive myelopathy due to disc extrusion at C2-C3, as shown in Figures 4 and 5. The patient was immediately hospitalised for pain control and surgical treatment.

Figure 4

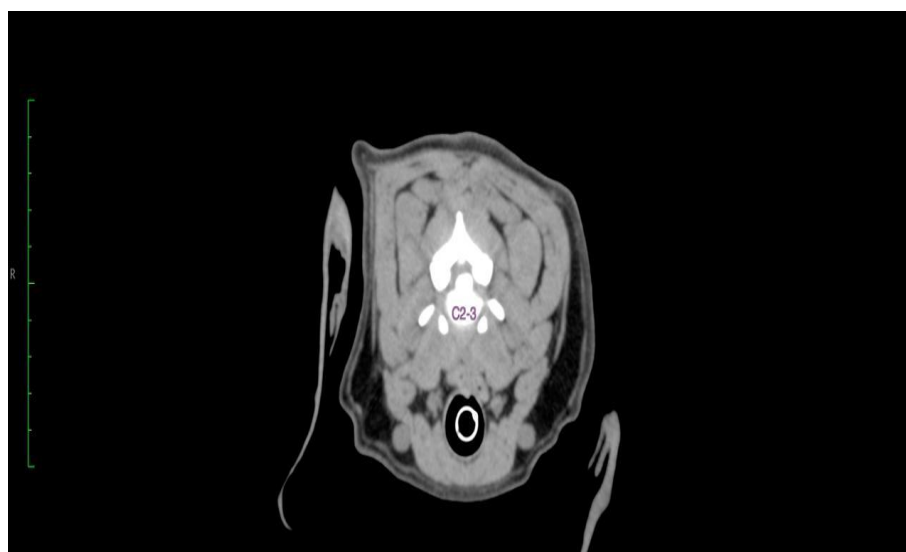
Computed tomography of the cervical spine with findings revealing signs of extradural compressive myelopathy due to disc extrusion at C2-C3



Source: centro Veterinário de Medicina Diagnostica e Especialidades – CORUS (2025).

Figure 5

Computed tomography of the cervical spine with findings revealing signs of extradural compressive myelopathy due to disc extrusion at C2-C3



Source: centro Veterinário de Medicina Diagnostica e Especialidades – CORUS (2025).

On the following day, he was submitted to the ventral slot fenestration technique and remained hospitalised for 8 days for the re-establishment of physiological parameters. During hospitalisation, he remained apathetic, changed recumbency on his own (lateral and ventral) and presented spontaneous feeding, receiving medication for pain control, as shown in Figure 6.

Figure 6

Post-surgical recovery: ventral slot decompression technique



Source: personal archive.

On the 9th of April, he underwent evaluation in rehabilitation. On examination, he presented a surgical incision in the ventral region of the neck in the process of healing, regional subcutaneous oedema, moderate analgesia, ventral/lateral recumbency, urinary retention, cutaneous hyperaesthesia, cervical deviation to the right side, loss of muscular support in all limbs (tetraparesis), withdrawal reflex and deep pain present in all limbs, panniculus reflex present, proprioception preserved in the right thoracic and pelvic limbs and diminished/absent in the left thoracic and pelvic limbs. Post-surgical treatment included pregabalin, analgesics and nutraceuticals.

After physiotherapeutic evaluation, the following integrative therapeutic modalities were instituted: laser therapy, magnetotherapy, Intravascular Laser Irradiation of Blood (ILIB), moxa therapy with the herb *Artemisia sinensis* of the Dragon brand, acupuncture and kinesiotherapy. In the integrative evaluation, the following dorsal alarm points were identified: B11, B12, B18, B19, B20, B21 and B22. The clinical history and the tongue analysis — thin, racquet-shaped, pinkish on the sides and purplish in the centre, thin and white coating, with fissures in the liver and spleen channel and a central fissure up to the tip — suggested, according to Traditional Chinese Medicine (TCM), stagnation of Qi and Xue, with Yin deficiency in the kidney and excess heat (Figure 7). At the end of the consultation, magnetotherapy was applied to reduce the local oedema, at a dose of 90 Gauss (G) and 25 Hertz (Hz), for 30 minutes. Two weekly sessions of physiotherapy and acupuncture were recommended, beginning on the eleventh of April 2025 (day 0).

Figure 7*Tongue evaluation*

Source: personal archive.

The session began with the application of the ILIB technique on the right femoral artery for 10 minutes, using an infrared light spectrum with an 808 nm/120 mW pen, followed by laser therapy using the red cluster (660 nm/450 mW) and infrared (808 nm/450 mW), totalling 900 mW, in continuous mode, with a dosage of 4 J, in the region of the intervertebral spaces of the upper cervical spine, the surgical scar and the adjacent musculature. Subsequently, the magnetotherapy solenoids were applied at an intensity of 90 G and a frequency of 70 Hz for 30 minutes in the same region. Home physiotherapy was indicated with the implementation of passive mobilisation, brushing of the pads and limbs for proprioceptive stimulation, adaptation of the floor and adjustment of the height of the feeder and water bowl. In the acupuncture session, the points needled were: Sishencong (4 horsemen), Baihui (GV20), Yintang, the extra points of the paws (Bafeng and Baxie), LI4, ST36, B39, B40, B18, B19, B20, B21, B22, B11 and B12, for 15 minutes. The acupuncture needles were of surgical steel with a silver handle, in the following dimensions: 0.25x15 mm and 0.25x30 mm.

On the fifteenth of April/25 (day 04), the patient returned with intense pain and muscular spasms in the cervical region, muscular weakness, remaining in right lateral recumbency. The magnetic field protocol was modified for acute pain (30 G, 5 Hz, 30 min) in the cervical and bilateral scapulohumeral region, maintaining ILIB and laser therapy. Subsequently, a new evaluation of the Mu points was performed; the acupoints B11, B20 and B22 still indicated energetic stagnation in relation to those observed in previous sessions. For

the first time, *Artemisia sinensis* moxa was applied by the indirect technique using a stick applicator, and subsequently the needling of the following points: Sishencong, Baihui, Yintang, Bafeng, Baxie, LI4, LI11, GB31, GB32, B11, B20 and B22. At the end, clinical improvement was observed, with the patient in sternal recumbency and trying to stand up, as shown in Figure 8.

Figure 8

Patient maintaining sternal recumbency during the acupuncture session



Source: personal archive.

On the twenty-second of April/25 (11th day), absence of cervicalgia was noted; proprioception of the right-side limbs was present, and on the left side it was still reduced. With assistance, he stood up and ambulated in an uncoordinated manner, remaining in the sphinx position (Figure 8). The previous protocols of laser therapy and MF were maintained, extending the photobiomodulation with infrared/red light to the lumbosacral spine, the suprascapular and infrascapular region, the coxofemoral region and the adjacent supporting musculature, as shown in Figures 9 and 10. Kinesiotherapy was started with a standing isometric exercise for 10 seconds, 3 repetitions. In the acupuncture, the needling of point B40 was added.

Figure 9

*Patient on the 11th day after surgery in a joint physiotherapy and acupuncture session.
Application of photobiomodulation*



Source: personal archive.

Figure 10

Physiotherapy session — application of the magnetic field in the cervical region



Source: personal archive.

On the twenty-fifth of April/25 (14th day), the guardian reported that the pet was already able to stand up on its own, remaining standing for a prolonged time and walking in an uncoordinated manner to the feeder and water bowl. The proprioception of the left side was still deficient. The treatment protocols were repeated: laser therapy, magnetotherapy, ILIB, moxa therapy and acupuncture, adding to the kinesiotherapy isometry with proprioception on

a Bosu with spikes on all four limbs (15 seconds, 4 repetitions) and isometry with weight-bearing on the ground (15 seconds, 4 repetitions).

On the twenty-ninth of April/25 (18th day), with clinical improvement, gain of muscular strength and progression of gait and proprioception on the left side, mainly in the right thoracic limb, the sessions became weekly. The magnetotherapy, ILIB and photobiomodulation (laser therapy) protocols had a reduction only in application time. In the acupuncture, new points were added to the previous ones: B37, B54, SP4, SP5, GB29, GB30 and GB31. In the kinesiotherapy, new exercises were introduced, such as a track with cones for slalom and cavaletti, a circuit with 3 repetitions (forth/back), isometric exercises on the balance board (Figure 11), on the Bosus with spikes and weight-bearing while lifting one limb at a time, all for 15–20 seconds, 4 repetitions.

Figure 11

Kinesiotherapy — isometry and supporting strength exercise on the balance board



Source: personal archive.

After twenty-five days (06/05/2025), totalling 5 sessions, the patient was already ambulating with mild lameness of the left pelvic limb, attempting to run and play with a ball, and was discharged from acupuncture. Two further weekly appointments were carried out — after thirty-three and thirty-nine days from the start of physiotherapy, only with the application of laser therapy and kinesiotherapy. As there was a return of proprioception, the patient

returned to playing, lifting the trunk and maintaining support on the pelvic limbs with the support of the owner. In addition, he began to take walks to urinate and defecate, being then integrated with contacting dogs for socialisation, and was discharged from physiotherapy.

3 DISCUSSION

The reported case confirms the high predisposition of chondrodystrophic breeds to intervertebral disc disease (Padilha Filho; Selmi, 1999, Amorim *et al.*, 2024, Santos *et al.*, 2015), given that the patient in question was a beagle. In addition, agreement is observed between the location and direction of the lesion — ventral and slightly to the left — in the upper cervical region (C2–C3) (Padilha Filho, Selmi, 1999).

However, when considering the neurological classification criteria described by Costa; Parent (2007), it is verified that the patient, initially classified as Grade I (cervical hyperaesthesia), evolved in the post-surgical period to Grade V, characterised by non-ambulatory tetraparesis, with more pronounced hemiparesis on the left side and loss of proprioception in these limbs. Such evolution indicates a significant neurological worsening in relation to the expected prognosis and to that described in the literature. Among the possible causes associated with complications arising from ventral decompression techniques, damage to the dorsal portion of the spinal cord and inadequate decompression stand out, with vertebral subluxation and consequent neurological deterioration possibly also occurring (Mccartney, 2007). According to Shamir; Chai; Loeb (2008), intervertebral luxations secondary to the procedure are more frequently observed in caudal cervical vertebrae than in upper cervical vertebrae, being attributed to post-surgical biomechanical factors or to manipulation of the region, which may lead to cervical laxity. Thus, the postoperative evolution observed in this case does not corroborate the resolution rates described in the literature, especially when comparing surgical treatment with conservative treatment. This is because recurrences and worsening of the clinical condition are more commonly associated with conservative management (Jeffery, 1995, p. 236; Sharp; Wheeler, 2005).

Despite the unfavourable prognosis in the immediate postoperative period, the patient presented positive clinical evolution and a satisfactory response to the integrative management instituted. In this context, the observed evolution proves to be compatible with findings previously described for thoracolumbar disc disease (TLDD), when compared with cervical disc disease (CDD) in terms of success rates and recovery time (Santos *et al.*, 2015; Janssens, 2004). It is noteworthy that the patient's recovery time was shorter than that described in the literature, with clinical resolution in less than eight weeks. The physiotherapeutic intervention associated with acupuncture in the postoperative period

demonstrated a determining role in the neuromotor recovery of the patient, contributing significantly to tissue healing, reduction of local oedema and modulation of pain.

Magnetic field (MF) therapy was fundamental for reducing oedema in the musculature and adjacent tissues after surgical manipulation, and had an adjuvant effect on the other therapies in accelerating tissue healing, nerve regeneration and analgesia. These effects corroborate those attributed by several authors (Sakata, 2018; Hummel; Vicente, 2019) to the use of MF for: promoting circulatory regulation by stimulating venous return; improving the trophism of the treated area; stimulating the myorelaxant effect in contracted areas; optimising collagen production; potentiating analgesia by reducing inflammation and regulating the membrane potential in sensory nerve fibres, which consequently raises the pain threshold; in addition to relaxation and sedation in a global manner, reducing stress and its consequences, by stimulating the release of norepinephrine and epinephrine, which helps to regulate the circadian sleep cycle and thus promote well-being. Hummel; Vicente (2019) describe doses of 50 Hz to induce improvement of local circulation and 75 Hz for tissue oedema of ischaemic lesions in scientific works gathered by them. In the patient in question, the dose was 25 Hz for 30 minutes, with a very significant reduction of oedema in a single application. As for the initial dose for analgesia, healing stimulus and spinal cord reinnervation, the dose was 90 G/70 Hz/30 minutes, and the other applications: 30 G/5 Hz/30 minutes. These authors (Hummel; Vicente, 2019) argue that in the practice of veterinary physiotherapy these doses differ, because we work with animals with pathologies that, for the most part, are not among those of experimental models. They also report that the application time in the acute phase and after herniation decompression should have a lower-intensity flow and not exceed 30 minutes, and they use two frequency variations on the same day. In the present report, I opted for a higher frequency and intensity than that reported by them in the first session and in the others I reduced to similar values, and I obtained good responses when used with other complementary techniques.

Phototherapy consists of the application of lasers and other light sources that emit electromagnetic waves onto the target tissues, being widely used in the control of pain, inflammation and in the stimulation of healing. It is a therapeutic modality disseminated worldwide from the 1970s and 1980s, although there are reports of the use of light for therapeutic purposes since Antiquity. Lasers are classified into classes ranging from I to IV, according to their emission potential and biological risk. In veterinary physiatry, the most used therapeutic lasers belong to classes IIIb and IV, emitting radiation at wavelengths within or near the spectrum of visible light. The wavelengths employed generally lie between 600 and 980 nanometres (nm). Power, in turn, is directly related to the speed of application of the

therapy and is expressed in milliwatts (mW) or watts (W). Class IIIb equipment has a maximum power of up to 500 mW, while class IV equipment generally ranges from 1 to 15 W, and the therapeutic dose is measured in joules (J) per cm² (Lopes; Diniz, 2018; Diniz, 2019).

Laser therapy was associated with the other therapeutic techniques owing to its biomodulation potential, acting on the regulation of biological processes through the interaction of photons with photosensitive cellular receptors. The enzymes of the respiratory chain and/or chromophores present in the cell membrane or in the mitochondria absorb the photons, triggering an increase in ATP production and a reduction in the levels of reactive oxygen species. These effects contribute to the normalisation of cellular function, acceleration of tissue regeneration, promotion of analgesia and modulation of the inflammatory process (Lopes; Diniz, 2018).

In this context, laser therapy exerts an integrated action on tissue repair by potentiating the proliferation of fibroblasts, activating macrophages and stimulating the release of growth factors. In addition, it promotes increased collagen deposition at the lesion site and improvement of local microcirculation. A reduction of the inflammatory infiltrate is also observed, associated with a decrease in the levels of C-reactive protein, inhibition of the synthesis of inflammatory prostaglandins and stimulation of lymphatic flow, as well as stabilisation of the cell membrane and induction of angiogenesis. Additionally, laser therapy contributes to analgesia through the release of endorphins, increased production of nitric oxide (NO) and stimulation of nerve regeneration, according to some literature (Lopes; Diniz 2018, Diniz, 2019, Hummel *et al.*, 2019).

The apparatus used for emitting the doses was the Eccovet Genesis model, with a dose of 4 J/cm² instituted in the report, being within the range indicated in the literature to obtain an analgesic effect and close to the range recommended for anti-inflammatory and cutaneous healing action (Diniz, 2019), although in the written literature there was no report for nerve tissue regeneration. However, Hummel; Vicente (2019), in the use of pulsed phototherapy with LEDs, found citations of doses of 2.5 J/cm² for anti-inflammatory action and 1–150 J/cm² for nerve injuries, both in the acute phase. It should be noted, however, that although this therapeutic modality presents a relevant analgesic effect — by reducing the conduction of type C nerve fibres associated with persistent pain (Kistemacher, 2017, Mikail; Pedro, 2009) — it did not constitute the only strategy employed in pain control, the association with other physiotherapeutic techniques and the maintenance of allopathic drug therapy being necessary. In this context, the inclusion of the techniques of moxibustion and dry-needling acupuncture proved to be indicated as a complementary strategy in the

management of the clinical condition. The two therapeutic methods have their bases founded on Traditional Chinese Medicine (TCM), which considers the concepts of Yin and Yang, of the five elements, of the eight principles, of the twelve meridians and of the vital substances (Luna, 2002; Schwartz, 2008).

Acupuncture has been indicated in Veterinary Medicine as a therapeutic resource for the treatment and control of pain, in addition to various neurological diseases, including vertebral traumas, intervertebral disc diseases and idiopathic Horner's syndrome (Luna, 2002; Hayashi *et al.*, 2007).

According to the principles of Traditional Chinese Medicine (TCM), the insertion of needles into specific anatomical points, called acupoints, promotes the circulation of the vital electromagnetic field (Qi) through the meridians, establishing communication between the organs. The imbalance of this energetic flow may manifest itself either through accumulation (Yang – hot, active) or through deficiency (Yin – cold, passive). The stimulation of the Yin and Yang acupoints makes it possible to restore the energetic balance (Draehmpael; Zohmann, 1997, p.254; Ulett, *et al.*, 1998; Lin, 2006; Povolny, 2008).

The identification of the treatment points occurred during the clinical evaluation, through the pressure of the acupoints (dorsal Shu – association points), the detection of areas of painful sensitivity and the evaluation of the tongue. According to Klide; Gaynor (2006), conditions of excess or deficiency of Qi or blood are directly related to the occurrence of pain. The diagnosis of pressure points (pain/sensitivity) suggests energetic disturbances; these generate a viscerocutaneous reflex that follows from the affected viscera, through the neurogenic pathway via the sympathetic chain, to the skin, muscles and blood vessels (Janssens, 2004). In this sense, the selection of points proximal or distal to the affected region constitutes one of the tools for the restoration of energetic balance and the normalisation of the cause of pain. As for the use of the acupuncture technique in patients with disc protrusions or herniations, Janssens (2004) reports that there is a diversity of existing protocols, and that all have similar success rates; however, the location of the lesion interferes with the success rates when the technique is the only method of pain control or treatment. Thus, in CDD compared with TLDD, the chance of success is 80% in patients with neck pain, and two-thirds of those with pain plus paresis are cured within 2 to 4 weeks. And when treated more frequently the results are more beneficial, especially when all the acupoints are stimulated in the neck region, this being of extreme importance in patients who suffer from pain even after surgery, as was the case reported for our patient.

The choice of applying moxibustion along the cervical spine, in the adjacent musculature and along the path of the meridians corresponding to the identified acupoints

was motivated by the therapeutic properties of *Artemisia vulgaris* and the effects of heat application. This plant presents anti-inflammatory and healing action (Yamamura, 2001), and there are also reports of improvement of the immune response, and that the technique may be used in both chronic and acute diseases (Myasava; de Alcântara, 2020). The heat generated by its burning assists in the dispersion of wind, cold and dampness, promotes the relaxation of muscles and tendons, warms and favours circulation in the main meridians and collateral channels, in addition to relieving pain caused by stagnation of Qi and Xue (Young, 2012). The cited property is related to the increase in the speed of energetic circulation in the channels, which consequently regularises the organic Fire, as a result of the potentiation of nutrition and the circulation of energy, and of the activity of the Zang Fu and the Curious Viscera (Yamamura, 2001). In the literature, arguments are observed for various techniques and mechanisms of action, and all are scientifically proven; however, the main factor, regardless of the technique, is the generation of heat and of infrared rays that diffuse into the organism to circulate Qi and Xue, thus regularising the physiological functions (Myasava; de Alcântara, 2020). Deng; Shen (2013) argue that the indication of moxa therapy goes beyond cold-deficiency conditions, and may also be employed in some cases of heat-excess, since it can reduce both deficiency and excess, contribute to the correction of imbalance and activate the self-regulation system of the point, promoting its harmonisation. The application of moxa requires two types of techniques: direct and indirect. In the direct one, it is applied immediately onto the skin, while in the indirect one it is performed through fumigation with smoke or vapour, by the use of heaters, boxes or 'thermies', direct application onto the acupuncture needles, suspended with sticks or *Artemisia* cigarettes, and on the walnut shell (Wilcox, 2008). In the patient of the report, the technique used was the indirect one, in which a portable copper heater was used carrying inside it a stick of *Artemisia sinensis* for acupuncture — Green of the Dragon brand. In China the technique transcends the Qin dynasty (221 BC to 206 BC) and uses *Artemisia vulgaris* (Scognamillo-Szabó; Bechara, 2010). In the patient, moxibustion demonstrated achievement of the expected effects even though *Artemisia sinensis* was used; I believe that because they are of the same genus, the properties reported by Xinnong (1999) are similar, such as the production of moderate heat through its Yang nature, and in the patient in question it was able to penetrate deeply into the muscles and eliminate the cold that caused the cervicalgia, since soon after the first session in which the technique was introduced, the animal's guardian reported almost immediate clinical improvement.

And finally, the technique of extravascular application of therapeutic Laser (modified ILIB), when applied to the femoral artery, provided an antioxidant effect, acting in the combat

of free radicals with an increase in the production of the enzyme Superoxide Dismutase (SOD). Other correlated actions are: increase of microcirculation, the supply of oxygen and nutrients; increase of immunity and efficiency of metabolism; improvement of oxygenation and stimulation of prostaglandin production, which acts by decreasing pain and in the release of the hormone serotonin, providing well-being to the patient (Momenzadeh, et.al; 2015).

4 FINAL CONSIDERATIONS

The integrative approach employed in veterinary rehabilitation proved to be effective in the functional recovery of a patient affected by flaccid tetraparesis and proprioceptive deficit. The case described highlights the relevance of interdisciplinary action and of the incorporation of complementary therapies into veterinary clinical practice, considering that significant clinical improvement was observed only after the implementation of the proposed therapeutic interventions and that discharge was achieved in a shorter time than that reported in the literature.

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EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON OBSTRUCTIVE SLEEP APNOEA IN PATIENTS WITH OBESITY

EFEITOS DOS AGONISTAS DE GLP-1 NA APNEIA OBSTRUTIVA DO SONO EM PACIENTES OBESOS

EFFECTS OF LOS AGONISTAS DEL RECEPTOR DE GLP-1 EN LA APNEA OBSTRUCTIVA DEL SUEÑO EN PACIENTES OBESOS



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ABSTRACT

Obstructive sleep apnoea (OSA) is a respiratory disorder characterised by recurrent episodes of upper airway obstruction during sleep, frequently associated with obesity and significant cardiovascular and metabolic consequences. In this context, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a promising therapeutic alternative owing to their effectiveness in promoting weight loss and improving cardiometabolic parameters. This study aimed to synthesise and critically analyse the scientific evidence regarding the effects of GLP-1 receptor agonists on obstructive sleep apnoea in patients with obesity. An integrative literature review was conducted using the PubMed/MEDLINE, Web of Science and ScienceDirect databases. Studies published between 2016 and 2025 addressing the effects of liraglutide, semaglutide and tirzepatide in individuals with obesity and OSA were included. After applying the eligibility criteria, 9 studies were selected for the final sample. The findings demonstrated that GLP-1 receptor agonists significantly reduced the apnoea-hypopnoea index, promoted body weight loss, improved oxygenation parameters and provided cardiometabolic benefits. Among the evaluated medications, tirzepatide showed the most robust results, particularly in the SURMOUNT-OSA studies. It is concluded that GLP-1 receptor agonists represent a promising therapeutic strategy for obese patients with obstructive sleep apnoea, contributing to disease severity reduction and improvement of associated metabolic outcomes. However, further studies are required to establish their definitive role in OSA treatment.

Keywords: Obstructive Sleep Apnoea. Obesity. GLP-1 Receptor Agonists. Liraglutide. Tirzepatide.

RESUMO

A apneia obstrutiva do sono (AOS) é um distúrbio respiratório caracterizado por episódios recorrentes de obstrução das vias aéreas superiores durante o sono, frequentemente associado à obesidade e a importantes repercussões cardiovasculares e metabólicas. Nesse contexto, os agonistas do receptor do peptídeo semelhante ao glucagon tipo 1 (GLP-1) têm emergido como uma alternativa terapêutica promissora devido à sua eficácia na promoção da perda ponderal e na melhora de parâmetros cardiometabólicos. O presente estudo teve como objetivo sintetizar e analisar criticamente as evidências científicas acerca dos efeitos dos agonistas do receptor de GLP-1 na apneia obstrutiva do sono em pacientes obesos. Trata-se de uma revisão integrativa da literatura, realizada por meio de buscas nas bases de dados PubMed/MEDLINE, Web of Science e ScienceDirect. Foram incluídos estudos publicados entre 2016 e 2025 que abordaram os efeitos da liraglutida, semaglutida e tirzepatida em indivíduos com obesidade e AOS. Após a aplicação dos critérios de elegibilidade, foram selecionados 9 estudos para compor a amostra final. Os resultados demonstraram que os agonistas do receptor de GLP-1 promoveram redução significativa do índice de apneia-hipopneia, perda de peso corporal, melhora dos parâmetros de oxigenação e benefícios cardiometabólicos. Entre os medicamentos avaliados, a tirzepatida apresentou os resultados mais expressivos, especialmente nos estudos SURMOUNT-OSA. Conclui-se que os agonistas do receptor de GLP-1 constituem uma estratégia terapêutica promissora para pacientes obesos com apneia obstrutiva do sono, contribuindo para a redução da gravidade da doença e para a melhora de desfechos metabólicos associados. Entretanto, novos estudos são necessários para consolidar seu papel no tratamento da AOS.

Palavras-chave: Apneia Obstrutiva do Sono. Obesidade. Agonistas do Receptor de GLP-1. Liraglutida. Tirzepatida.

RESUMEN

La apnea obstructiva del sueño (AOS) es un trastorno respiratorio caracterizado por episodios recorrentes de obstrucción de las vías aéreas superiores durante el sueño,

frecuentemente asociado a la obesidad y a importantes repercusiones cardiovasculares y metabólicas. En este contexto, los agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1) han emergido como una alternativa terapéutica prometedora debido a su eficacia en la promoción de la pérdida de peso y en la mejora de los parámetros cardiometabólicos. El presente estudio tuvo como objetivo sintetizar y analizar críticamente la evidencia científica sobre los efectos de los agonistas del receptor de GLP-1 en la apnea obstructiva del sueño en pacientes obesos. Se trata de una revisión integradora de la literatura, realizada mediante búsquedas en las bases de datos PubMed/MEDLINE, Web of Science y ScienceDirect. Se incluyeron estudios publicados entre 2016 y 2025 que abordaron los efectos de la liraglutida, semaglutida y tirzepatida en individuos con obesidad y AOS. Tras aplicar los criterios de elegibilidad, se seleccionaron 9 estudios para componer la muestra final. Los resultados demostraron que los agonistas del receptor de GLP-1 promovieron una reducción significativa del índice de apnea-hipopnea, pérdida de peso corporal, mejora de los parámetros de oxigenación y beneficios cardiometabólicos. Entre los medicamentos evaluados, la tirzepatida presentó los resultados más expresivos, especialmente en los estudios SURMOUNT-OSA. Se concluye que los agonistas del receptor de GLP-1 constituyen una estrategia terapéutica prometedora para pacientes obesos con apnea obstructiva del sueño, contribuyendo a la reducción de la gravedad de la enfermedad y a la mejora de los desenlaces metabólicos asociados. Sin embargo, son necesarios nuevos estudios para consolidar su papel en el tratamiento de la AOS.

Palabras clave: Apnea Obstructiva del Sueño. Obesidad. Agonistas del Receptor de GLP-1. Liraglutida. Tirzepatida.

1 INTRODUCTION

Obstructive sleep apnoea (OSA) is a respiratory disorder characterised by recurrent episodes of partial or complete obstruction of the upper airways during sleep, resulting in intermittent hypoxia, sleep fragmentation and significant systemic consequences. Recognised as a major worldwide public health problem, OSA is associated with an increased risk of cardiovascular, metabolic and cerebrovascular diseases, and it significantly compromises the quality of life and functionality of affected individuals. It is estimated that more than 900 million people present with some degree of the disease worldwide, of whom approximately 425 million have moderate to severe forms, highlighting its high epidemiological and clinical relevance (MALHOTRA *et al.*, 2024). Among the modifiable risk factors associated with the development and progression of the syndrome, obesity stands out as the main determinant, favouring anatomical and functional alterations capable of promoting collapse of the upper airways during sleep.

The association between obesity and OSA is widely documented in the scientific literature and has a bidirectional character. The excessive accumulation of adipose tissue, especially in the cervical and abdominal regions, contributes to the narrowing of the upper airways, alterations in respiratory mechanics and increased resistance to airflow, factors directly related to the worsening of the disease. Conversely, the sleep fragmentation and recurrent episodes of hypoxia observed in OSA trigger neuroendocrine and metabolic changes that favour weight gain, insulin resistance and systemic inflammation. In this way, a pathophysiological cycle is established capable of perpetuating both conditions and hindering their clinical management (BLACKMAN *et al.*, 2016; LI *et al.*, 2025).

Historically, the treatment of OSA has been based mainly on the use of continuous positive airway pressure (CPAP), considered the standard therapy for moderate and severe cases. Despite its effectiveness in reducing respiratory events during sleep, adherence to treatment is often unsatisfactory, limiting its long-term benefits. In this context, strategies aimed at reducing body weight have received increasing attention because they act directly on one of the main aetiological mechanisms of the disease. Clinical evidence demonstrates that weight loss is associated with a significant reduction in the apnoea-hypopnoea index (AHI), the main parameter used to measure the severity of OSA, in addition to promoting improvements in relevant cardiovascular and metabolic outcomes (BLACKMAN *et al.*, 2016; JIANG *et al.*, 2023).

Given the importance of weight reduction in the control of OSA, pharmacological therapies capable of promoting sustained weight loss have aroused increasing scientific interest. In this scenario, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged

as a relevant therapeutic alternative for the treatment of obesity. Drugs such as liraglutide, semaglutide and tirzepatide have demonstrated high efficacy in promoting weight loss, associated with improved glycaemic control, reduced blood pressure and decreased inflammatory markers. The studies of the STEP programme demonstrated clinically significant weight reductions in individuals with obesity treated with semaglutide, providing a solid scientific basis for investigating the potential indirect effects of these medications on OSA. In parallel, more recent research has demonstrated promising results of tirzepatide in patients with obesity and obstructive sleep apnoea, broadening the therapeutic perspectives for this population (WILDING *et al.*, 2021; MALHOTRA *et al.*, 2024).

The available evidence suggests that GLP-1 receptor agonists may contribute to reducing the severity of OSA through weight loss and the improvement of cardiometabolic parameters associated with the disease. Recent randomised clinical trials and quantitative syntheses have demonstrated significant reductions in the apnoea-hypopnoea index, body weight, hypoxic burden and cardiovascular risk factors in patients undergoing these therapies, with the results observed with liraglutide and tirzepatide standing out (BLACKMAN *et al.*, 2016; LI *et al.*, 2025; DUTTA *et al.*, 2025). Despite the advances observed in recent years, the evidence remains dispersed among clinical trials, observational studies and systematic reviews, making it necessary to critically consolidate the knowledge produced on the topic. Given this scenario, the present study aims to synthesise and critically analyse the available scientific evidence regarding the effects of GLP-1 receptor agonists on obstructive sleep apnoea in obese patients, evaluating their impact on disease severity, sleep respiratory parameters and associated anthropometric and cardiometabolic outcomes.

2 METHODOLOGY

This is an integrative literature review developed with the aim of synthesising and critically analysing the available scientific evidence regarding the effects of glucagon-like peptide-1 (GLP-1) receptor agonists on obstructive sleep apnoea (OSA) in obese patients.

The bibliographic search was carried out between June and July 2026 in the PubMed/MEDLINE, Web of Science and ScienceDirect databases, selected because of their broad coverage of scientific publications in the field of Health Sciences. To identify the studies, controlled descriptors and free terms related to the topic were used, combined through the Boolean operators AND and OR.

The search strategy was structured from the combination of the following terms:

("GLP-1 receptor agonist" OR "glucagon-like peptide-1 receptor agonist" OR liraglutide OR semaglutide OR tirzepatide) AND (obesity OR "obese patients") AND ("obstructive sleep apnea" OR "sleep apnea syndrome").

The inclusion criteria comprised original articles, randomised clinical trials, observational studies, systematic reviews and meta-analyses published between January 2016 and December 2025, available in full text in English, Portuguese or Spanish, and which addressed the effects of GLP-1 receptor agonists on obstructive sleep apnoea in individuals with obesity. Case reports, case series, editorials, letters to the editor, conference abstracts, experimental animal studies, duplicate publications and studies that had no direct relationship with the investigated topic were excluded.

The selection of studies was carried out in successive stages. Initially, the publications were identified in the selected databases. Subsequently, duplicate records were removed and the titles and abstracts were read to verify thematic relevance. Afterwards, the potentially eligible studies were submitted to full-text reading, and those that met the previously established criteria were included. At the end of the selection process, the sample was composed of nine studies considered relevant to answer the guiding question of this review.

Data extraction took place in a standardised manner, covering information regarding the authors, year of publication, methodological design, characteristics of the studied population, evaluated intervention, main analysed outcomes and the results found. To facilitate the organisation and interpretation of the findings, the studies were grouped according to the type of scientific evidence, including randomised clinical trials, phase III studies, systematic reviews and meta-analyses.

Data analysis was carried out through a qualitative, descriptive and comparative approach. The results were examined with regard to the effects of GLP-1 receptor agonists on the severity of obstructive sleep apnoea, especially in relation to the apnoea-hypopnoea index, oxygenation parameters, weight loss and associated cardiometabolic outcomes. Subsequently, the findings were organised into thematic categories, allowing the critical synthesis of the evidence and the identification of convergences and divergences among the included studies.

3 RESULTS

After applying the eligibility criteria, 9 studies were included in the final sample of this integrative review, published between 2016 and 2025. The selected works comprised randomised clinical trials, phase III studies, systematic reviews and meta-analyses, mainly addressing the GLP-1 receptor agonists liraglutide, semaglutide and tirzepatide. There was

a predominance of studies conducted in obese individuals with obstructive sleep apnoea (OSA), focusing on the assessment of the apnoea-hypopnoea index (AHI), anthropometric parameters and cardiometabolic outcomes (BLACKMAN *et al.*, 2016; MALHOTRA *et al.*, 2024).

The clinical studies demonstrated favourable effects of GLP-1 receptor agonists on the severity of OSA. In the SCALE Sleep Apnea study, patients treated with liraglutide showed a significantly greater reduction in AHI compared with the placebo group, accompanied by relevant weight loss and improvement in metabolic parameters (BLACKMAN *et al.*, 2016). Similarly, Jiang *et al.* (2023) observed a reduction in AHI, improvement in nocturnal oxygenation and a decrease in body mass index in patients with type 2 diabetes mellitus and severe OSA undergoing treatment with liraglutide.

The most expressive results were observed in the SURMOUNT-OSA studies, which evaluated tirzepatide in obese individuals with moderate to severe OSA. The treated participants showed substantial reductions in the apnoea-hypopnoea index, the sleep-related hypoxic burden and body weight, in addition to an improvement in cardiometabolic parameters, including a reduction in systolic blood pressure. These findings reinforce the therapeutic potential of tirzepatide in the management of OSA associated with obesity (MALHOTRA *et al.*, 2024).

The meta-analyses included in this review corroborated the results observed in the clinical trials. Li *et al.* (2025) identified a significant reduction in AHI, associated with weight loss and a decrease in blood pressure in patients treated with GLP-1 receptor agonists. Similarly, Dutta *et al.* (2025) demonstrated improvement in sleep respiratory parameters, reduction in body weight and a decrease in blood pressure levels, reinforcing the consistency of the benefits observed in the primary studies.

Although the studies of the STEP programme were not specifically developed to evaluate OSA, their results demonstrated clinically relevant and sustained weight loss with the use of semaglutide in individuals with obesity. These findings provide important pathophysiological support for the hypothesis that the reduction in body weight may contribute to the improvement in OSA severity, broadening the understanding of the role of GLP-1 receptor agonists in the treatment of obese patients (WILDING *et al.*, 2021).

4 DISCUSSION

The findings of this review indicate that GLP-1 receptor agonists represent a promising therapeutic strategy for the management of obstructive sleep apnoea in obese individuals. The studies analysed demonstrated consistent improvement in sleep respiratory parameters,

especially in the apnoea-hypopnoea index (AHI), accompanied by a significant reduction in body weight and cardiometabolic markers. These results suggest that the observed benefits arise mainly from the capacity of these drugs to promote sustained weight loss, considered one of the main determinants of OSA severity. The findings of the clinical trials with liraglutide were subsequently corroborated by systematic reviews and meta-analyses, which confirmed significant reductions in AHI and improvement in metabolic parameters in patients treated with GLP-1 receptor agonists (BLACKMAN *et al.*, 2016; JIANG *et al.*, 2023; LI *et al.*, 2025; DUTTA *et al.*, 2025).

The relationship between obesity and OSA constitutes one of the main pathophysiological foundations for the use of GLP-1 receptor agonists in this population. The accumulation of adipose tissue in the cervical and pharyngeal regions favours the narrowing of the upper airways and increases their collapsibility during sleep. Consequently, the reduction in body weight promoted by these medications may contribute to decreasing the frequency of obstructive respiratory events and to improving nocturnal oxygenation parameters. In this sense, both the SCALE Sleep Apnea study and the more recent studies with tirzepatide demonstrated an association between weight loss and improvement in respiratory outcomes, reinforcing the importance of weight control as a central component in the treatment of obesity-related OSA (BLACKMAN *et al.*, 2016; JIANG *et al.*, 2023; MALHOTRA *et al.*, 2024).

Among the drugs evaluated, tirzepatide showed the most robust results. The SURMOUNT-OSA studies revealed substantial reductions in the apnoea-hypopnoea index and the hypoxic burden, associated with weight losses greater than those observed in previous studies with liraglutide. These findings were reinforced by the meta-analysis conducted by Li *et al.* (2025), which demonstrated a greater reduction in AHI among patients treated with tirzepatide compared with those treated with liraglutide. Such a difference may be related to the dual pharmacological mechanism of tirzepatide, which combines agonism of the GLP-1 and GIP receptors, potentiating the effects on energy metabolism, glycaemic control and body weight loss. Thus, the available results suggest that tirzepatide may represent a particularly promising therapeutic alternative for obese patients with moderate to severe OSA (MALHOTRA *et al.*, 2024; LI *et al.*, 2025).

Another relevant aspect refers to the cardiometabolic benefits observed in the studies analysed. In addition to the reduction in body weight, improvements were described in glycaemic control, reduction in blood pressure and a decrease in cardiovascular risk markers. Considering that OSA is frequently associated with obesity, type 2 diabetes mellitus and systemic arterial hypertension, GLP-1 receptor agonists may offer a therapeutic approach

capable of acting simultaneously on multiple clinical conditions that frequently coexist in this population. This characteristic broadens the clinical potential of this pharmacological class and reinforces its relevance in the integrated management of patients with associated metabolic and respiratory diseases (BLACKMAN *et al.*, 2016; JIANG *et al.*, 2023; DUTTA *et al.*, 2025).

The studies of the STEP programme reinforce the hypothesis that weight loss constitutes one of the main mechanisms responsible for the improvement in obstructive sleep apnoea observed with GLP-1 receptor agonists. In the STEP 1 study, Wilding *et al.* (2021) demonstrated an average weight loss close to 15% in individuals with obesity treated with semaglutide, a result significantly higher than that observed in the placebo group. Similar findings were described by Wadden *et al.* (2021), in STEP 3, which revealed additional benefits when semaglutide was combined with intensive behavioural interventions. In addition, the STEP 4 and STEP 5 studies demonstrated the maintenance of weight loss in the medium and long term, highlighting the importance of therapeutic continuity for sustaining the results obtained (RUBINO *et al.*, 2021; GARVEY *et al.*, 2022). Although these studies did not directly evaluate sleep respiratory parameters, their results provide important pathophysiological support to explain the benefits observed in OSA, since the reduction in body weight is directly related to the decrease in disease severity (WILDING *et al.*, 2021; WADDEN *et al.*, 2021; RUBINO *et al.*, 2021; GARVEY *et al.*, 2022).

Despite the promising results, some limitations must be considered. The number of studies specifically aimed at evaluating OSA is still relatively small, and part of the available evidence derives from studies conducted in populations with obesity associated with other metabolic comorbidities. In addition, methodological differences related to study design, follow-up time and the outcomes evaluated hinder direct comparisons among the different GLP-1 receptor agonists. Additionally, most of the available studies focus on patients with moderate to severe obesity, limiting the extrapolation of the results to individuals without excess weight or with distinct clinical presentations of the disease. Thus, new randomised clinical trials with longer duration and larger samples are necessary to confirm the magnitude of the benefits observed and to establish the definitive role of these therapies in the treatment of obstructive sleep apnoea (LI *et al.*, 2025; DUTTA *et al.*, 2025; MALHOTRA *et al.*, 2024).

5 CONCLUSION

The results of this integrative review demonstrate that glucagon-like peptide-1 (GLP-1) receptor agonists present promising potential in the management of obstructive sleep apnoea in obese patients. The evidence analysed indicates that drugs such as liraglutide,

semaglutide and, especially, tirzepatide are associated with a reduction in disease severity, expressed by the decrease in the apnoea-hypopnoea index, in addition to promoting significant weight loss and improvement in relevant cardiometabolic parameters.

The included studies suggest that the observed benefits arise, to a large extent, from the sustained reduction in body weight, a factor directly related to the pathophysiology of obstructive sleep apnoea. In addition, the improvement in glycaemic control, blood pressure and other metabolic indicators reinforces the potential of these medications as a comprehensive therapeutic strategy for individuals presenting with obesity and associated comorbidities.

Among the agonists evaluated, tirzepatide stood out for the most expressive results in reducing sleep respiratory events and in promoting weight loss, revealing a promising perspective for the treatment of this population. However, although the available results are consistent, the number of studies specifically aimed at obstructive sleep apnoea is still limited, which demonstrates the need for new research with larger samples and longer follow-up periods.

Thus, it is concluded that GLP-1 receptor agonists represent a relevant therapeutic alternative for obese patients with obstructive sleep apnoea, contributing to the reduction of disease severity and to the improvement of associated metabolic outcomes. However, the consolidation of their role in the treatment of OSA will depend on the expansion of scientific evidence from randomised clinical trials and long-term studies.

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ARTIFICIAL INTELLIGENCE AND PREVENTIVE PHYSIOTHERAPY: TECHNOLOGICAL STRATEGIES FOR QUALITY OF LIFE AND HEALTH PROMOTION

**INTELIGÊNCIA ARTIFICIAL E FISIOTERAPIA PREVENTIVA: ESTRATÉGIAS
TECNOLÓGICAS PARA QUALIDADE DE VIDA E PROMOÇÃO DA SAÚDE**

**INTELIGENCIA ARTIFICIAL Y FISIOTERAPIA PREVENTIVA: ESTRATEGIAS
TECNOLÓGICAS PARA LA CALIDAD DE VIDA Y LA PROMOCIÓN DE LA
SALUD**



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ABSTRACT

Artificial intelligence has promoted significant transformations in health services, expanding the possibilities for prevention, monitoring and follow-up of individuals in different care contexts. Within the field of preventive physiotherapy, the incorporation of intelligent technologies has fostered the development of strategies aimed at the early identification of risk factors, continuous functional monitoring and the promotion of healthy habits, contributing to the improvement of quality of life and the strengthening of health promotion actions. The present study aimed to analyse the application of artificial intelligence in preventive physiotherapy, considering the use of technological strategies aimed at improving quality of life and strengthening health promotion actions in different clinical and preventive contexts. Methodologically, the research was characterised as qualitative and used a literature review as its investigative procedure. The analysis was grounded in 24 scientific sources, comprising books and articles published in specialised journals, selected according to their relevance for understanding the relationships between artificial intelligence, preventive physiotherapy, quality of life and health promotion. The results of this research demonstrated that artificial intelligence has contributed significantly to strengthening preventive physiotherapy through the use of technological strategies aimed at functional monitoring, human movement analysis, personalisation of interventions and continuous follow-up of individuals. It was found that these tools foster the prevention of dysfunctions, the improvement of functionality, health promotion and quality of life, in addition to expanding the possibilities for health education and the encouragement of healthy habits. It is concluded that the integration between artificial

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intelligence and preventive physiotherapy represents an important perspective for the development of more efficient, accessible and prevention-oriented care practices.

Keywords: Artificial Intelligence. Preventive Physiotherapy. Quality of Life. Health Promotion.

RESUMO

A inteligência artificial tem promovido transformações significativas nos serviços de saúde, ampliando as possibilidades de prevenção, monitoramento e acompanhamento dos indivíduos em diferentes contextos assistenciais. No âmbito da fisioterapia preventiva, a incorporação de tecnologias inteligentes tem favorecido o desenvolvimento de estratégias voltadas à identificação precoce de fatores de risco, ao acompanhamento funcional contínuo e à promoção de hábitos saudáveis, contribuindo para a melhoria da qualidade de vida e para o fortalecimento das ações de promoção da saúde. O presente estudo teve como objetivo analisar a aplicação da inteligência artificial na fisioterapia preventiva, considerando o uso de estratégias tecnológicas voltadas à melhoria da qualidade de vida e ao fortalecimento das ações de promoção da saúde em diferentes contextos clínicos e preventivos. Metodologicamente, a pesquisa caracterizou-se como qualitativa e utilizou a revisão bibliográfica como procedimento de investigação. A análise foi fundamentada em 24 fontes científicas, constituídas por livros e artigos publicados em periódicos especializados, selecionados em função de sua relevância para a compreensão das relações entre inteligência artificial, fisioterapia preventiva, qualidade de vida e promoção da saúde. Os resultados desta pesquisa evidenciaram que a inteligência artificial tem contribuído significativamente para o fortalecimento da fisioterapia preventiva por meio da utilização de estratégias tecnológicas voltadas ao monitoramento funcional, à análise do movimento humano, à personalização das intervenções e ao acompanhamento contínuo dos indivíduos. Constatou-se que essas ferramentas favorecem a prevenção de disfunções, a melhoria da funcionalidade, a promoção da saúde e a qualidade de vida, além de ampliarem as possibilidades de educação em saúde e incentivo à adoção de hábitos saudáveis. Conclui-se que a integração entre inteligência artificial e fisioterapia preventiva representa uma importante perspectiva para o desenvolvimento de práticas assistenciais mais eficientes, acessíveis e orientadas à prevenção.

Palavras-chave: Inteligência Artificial. Fisioterapia Preventiva. Qualidade de Vida. Promoção da Saúde.

RESUMEN

La inteligencia artificial ha promovido transformaciones significativas en los servicios de salud, ampliando las posibilidades de prevención, monitorización y seguimiento de los individuos en diferentes contextos asistenciales. En el ámbito de la fisioterapia preventiva, la incorporación de tecnologías inteligentes ha favorecido el desarrollo de estrategias orientadas a la identificación precoz de factores de riesgo, al seguimiento funcional continuo y a la promoción de hábitos saludables, contribuyendo a la mejora de la calidad de vida y al fortalecimiento de las acciones de promoción de la salud. El presente estudio tuvo como objetivo analizar la aplicación de la inteligencia artificial en la fisioterapia preventiva, considerando el uso de estrategias tecnológicas orientadas a la mejora de la calidad de vida y al fortalecimiento de las acciones de promoción de la salud en diferentes contextos clínicos y preventivos. Metodológicamente, la investigación se caracterizó como cualitativa y utilizó la revisión bibliográfica como procedimiento de investigación. El análisis se fundamentó en 24 fuentes científicas, constituidas por libros y artículos publicados en revistas especializadas, seleccionados en función de su relevancia para la comprensión de las relaciones entre inteligencia artificial, fisioterapia preventiva, calidad de vida y promoción de la salud. Los resultados de esta investigación evidenciaron que la inteligencia artificial ha

contribuido significativamente al fortalecimiento de la fisioterapia preventiva mediante la utilización de estrategias tecnológicas orientadas a la monitorización funcional, al análisis del movimiento humano, a la personalización de las intervenciones y al seguimiento continuo de los individuos. Se constató que estas herramientas favorecen la prevención de disfunciones, la mejora de la funcionalidad, la promoción de la salud y la calidad de vida, además de ampliar las posibilidades de educación en salud y de incentivo a la adopción de hábitos saludables. Se concluye que la integración entre inteligencia artificial y fisioterapia preventiva representa una importante perspectiva para el desarrollo de prácticas asistenciales más eficientes, accesibles y orientadas a la prevención.

Palabras clave: Inteligencia Artificial. Fisioterapia Preventiva. Calidad de Vida. Promoción de la Salud.

1 INTRODUCTION

The advancement of digital technologies has promoted significant changes in the different fields of health, expanding the possibilities for the prevention, monitoring and follow-up of individuals in distinct clinical conditions. In this context, artificial intelligence (AI) stands out as one of the most relevant innovations of our time, owing to its capacity to process large volumes of data, identify complex patterns and generate information that supports professional decision-making. Its application has been progressively expanding into areas such as diagnosis, health service management, remote monitoring and the development of preventive strategies, contributing to the construction of more efficient and evidence-oriented care models.

Within the field of preventive physiotherapy, the use of artificial intelligence has favoured the incorporation of technological resources aimed at the early identification of risk factors, the continuous monitoring of functionality and the promotion of habits related to health and body movement. Tools such as body sensors, wearable devices, movement analysis systems and machine learning algorithms make it possible to obtain detailed information about the functional performance of individuals, expanding the capacity to develop more personalised preventive interventions. In this way, the integration between artificial intelligence and physiotherapy has contributed to the improvement of quality of life, the reduction of functional limitations and the strengthening of health promotion actions across different population groups.

In view of this scenario, the present study has as its general objective to analyse the application of artificial intelligence in preventive physiotherapy, considering the use of technological strategies aimed at improving quality of life and strengthening health promotion actions in different clinical and preventive contexts. To achieve this purpose, the following specific objectives were established: to investigate the technological strategies based on artificial intelligence applied to preventive physiotherapy, with emphasis on monitoring systems, movement analysis and support for clinical decision-making; to evaluate the contributions of artificial intelligence to the improvement of quality of life of individuals undergoing preventive physiotherapy programmes, considering functional, motor and physical well-being aspects; and to analyse the role of artificial intelligence in health promotion through the development of preventive practices, continuous follow-up and the encouragement of healthy habits across different population groups.

Regarding methodological aspects, the research was developed from a qualitative approach, associated with the literature review research procedure. This choice made it possible to analyse and critically interpret scientific productions related to artificial

intelligence, preventive physiotherapy, quality of life and health promotion, allowing the construction of a discussion grounded in the evidence available in the specialised literature.

To meet the proposed objectives, the article was organised into four main sections. The first corresponds to the Introduction, in which the theme, the contextualisation of the research, the objectives and the methodological aspects are presented. The second section comprises the Methodology, describing the procedures adopted to carry out the study. The third section presents the Theoretical Background, responsible for discussing the main concepts, applications and contributions of artificial intelligence in the context of preventive physiotherapy. Finally, the fourth section gathers the Final Considerations, in which the main results of the investigation and their implications for the field of study are synthesised.

2 METHODOLOGY

The present research was developed from the understanding that artificial intelligence has occupied an increasing space in the processes of prevention, functional monitoring and health promotion within the field of contemporary physiotherapy. The advancement of digital technologies, associated with the need to expand the efficiency of preventive actions, has driven the incorporation of intelligent resources capable of assisting in the early identification of risks, the continuous follow-up of individuals and the adoption of strategies aimed at improving quality of life. In view of this context, investigating the relationships between artificial intelligence and preventive physiotherapy becomes relevant to scientific production, since it makes it possible to gather evidence on technological applications that have been transforming care practices and strengthening approaches centred on health promotion and the maintenance of functionality.

Regarding the methodological approach, this study is characterised as qualitative research. This type of investigation seeks to understand phenomena through the interpretation of meanings, relationships, contexts and theoretical productions, favouring more comprehensive analyses of complex objects of study (Baptista & Campos, 2013; Pereira *et al.*, 2018). In the international scientific scenario, the qualitative approach plays a relevant role by allowing an in-depth understanding of social, technological and scientific phenomena that cannot be fully explained by numerical indicators. In addition, it contributes to the construction of contextualised knowledge and to the critical interpretation of evidence available in the literature, especially in areas marked by constant transformations, such as those related to health and digital technologies (Mattar, 2017).

With respect to the technical procedures, the literature review was employed as an investigative strategy. This procedure consists of the identification, selection, analysis and

interpretation of previously published scientific productions, allowing the researcher to become acquainted with the state of knowledge about a given theme, to identify theoretical convergences and divergences and to construct consistent foundations for the discussion of results (Pereira *et al.*, 2018). In the context of worldwide scientific research, the literature review constitutes one of the most widely used procedures for the systematisation of accumulated knowledge, contributing to the critical organisation of the available evidence and to the development of new scientific reflections (Baptista & Campos, 2013; Mattar, 2017). For the conduct of this study, the literature review was grounded in the analysis of 24 scientific research sources, comprising books and articles published in scientific journals related to artificial intelligence, preventive physiotherapy, health promotion and quality of life.

The combination between the qualitative approach and the literature review procedure proved to be adequate to the objectives proposed in this investigation. This methodological choice made it possible to examine systematically the contributions of artificial intelligence to preventive physiotherapy, enabling the critical analysis of different theoretical perspectives and scientific evidence available in the specialised literature. In addition, the articulation between qualitative interpretation and bibliographic survey favoured a comprehensive understanding of the technological applications aimed at health promotion, functional monitoring and the improvement of quality of life, offering consistent bases for the discussion of the theme and for the achievement of the objectives established in this research.

3 THEORETICAL BACKGROUND

The theoretical background was structured into three complementary thematic axes, organised so as to encompass the main aspects related to the application of artificial intelligence in preventive physiotherapy. Initially, topic 3.1 Technological Strategies Based on Artificial Intelligence in Preventive Physiotherapy addresses the technological resources used in physiotherapeutic practice, with emphasis on body sensors, wearable devices, biomechanical analysis software, functional monitoring systems and tools based on machine learning. Subsequently, topic 3.2 Artificial Intelligence, Functionality and Quality of Life in Preventive Physiotherapy Programmes discusses the contributions of these technologies to the improvement of mobility, functionality and physical well-being, considering their influence on the prevention of functional limitations and on the promotion of quality of life. Finally, topic 3.3 Artificial Intelligence and Health Promotion: Preventive Perspectives in Contemporary Physiotherapy examines the role of artificial intelligence in the development of preventive actions, health education, remote monitoring and the encouragement of healthy habits related to body movement and functional health. This thematic organisation allowed for a

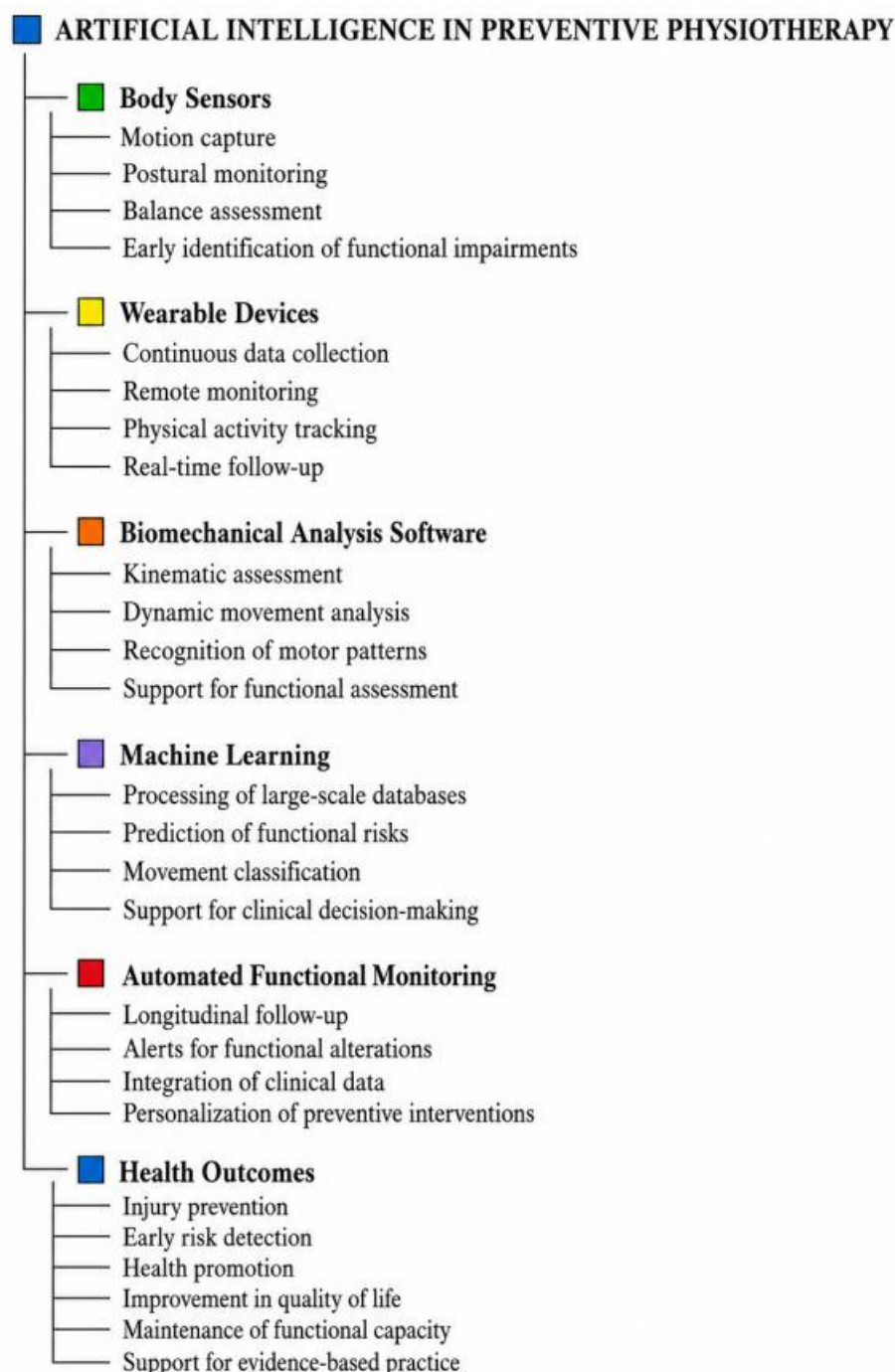
progressive and articulated analysis of the object of study, favouring an understanding of the multiple interfaces between artificial intelligence, preventive physiotherapy, quality of life and health promotion.

3.1 TECHNOLOGICAL STRATEGIES BASED ON ARTIFICIAL INTELLIGENCE IN PREVENTIVE PHYSIOTHERAPY

The incorporation of artificial intelligence (AI) into preventive physiotherapy has promoted significant changes in the way risk factors are identified, monitored and followed up over time. Unlike traditional assessment models, which frequently depend on isolated observations carried out in the clinical environment, intelligent systems allow the continuous collection of information related to the functional performance of individuals. In this context, body sensors, digital platforms and data processing algorithms expand the capacity to track early changes in movement patterns, favouring more timely and individualised preventive interventions. As highlighted by Toledo (2024), the integration between advanced computational resources and physiotherapeutic practice has expanded the possibilities for health monitoring, contributing to actions directed at the maintenance of functionality and quality of life.

Among the main technological strategies used in preventive physiotherapy, wearable devices, also known as wearables, stand out. These devices make it possible to continuously record variables related to mobility, posture, balance, physical activity and biomechanical parameters during the daily activities of individuals. From the analysis of these data, it becomes possible to identify patterns associated with the emergence of musculoskeletal dysfunctions or with the increased risk of injuries. According to Corrêa *et al.* (2023), intelligent devices represent one of the most promising applications of AI in physiotherapy, since they allow remote monitoring and the acquisition of real-time information, favouring preventive strategies grounded in objective evidence.

With the purpose of synthesising the main technological components discussed in this section and their respective contributions to preventive physiotherapy, Figure 1 presents a concept map that relates the strategies based on artificial intelligence, the technological resources employed and the expected results in terms of functional monitoring, prevention of disorders, health promotion and quality of life.

Figure 1**Technological Strategies Based on Artificial Intelligence in Preventive Physiotherapy**

Source: prepared by the author based on Reis *et al.* (2024), Toledo (2024), Mendes Neto *et al.* (2023), Lins *et al.* (2024), Corrêa *et al.* (2023) and Alsobhi *et al.* (2022).

Another widely used resource corresponds to biomechanical analysis software associated with machine learning algorithms. These tools are capable of processing large volumes of data related to the kinematics and dynamics of human movement, identifying patterns that are often imperceptible during conventional assessments. According to Reis *et al.* (2024), machine learning methods have been employed for movement classification, prediction of functional risks and support for clinical decision-making in different contexts of

physiotherapy. This analytical capacity contributes to the early recognition of motor alterations and to the elaboration of preventive programmes more compatible with the individual characteristics of each patient.

The advances observed in the field of digital rehabilitation also demonstrate the growing use of automated functional monitoring systems. These platforms combine sensors, clinical databases and computational models capable of following the evolution of physical performance in a continuous manner. Mendes Neto *et al.* (2023) highlight that artificial intelligence makes it possible to automate assessment and therapeutic follow-up processes, reducing limitations associated with exclusively in-person observation. As a result, professionals are able to access updated information that assists in the identification of functional trends and in the adoption of preventive measures before more significant alterations become established.

The application of these technologies has also been observed in specific populations that require constant monitoring. Lins *et al.* (2024), when discussing the use of AI in paediatric physiotherapy aimed at rare diseases, demonstrate that intelligent systems can contribute to functional assessment, longitudinal follow-up and the personalisation of interventions. Although the focus of the study is directed at the paediatric population, the results highlight possibilities for use in different preventive scenarios, especially in the identification of subtle changes in motor performance and in the elaboration of strategies aimed at the preservation of functionality throughout the life cycle.

Despite the technological advances observed, the implementation of artificial intelligence in preventive physiotherapy still faces challenges related to technological infrastructure, professional training, data security and the integration of these tools into everyday clinical practice. Alsobhi *et al.* (2022) identified that factors such as adequate training of professionals, the quality of the data collected and the acceptance of technologies by users directly influence the adoption of these solutions. Nevertheless, the literature demonstrates that the combination of intelligent sensors, wearable devices, biomechanical analysis software, machine learning and automated monitoring systems constitutes a set of strategies capable of strengthening preventive actions, expanding the efficiency of functional follow-up and favouring initiatives aimed at health promotion and the improvement of quality of life.

3.2 ARTIFICIAL INTELLIGENCE, FUNCTIONALITY AND QUALITY OF LIFE IN PREVENTIVE PHYSIOTHERAPY PROGRAMMES

The growing incorporation of artificial intelligence (AI) into preventive physiotherapy programmes has expanded the possibilities for functional monitoring and individualised follow-up of patients. This transformation occurs mainly through the capacity of intelligent systems to process large volumes of clinical, behavioural and biomechanical data, allowing a more precise understanding of the functional conditions of individuals over time. In this scenario, AI contributes to the early identification of alterations that may compromise mobility and functional independence, favouring more targeted preventive interventions. According to Battistella (2025), the use of technologies based on artificial intelligence represents one of the most relevant advances in contemporary healthcare, especially owing to its contribution to the preservation of functionality and to the promotion of better living conditions.

The relationship between artificial intelligence and quality of life is directly associated with the capacity of these tools to support continuous assessments and more well-grounded clinical decisions. Intelligent systems are able to integrate information from examinations, functional assessments and follow-up records, offering support for the elaboration of conducts compatible with the needs of each individual. Toledo (2024) highlights that the use of AI in physiotherapy favours the optimisation of care processes, expanding the precision of analyses and strengthening strategies aimed at the maintenance of physical and functional health. As a consequence, a greater capacity for the prevention of disorders that could compromise the participation of individuals in their daily activities is observed.

Another relevant aspect refers to the improvement of mobility and the control of functional limitations. Tools based on intelligent algorithms make it possible to identify movement patterns associated with motor deficits, biomechanical compensations and future risks of functional impairment. According to Nunes (2024), the application of artificial intelligence in physiotherapy has contributed to making diagnostic processes more sensitive to the particularities of each patient, favouring earlier interventions. In preventive programmes, this analytical capacity enables the adoption of measures aimed at the preservation of mobility and the reduction of factors that may negatively interfere with functional performance.

The personalisation of interventions constitutes another relevant contribution of AI to preventive physiotherapy programmes. Through the continuous analysis of the data collected during clinical follow-up, algorithms can assist in the adaptation of exercises, therapeutic goals and monitoring strategies according to the functional evolution observed. Ribeiro (2024) emphasises that the use of algorithms aimed at the personalisation of treatments has

favoured approaches more compatible with the individual characteristics of patients, contributing to better results related to functionality and physical well-being. This process makes follow-up more dynamic and allows frequent adjustments based on evidence generated during clinical practice itself.

The prevention of musculoskeletal dysfunctions also benefits from the use of intelligent resources. Movement analysis systems, digital follow-up platforms and clinical support tools are able to identify biomechanical alterations which, when not recognised early, may favour the development of painful conditions, functional limitations and absence from habitual activities. Heck (2025) argues that clinical assistants based on artificial intelligence have been expanding the capacity of physiotherapists to interpret complex information and transform data into support for preventive decisions. In this way, technology comes to act as a complementary resource in the identification of risks and in the planning of strategies aimed at the maintenance of musculoskeletal health.

In order to synthesise the main contributions of artificial intelligence to functionality, mobility, the prevention of musculoskeletal dysfunctions and quality of life in preventive physiotherapy programmes, Table 1 presents an organisation of the benefits observed in the literature and their respective applications in the physiotherapeutic context. It is recommended that the table be inserted after the fourth paragraph of this section, immediately before the discussion on the prevention of musculoskeletal dysfunctions.

Table 1

Contributions of Artificial Intelligence to Functionality and Quality of Life in Preventive Physiotherapy Programmes

Dimension Assessed	Application of Artificial Intelligence	Contributions to Preventive Physiotherapy
Functionality	Continuous monitoring by intelligent systems	Early identification of functional alterations
Mobility	Automated analysis of movement patterns	Improvement of motor performance and prevention of limitations
Clinical Assessment	Integration of clinical and functional data	Greater precision in physiotherapeutic follow-up
Therapeutic Personalisation	Conduct adaptation algorithms	Individualised adjustments of exercises and interventions
Musculoskeletal Prevention	Detection of biomechanical risks	Reduction of the probability of injuries and dysfunctions
Physical Well-being	Longitudinal follow-up of patients	Maintenance of functional independence
Health Promotion	Remote monitoring and clinical decision support	Strengthening of preventive actions

Quality of Life	Earlier and more targeted interventions	Preservation of autonomy and social participation
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Source: prepared by the author based on Battistella (2025), Toledo (2024), Nunes (2024), Ribeiro (2024), Heck (2025) and Fernandes (2025).

Considering the different contributions of artificial intelligence to functionality and quality of life in preventive physiotherapy programmes, it is observed that these technologies exert influence on multiple dimensions of care. In addition to favouring continuous monitoring, the personalisation of interventions and the prevention of dysfunctions, AI expands the capacity for longitudinal follow-up of patients, strengthening actions directed at health promotion. Fernandes (2025) highlights that the integration between clinical knowledge and intelligent tools has significantly modified physiotherapeutic practice, enabling interventions that are more responsive to the needs of individuals. Together, these contributions reinforce the role of artificial intelligence as a resource capable of supporting preventive programmes oriented towards the preservation of functionality, autonomy and quality of life.

3.3 ARTIFICIAL INTELLIGENCE AND HEALTH PROMOTION: PREVENTIVE PERSPECTIVES IN CONTEMPORARY PHYSIOTHERAPY

Health promotion has assumed an increasingly relevant role in the context of contemporary physiotherapy, especially in view of the growth of digital technologies applied to preventive care. In this scenario, artificial intelligence (AI) has been incorporated as a resource capable of expanding the capacity for monitoring, analysing and following up the functional conditions of the population. Its use makes it possible to transform data from different sources into useful information for the planning of preventive actions, favouring interventions more aligned with individual and collective needs. According to Bernasiukpucrs and Sarlet (2024), the expansion of AI in the health sector has promoted important changes in the organisation of care, influencing everything from care processes to strategies aimed at prevention and health promotion.

In the field of physiotherapy, the use of intelligent systems has contributed to the construction of care models more oriented by the anticipation of risks and by the maintenance of functionality. The capacity to process clinical, behavioural and biomechanical information favours the identification of factors associated with the emergence of functional limitations before they produce more significant repercussions on the health of individuals. Corrêa *et al.* (2023) highlight that the integration between physiotherapy and artificial intelligence has been expanding the possibilities for functional follow-up and strengthening practices directed at the prevention of disorders, especially in contexts that require continuous monitoring.

The development of preventive actions based on AI is also associated with the advancement of human movement monitoring technologies. Inertial sensors and machine learning algorithms make it possible to analyse the execution of physiotherapeutic exercises with a high level of detail, offering information that assists both professionals and patients. In this sense, Alfakir *et al.* (2022) demonstrated the feasibility of using sensors associated with machine learning techniques to detect and classify exercises aimed at the treatment of lumbar conditions, highlighting the application of these technologies in remote follow-up and in the promotion of adherence to preventive conducts.

In addition to body sensors, computer vision systems have been expanding the possibilities for functional assessment in non-clinical environments. Arrowsmith *et al.* (2023) demonstrated that postural detection algorithms associated with machine learning are capable of classifying physiotherapeutic exercises using only a camera, reducing barriers related to access and professional follow-up. From the perspective of health promotion, these tools favour the remote supervision of physical activities, allowing faster corrections in the execution of movements and contributing to the adoption of behaviours related to the maintenance of musculoskeletal health.

Health education has also been influenced by the incorporation of artificial intelligence into care processes. Intelligent digital platforms make it possible to provide personalised guidance, the clarification of frequent doubts and the continuous follow-up of the goals established by preventive programmes. Rowe, Nicholls and Shaw (2021) argue that the redistribution of knowledge promoted by intelligent technologies modifies the traditional forms of interaction between professionals and users of health services, creating new possibilities for the dissemination of information related to the prevention of diseases, self-care and the management of one's own health.

Another relevant aspect refers to the training of professionals for the use of these tools in the clinical and preventive context. The adoption of intelligent systems depends not only on technological availability, but also on the knowledge necessary to interpret the data generated and incorporate them adequately into the decision-making process. In this sense, Alsobhi *et al.* (2022) observed that physiotherapists present favourable perceptions regarding the applications of artificial intelligence in health and rehabilitation, although there are still challenges related to professional training and familiarity with the technological resources available.

The advances observed in the automated analysis of movement equally reinforce the contribution of AI to the promotion of healthy habits related to physical activity and body movement. The use of specialised software makes it possible to assess motor patterns,

identify biomechanical compensations and follow the functional evolution of individuals over time. Zsarnoczky-Dulhaz *et al.* (2024) highlight that movement analysis systems based on artificial intelligence present relevant applications both in sport and in physiotherapy, providing information that can guide preventive strategies aimed at the reduction of functional risks and the improvement of physical performance.

In a complementary manner, the literature demonstrates that the combination of artificial intelligence, remote monitoring and data analysis has favoured the construction of more dynamic preventive programmes that are responsive to the needs of the population. Tack (2019) highlights that machine learning applications in musculoskeletal physiotherapy expand the capacity to understand clinical and functional patterns, while Owens *et al.* (2020) emphasise that new technologies have been transforming physiotherapeutic practice through the expansion of the possibilities for the follow-up and assessment of patients. Together, these contributions demonstrate that artificial intelligence has been consolidating itself as a relevant tool for the strengthening of health promotion, preventive education and the adoption of habits favourable to the maintenance of functionality and quality of life.

4 FINAL CONSIDERATIONS

The growing insertion of artificial intelligence into the different levels of health care has expanded the possibilities of action of preventive physiotherapy, especially with respect to functional monitoring, the early identification of risk factors and the development of strategies aimed at health promotion. In this context, the present research demonstrated the relevance of the integration between intelligent technological resources and preventive physiotherapeutic practices, highlighting that the use of tools based on artificial intelligence has been contributing to the construction of more personalised, continuous and data-oriented care models. The importance of this study is associated with the need to understand how these technologies can strengthen preventive actions, favour the maintenance of functionality and contribute to the improvement of quality of life in different population contexts.

In relation to the established objectives, it is verified that all were satisfactorily achieved. It was possible to analyse the application of artificial intelligence in preventive physiotherapy, identifying its main contributions to quality of life and health promotion. The technological strategies used in this context were also investigated, the repercussions of these tools on functional and motor aspects of individuals were evaluated, and the ways in which artificial intelligence has been employed in the development of preventive practices, continuous follow-up and the encouragement of the adoption of healthy habits were examined.

In the development of topic 3.1 Technological Strategies Based on Artificial Intelligence in Preventive Physiotherapy, it was demonstrated that resources such as body sensors, wearable devices, biomechanical analysis software, automated functional monitoring systems and machine learning algorithms have been expanding the capacity for assessment, follow-up and support for clinical decision-making. These technologies allow the acquisition of detailed information about human movement and favour preventive interventions more directed at the individual needs of patients.

As for topic 3.2 Artificial Intelligence, Functionality and Quality of Life in Preventive Physiotherapy Programmes, it was observed that artificial intelligence contributes to the improvement of mobility, to the preservation of functionality and to the reduction of limitations that may compromise the autonomy of individuals. The literature analysed indicated that intelligent systems favour the personalisation of physiotherapeutic interventions, expand the capacity for continuous monitoring and assist in the prevention of musculoskeletal dysfunctions, reflecting positively on quality of life and physical well-being.

In topic 3.3 Artificial Intelligence and Health Promotion: Preventive Perspectives in Contemporary Physiotherapy, it was verified that artificial intelligence has played a relevant role in the strengthening of health promotion actions, especially through health education, remote follow-up and the use of digital tools aimed at the adoption of healthy habits. The studies analysed demonstrated that the integration between intelligent technologies and preventive physiotherapy favours self-care strategies, expands access to specialised guidance and strengthens initiatives aimed at the prevention of disorders related to functional health and body movement.

In view of the results obtained, it is recommended that future research investigate the clinical effectiveness of systems based on artificial intelligence applied to preventive physiotherapy in different populations and care contexts. Studies aimed at evaluating the impact of these technologies on indicators of quality of life, adherence to preventive interventions, functionality and health promotion in the long term are also pertinent. In addition, future investigations may explore aspects related to professional training, ethics in the use of health data and the challenges of implementing these tools in public and private health care systems.

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TRAINING IN THE PUBLIC SECTOR: TOWARDS JOB SATISFACTION AND WELL-BEING

CAPACITAÇÃO NO SETOR PÚBLICO: RUMO À SATISFAÇÃO E BEM-ESTAR NO TRABALHO

CAPACITACIÓN EN EL SECTOR PÚBLICO: HACIA LA SATISFACCIÓN Y EL BIENESTAR EN EL TRABAJO

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ABSTRACT

This article aimed to analyse the contribution of training actions in the public sector to promoting job satisfaction and well-being among civil servants. It is a bibliographical research, with a qualitative and descriptive approach, based on the analysis of scientific articles, periodicals, and institutional documents related to human resource management, training, and development in the public sector. The results showed that training exerts a positive influence on satisfaction and well-being, but indirectly, being mediated by factors such as professional recognition, career progression, motivation, work values, and organisational conditions. It was also found that isolated or disjointed training programmes tend to have a limited impact, while structured initiatives integrated into strategic human resource management demonstrate greater effectiveness. It is concluded that training only becomes a relevant instrument for promoting well-being and satisfaction when aligned with institutional policies that value the civil servant and favour the practical application of the developed competencies.

Keywords: Training. Satisfaction. Well-being.

RESUMO

O presente artigo teve como objetivo analisar a contribuição das ações de capacitação no setor público para a promoção da satisfação e do bem-estar no trabalho dos servidores. Trata-se de uma pesquisa de natureza bibliográfica, com abordagem qualitativa e caráter descritivo, fundamentada na análise de artigos científicos, periódicos e documentos institucionais relacionados à gestão de pessoas, treinamento e desenvolvimento no setor público. Os resultados evidenciaram que a capacitação exerce influência positiva sobre a satisfação e o bem-estar, porém de forma indireta, sendo mediada por fatores como reconhecimento profissional, progressão na carreira, motivação, valores do trabalho e condições organizacionais. Verificou-se ainda que programas formativos isolados ou desarticulados tendem a apresentar impacto limitado, enquanto iniciativas estruturadas e integradas à gestão estratégica de pessoas demonstram maior efetividade. Conclui-se que a capacitação somente se configura como instrumento relevante de promoção do bem-estar

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e da satisfação quando alinhada a políticas institucionais que valorizem o servidor e favoreçam a aplicação prática das competências desenvolvidas.

Palavras-chave: Capacitação. Satisfação. Bem-estar.

RESUMEN

Este artículo analizó la contribución de las acciones de capacitación en el sector público a la promoción de la satisfacción laboral y el bienestar de los funcionarios. Se trata de una investigación bibliográfica, cualitativa y descriptiva, basada en el análisis de artículos científicos, publicaciones periódicas y documentos institucionales relacionados con la gestión de recursos humanos, la capacitación y el desarrollo en el sector público. Los resultados mostraron que la capacitación ejerce una influencia positiva en la satisfacción y el bienestar, aunque indirecta, mediada por factores como el reconocimiento profesional, la progresión profesional, la motivación, los valores laborales y las condiciones organizacionales. Asimismo, se constató que los programas de capacitación aislados o inconexos tienden a tener un impacto limitado, mientras que las iniciativas estructuradas e integradas en la gestión estratégica de recursos humanos demuestran mayor eficacia. Se concluye que la capacitación solo se convierte en un instrumento relevante para promover el bienestar y la satisfacción cuando se alinea con políticas institucionales que valoran al funcionario y favorecen la aplicación práctica de las competencias desarrolladas.

Palabras clave: Capacitación. Satisfacción. Bienestar.

1 INTRODUCTION

Training in the public sector has been consolidated as an essential strategy for the improvement of management, the quality of services provided to the population, and the appreciation of civil servants. In a context marked by constant social, technological, and regulatory transformations, it becomes essential that public organisations invest in the continuous development of their professionals, promoting not only administrative efficiency but also job satisfaction and well-being. In this scenario, training and improvement policies, aligned with the principles of public administration set out in the Federal Constitution of 1988, gain strategic relevance.

In general, training in the public sector can be understood as a set of formative actions aimed at developing the technical, behavioural, and ethical competencies necessary for the exercise of public functions. Beyond the instrumental dimension, such actions directly impact motivation, engagement, and the perception of professional appreciation, factors closely related to satisfaction and well-being in the work environment. Thus, continuous qualification ceases to be merely a functional requirement and comes to be recognised as a central element in the construction of healthier and more productive organisational environments.

The basic idea guiding this article is that structured training programmes in the public sector significantly contribute to promoting job satisfaction and well-being, by strengthening competencies, expanding professional autonomy, and valuing the civil servant as an active subject of the institutional process. It is based on the assumption that investment in continuous training benefits not only the organisation and the users of public services, but also promotes positive impacts on occupational health, self-esteem, and the professional fulfilment of workers.

The focus of the research is delimited to the analysis of the relationship between training policies and practices in the public sector and their effects on the satisfaction and well-being of civil servants, considering aspects such as recognition, career development, organisational climate, and quality of work life. It is not intended to address all dimensions of public management, but to concentrate specifically on the interface between professional training and the subjective and organisational conditions of work.

The theme is situated within the field of Public Administration and People Management in the public sector, dialoguing with studies on organisational development, work motivation, and policies for the appreciation of civil servants. In a scenario of increasing demand for efficiency, transparency, and quality in the provision of services, the qualification of professionals becomes an indispensable condition for institutional strengthening and for the consolidation of a public management oriented by results and by democratic principles.

Therefore, the present research aims to analyse the contribution of training actions in the public sector to promoting job satisfaction and well-being among civil servants.

The present research is justified by the social and institutional relevance of training in the public sector as a strategy for valuing civil servants and improving the services provided to society. In a scenario marked by increasing demands for efficiency, transparency, and quality in public management, investment in professional development becomes a central element for strengthening institutions and promoting healthier organisational environments.

From a theoretical point of view, the national literature already recognises the importance of training and development practices in organisations. Borges-Andrade (2002), in discussing the evaluation of training in Brazilian organisations, emphasises that structured training programmes produce significant impacts on individual and organisational performance, influencing the attitudes, motivation, and commitment of workers. This perspective is fundamental for understanding that training in the public sector is not limited to the acquisition of technical competencies, but also affects the psychosocial dimension of work.

With regard to well-being, Siqueira e Padovam (2008) argue that positive experiences in the organisational environment, such as recognition, support, and development opportunities, are directly related to job satisfaction and well-being. In this logic, training actions can be understood as management practices that strengthen the perception of professional appreciation, contributing to better levels of engagement and quality of work life.

Although there are consolidated studies on training, development, and well-being in the Brazilian organisational context, there is still a need for investigations that integrate these variables specifically within public administration, considering its structural and regulatory particularities. Thus, this research seeks to contribute to the advancement of the discussions by articulating training, satisfaction, and well-being from the perspective of the public sector.

In addition to the theoretical contribution, the study presents practical relevance by enabling reflections that support public managers in formulating more strategic and humanised training policies. By understanding training as an instrument for promoting well-being, the traditional view focused solely on productivity is expanded, favouring the construction of a public management oriented both towards results and towards the appreciation of people.

2 METHODOLOGY

The present research is characterised as bibliographical and descriptive, with a qualitative approach. It is bibliographical because it will be developed from the analysis of

materials already published, such as books, scientific articles, periodicals, and official documents that address training in the public sector, job satisfaction, and organisational well-being. It is descriptive because it seeks to analyse and understand the relationship between training actions and their impacts on the satisfaction and well-being of public servants, without direct interference in the investigated reality.

As for the technical procedures, the research is based mainly on the analysis of national and international scientific productions, with emphasis on articles published in indexed periodicals, such as *Revista do Serviço Público*, *Gestão e Sociedade*, *Estudos de Psicologia* (Natal), and *Administrative Sciences*. Institutional documents, legislation relevant to the training policy in the public sector, and materials made available in digital scientific databases will also be used.

The data collection procedure will follow the model of selective, analytical, and reflective reading. Initially, a selective reading will be carried out to identify the works most relevant to the theme. Next, the analytical reading will proceed, with note-taking and the organisation of the main ideas, concepts, and results presented by the authors. Finally, a reflective reading will be carried out, seeking to establish relationships between the analysed studies and the objectives proposed in this research.

The bibliographical searches will be carried out in electronic databases such as Google Acadêmico, SciELO, Portal de Periódicos CAPES, and official websites of scientific journals. Virtual libraries and institutional repositories that provide academic productions related to Public Administration and People Management in the public sector will also be consulted.

3 RESULTS

Table 1 shows the authors and results according to the objective and methodology used:

Table 1

Authors and results according to objective and methodology used

Author/Year	Title	Objective	Methodology	Main results
Duarte, Teixeira e Sousa (2019)	The relationship between motivation and job satisfaction of public servants	To analyse the relationship between motivation in public service and job satisfaction of civil servants of a federal educational institution.	Quantitative descriptive research, with the application of a questionnaire (Likert scale) to 423 civil servants of the IFES, analysed by regression with an ordered probit model.	A positive and significant relationship was identified between motivation and job satisfaction, with all dimensions of motivation being statistically

				relevant, with influence from factors such as age, position, and bonus function.
Ferreira <i>et al.</i> (2020)	Work values and job satisfaction of public servants in a section of the Federal Justice	To analyse the relationships between work values and job satisfaction of public servants who work in citizen service at the Federal Justice.	Quantitative, descriptive, and analytical research, with the application of a survey to 193 civil servants, using validated scales (EVT-R and EST) and analysis by structural equation modelling.	It was found that social relationship values positively influence job satisfaction, while prestige also presents a positive influence; stability presented a negative influence and professional achievement did not demonstrate a significant relationship with satisfaction.
Silva e Rodrigues (2025)	Training and Job Satisfaction in Portugal's Public Sector: A Sequential Mediation Model Based on Competency Acquisition, Performance Appraisal, and Career Progression	To examine how training influences the job satisfaction of public sector employees in Portugal, considering the mediating effects of competency acquisition, performance appraisal, and career progression.	Quantitative, cross-sectional study, with the application of a structured questionnaire to 340 public servants, using regression analysis and a sequential mediation model (PROCESS/AMOS).	Training presents a positive effect on job satisfaction, but indirectly, mainly when it promotes competency acquisition, improves performance appraisal, and favours career progression; professional progression was the most relevant mediator, evidencing that the impact of training depends on organisational recognition and concrete growth opportunities.
Ranzini e Bryan (2017)	Training and education for the public sector and the models of school of government in Brazil	To understand and systematise the different models of schools of government developed in Brazil, analysing their characteristics and fields of action.	Qualitative research, of a bibliographical nature, with analysis of documents, articles, and specialised literature to classify training models in the public sector.	The existence of multiple training models in the public sector was identified (schools of government, higher education institutions, corporate universities, NGOs, and party foundations), evidencing great diversity of structures and forms of action, as well as the need for

				integration among these models to improve the qualification of civil servants and the efficiency of public management.
Nascimento <i>et al.</i> (2025)	Developing leadership competencies in the public sector	To describe and analyse the experience of the LideraGOV Programme, highlighting its conception, objectives, pedagogical and methodological design, as well as its innovations and results in the training of leaders in the federal public sector.	Technical report of a qualitative nature, based on the analysis of the implementation of the programme, institutional documents, course evaluations, and participant accounts, with a focus on the practical experience of the training.	The programme demonstrated high effectiveness in training public leaders, with strong integration between theory and practice, the use of strategies such as mentoring, applied projects, and competency-based learning. It also evidenced a high completion rate, the strengthening of professional networks, and positive impacts on institutional performance, in addition to recent advances in promoting diversity and inclusion, especially with the incorporation of race and gender perspectives in the training.
Hussain, Hussain e Kanwai (2025)	The impact of public sector training programs on employee competency and job satisfaction	To investigate the impact of training programmes in the public sector on employee competency and job satisfaction in government institutions.	Quantitative research, with the application of a structured questionnaire to 108 employees, analysed through reliability analysis, correlation, and multivariate tests (MANOVA).	Training programmes presented a positive and significant effect on both competency and job satisfaction, being stronger on satisfaction; a positive relationship between competency and satisfaction was also observed, although the direct impact of training on competency was limited, indicating a need for improvement in the programmes.
Amorim <i>et al.</i> (2024)	Emotional health of human resources	To promote understanding of the importance of	Applied study with a qualitative approach, through practical	The intervention contributed to improving

	employees in the public sector	mental health and to improve interpersonal relationships in the Human Resources sector of the public sector.	intervention in an HR team, using activities such as emotional intelligence, suggestion box, and meetings for discussion and feedback.	communication, greater empathy, and interaction among employees, in addition to evidencing a high incidence of stress and problems related to mental health; the activities favoured positive behavioural changes and a better work environment.
Ribeiro e Marra (2021)	Relations between senses of work and job satisfaction: analysis of a public servants category	To analyse whether the senses of work are capable of influencing the level of job satisfaction of federal public servants.	Mixed-approach study, with the application of 186 questionnaires (Meaningful Work Scale – ETS and Job Satisfaction Scale – EST) and the conduct of 10 semi-structured interviews with technical-administrative servants of a federal university in the interior of Minas Gerais.	The results evidenced predominantly moderate associations between the senses of work and satisfaction, in addition to a significant predictive effect ($R^2 \approx 55.4\%$). Dimensions such as ethics, identification with work, development, autonomy, and interpersonal relationships showed a strong positive influence on satisfaction, indicating that the perception of meaningful work directly impacts the well-being and satisfaction of the servants.

Source: prepared by the authors (2026).

4 DISCUSSION

The discussion about training in the public sector demands the overcoming of a simplistic view that associates it directly and linearly with job satisfaction. Although the literature recognises the relevance of formative actions for professional development, the analysed findings indicate that this relationship does not occur immediately, but rather mediated by organisational and psychosocial variables. In this sense, training must be understood as an element inserted in a broader system of people management, in which its

effects depend on the institutional conditions that enable the application, recognition, and appreciation of the acquired competencies.

The results presented by Silva e Rodrigues (2025) reinforce this perspective by demonstrating that the impact of training on job satisfaction occurs predominantly in an indirect manner, being mediated by factors such as competency acquisition, performance appraisal, and, above all, career progression. Such evidence shifts the focus from training as an isolated event to its integration into structured professional trajectories, in which institutional recognition plays a central role. Thus, it is not training in itself that raises satisfaction, but the way the organisation transforms this investment into concrete opportunities for growth and appreciation of the civil servant.

Convergently, Hussain, Hussain e Kanwai (2025) identify that, although training programmes present positive effects both on competency and on job satisfaction, these impacts are neither homogeneous nor automatic. The authors point out, moreover, that the direct effect of training on competency development can be limited, suggesting that the effectiveness of these initiatives depends on their quality, alignment with institutional needs, and capacity to generate practical changes in the work context. Such a finding reinforces the idea that training, by itself, does not guarantee substantial improvements in the work experience, requiring an organisational environment that favours the internalisation and application of the acquired knowledge.

Thus, the understanding that training acts as an indirect mechanism for promoting job satisfaction and well-being is consolidated as the central axis of this discussion, operating through mediations such as professional recognition, career opportunities, autonomy, and meaning attributed to work. This approach allows advancing beyond descriptive analyses, evidencing that the effects of continuous training are conditioned by structural and subjective factors that, when articulated, enhance their results in the context of public administration.

When analysing training in the public sector from a structural perspective, it is observed that the central challenge does not lie in the absence of formative initiatives, but in the way these are organised and articulated institutionally. Ranzini e Bryan (2017) evidence that the field of training of public servants in Brazil is marked by a wide diversity of models, including schools of government, corporate universities, higher education institutions, non-governmental organisations, and foundations linked to political parties. This multiplicity of structures reveals a scenario rich in formative possibilities, but also fragmented, in which different initiatives coexist without, necessarily, establishing strategic connections among themselves.

This fragmentation compromises the effectiveness of training policies, insofar as it hinders the construction of continuous and coherent formative trajectories throughout the career of the civil servant. Instead of constituting an integrated system of professional development, many formative actions assume a one-off character disconnected from institutional needs, which limits their potential impact both on organisational performance and on job satisfaction. Thus, as pointed out by Ranzini e Bryan (2017), the absence of articulation among the different training models represents one of the main obstacles to strengthening competency-based public management. Advancing from this more theoretical perspective to the analysis of practical experiences, the findings of Nascimento *et al.* (2025) contribute to evidencing possible paths for overcoming this disarticulation. In describing the LideraGOV Programme, the authors demonstrate the effectiveness of a structured formative proposal that integrates different dimensions of professional development, such as technical competencies, leadership skills, and the practical application of knowledge. The programme stands out for adopting active methodologies, such as mentoring, applied projects, and competency-based learning, in addition to promoting the articulation between theory and practice in the real context of public administration.

The experience of LideraGOV evidences that the effectiveness of training is directly related to its degree of integration with institutional objectives and with the concrete demands of work. Unlike isolated initiatives, structured and strategically aligned programmes tend to generate more consistent impacts, both on performance and on the perception of appreciation of civil servants. In this sense, the contrast between the fragmentation pointed out by Ranzini e Bryan (2017) and the integrated approach presented by Nascimento *et al.* (2025) reinforces the argument that the main problem of training in the public sector is not its non-existence, but rather its disarticulation.

Thus, training must be understood as a systemic component of public management, which requires planning, coordination, and continuity. The absence of these elements transforms potentially transformative actions into low-impact initiatives, while their presence enables the construction of more effective formative policies, capable of contributing consistently to institutional development and to the appreciation of public servants.

The relationship between training, competency development, and institutional performance constitutes one of the most relevant technical axes of the discussion, since it evidences the mechanisms by which formative actions can — or cannot — generate concrete impacts in the public sector. In general, the literature points out that training has the potential to expand the knowledge, skills, and attitudes of civil servants, contributing to improvements in individual and organisational performance. However, this relationship is not presented in a

homogeneous manner, being strongly conditioned by the characteristics of the training programmes and by the context in which they are implemented.

In this sense, Hussain, Hussain e Kanwai (2025) demonstrate that training programmes in the public sector exert a positive effect both on the satisfaction and on the competency of civil servants, but with distinct intensity. The authors identify that, although there are gains in job satisfaction, the direct impact on competency development can be limited, suggesting that not all formative initiatives manage to promote substantive changes in professional capacities. This limitation indicates possible weaknesses in the training models adopted, such as content poorly aligned with the real demands of work, ineffective methodologies, or the absence of mechanisms that favour the practical application of the acquired knowledge.

In contrast, the findings of Nascimento *et al.* (2025) evidence that structured training programmes, based on competencies and articulated with professional practice, tend to present significantly more expressive results. The experience of the LideraGOV Programme demonstrates that the integration between theory and practice, combined with the use of active methodologies, such as mentoring, applied projects, and experiential learning, favours not only the acquisition of competencies, but also their effective incorporation into daily work. In addition, the results point to positive impacts on institutional performance, indicating that training, when well planned, can contribute to the improvement of public management and to the achievement of organisational objectives.

The confrontation between these studies allows advancing towards a more consistent critical analysis, evidencing that the effectiveness of training is not guaranteed by its simple implementation. On the contrary, the results suggest that "not all training works", with its effectiveness being directly dependent on the model adopted, on the alignment with institutional needs, and on the capacity to promote meaningful learning. Generic, decontextualised, or excessively theoretical programmes tend to generate limited impacts, while structured, contextualised, and competency-oriented initiatives present greater transformative potential.

In this way, training in the public sector must be conceived not only as an instrument of knowledge transmission, but as a strategic process of competency development aimed at improving institutional performance. This perspective reinforces the need for investments in more robust and integrated formative models, capable of overcoming traditional limitations and enhancing the effects of training actions on the quality of public management.

The analysis of the relationship between training and job satisfaction reveals that this link is not established directly, but through a set of organisational mediations that condition

its effects. In this sense, training must be understood as an enabling factor, whose impact depends on the existence of institutional mechanisms that convert competency development into concrete recognition, progression opportunities, and professional appreciation. Thus, mere participation in formative programmes does not, by itself, guarantee an increase in levels of satisfaction; it is necessary for the organisation to incorporate these processes into its people management logic.

The findings of Silva e Rodrigues (2025) are particularly elucidating in demonstrating that the effect of training on job satisfaction occurs predominantly in an indirect manner, being mediated by variables such as competency acquisition, performance appraisal, and career progression. Among these factors, professional progression stands out as the main mediator, evidencing that civil servants tend to perceive greater satisfaction when the effort invested in training results in concrete advances in their functional trajectories. In this way, training acquires meaning not only as a learning process, but as an instrument of mobility and recognition within the organisational structure.

This perspective can be expanded from the articulation with the results of Duarte, Teixeira e Sousa (2019), who evidence the existence of a positive relationship between motivation and job satisfaction in the context of public service. Although the authors do not directly address training as a central variable, their findings allow inferring that motivational factors, such as the perception of appreciation, institutional recognition, and working conditions, play a decisive role in the construction of satisfaction. In this context, training can act as an inducing element of motivation, provided it is associated with returns perceived by the civil servant, such as improvement in performance, recognition, and growth opportunities.

In a complementary manner, Ferreira *et al.* (2020) demonstrate that work values, especially those related to social relationships and prestige, exert a significant influence on the satisfaction of public servants. Such evidence reinforces the idea that job satisfaction is deeply linked to the perception of recognition and appreciation within the organisation. Thus, training only tends to produce positive effects when it is inserted in an environment that values professional development and recognises the effort of the civil servant, whether through symbolic rewards or through concrete advances in the career.

In view of this, a central point for this discussion is consolidated: without institutional recognition, training loses much of its transformative potential. When disconnected from processes of evaluation, progression, and appreciation, continuous training can be perceived merely as a formal requirement, without significant impact on the satisfaction of civil servants. On the other hand, when integrated into structured people management policies, training becomes a powerful instrument for promoting job satisfaction, acting in an indirect but

consistent manner in the construction of more motivating and value-enhancing organisational environments.

The understanding of job satisfaction in the public sector requires the incorporation of psychosocial factors that transcend the strictly technical dimensions of training, highlighting elements such as motivation, work values, and the meaning attributed to the activities performed. These factors configure the subjective experience of the civil servant in the organisational environment and exert a direct influence on their level of engagement, well-being, and satisfaction. In this context, training does not act as an isolated determinant, but as an element that can indirectly influence these dimensions, enhancing their effects when articulated with favourable organisational conditions.

The findings of Duarte, Teixeira e Sousa (2019) evidence that motivation in public service presents a positive and significant relationship with job satisfaction, being influenced by different variables, such as characteristics of the position, institutional recognition, and development opportunities. From this perspective, it is possible to infer that training can act as a stimulus to motivation, insofar as it expands the competencies of civil servants and strengthens their perception of preparation for the performance of their functions. However, this motivational effect depends on the way the organisation recognises and values the investment made by the worker in their qualification.

In a complementary manner, Ferreira *et al.* (2020) highlight that work values, especially those related to social relationships and prestige, exert a significant influence on the satisfaction of public servants. Such values reflect the importance attributed by individuals to recognition, social interaction, and the meaning of the activities performed. In this sense, training can contribute to the strengthening of these values by promoting greater integration among civil servants, expanding the perception of institutional belonging, and reinforcing the recognition of the acquired competencies. However, this process does not occur automatically, depending on organisational practices that value professional development.

The dimension of the meaning of work, in turn, is deepened by Ribeiro e Marra (2021), who demonstrate that the perception of meaning in the activities performed exerts a strong influence on job satisfaction, being associated with factors such as autonomy, identification with the tasks, personal development, and interpersonal relationships. From this approach, training can be understood as a mechanism that expands the autonomy and the capacity for action of civil servants, contributing to them attributing greater meaning to their functions. Thus, an indirect relationship is established in which training favours the development of competencies, which in turn expand autonomy, strengthen the meaning of work, and consequently raise the levels of satisfaction.

Therefore, it is evidenced that job satisfaction in the public sector is the result of a complex set of psychosocial factors, in which training exerts an indirect influence, mediated by elements such as motivation, values, and the meaning of work. This understanding reinforces the need to integrate formative actions into broader people management strategies, capable of enhancing these subjective factors and promoting more engaging, meaningful, and satisfying organisational environments for public servants.

The expansion of the analysis to the dimension of well-being at work allows understanding that satisfaction, although relevant, constitutes only one of the facets of the work experience in the public sector. Well-being involves a more comprehensive set of factors, including emotional health, the quality of interpersonal relationships, organisational climate, and the balance between demands and available resources. In this sense, training, although important, cannot be considered sufficient to promote well-being in isolation, requiring consideration of the broader organisational context in which civil servants are inserted.

The findings of Amorim *et al.* (2024) evidence that aspects related to emotional health and interpersonal relationships play a central role in the construction of well-being in the work environment. From a practical intervention in the human resources sector, the authors identified a high incidence of stress and emotional difficulties among civil servants, while also observing significant improvements in communication, empathy, and interaction after the implementation of strategies aimed at emotional development. These results indicate that well-being is deeply related to the quality of relationships in the organisational environment and to the existence of spaces that favour dialogue, mutual support, and the expression of subjective demands.

In a complementary manner, Duarte, Teixeira e Sousa (2019) point out that factors such as organisational climate, working conditions, and interpersonal relationships directly influence the satisfaction and, by extension, the well-being of public servants. Environments characterised by institutional support, recognition, and good relationships tend to present lower levels of stress and greater engagement, while contexts marked by overload, lack of appreciation, and interpersonal conflicts compromise the quality of work life. These elements reinforce the idea that well-being is not restricted to the individual perception of satisfaction, but results from the interaction between the individual and the organisational environment.

In this context, training can contribute to well-being by promoting the development of competencies and favouring integration among civil servants, but its effects are conditioned by the quality of the environment in which it is inserted. Formative programmes that do not consider aspects such as organisational climate, institutional support, and emotional health

tend to present limited impact, since they do not act on the structural conditions that sustain well-being. On the other hand, when articulated with broader people management policies, training can enhance improvements in the work environment, contributing to healthier relationships and to the construction of a more collaborative organisational culture.

Despite the advances identified in the literature regarding training in the public sector, it becomes essential to problematise its contradictions and limitations, at the risk of incurring excessively optimistic and uncritical analyses. One of the main points to be highlighted is that not every training action generates real impacts on the performance, satisfaction, or well-being of civil servants. As evidenced by Hussain, Hussain e Kanwai (2025), although training programmes present positive effects, these results are not uniform, with limitations observed in the effective development of competencies. Such a finding indicates that the mere provision of training does not guarantee substantive changes, especially when the programmes are not aligned with institutional needs or lack adequate methodologies.

Another relevant aspect refers to the absence of standardisation in training practices in the public sector, as discussed by Ranzini e Bryan (2017). The diversity of models, although it represents potential for innovation, also evidences the lack of integrated guidelines that orient the training of civil servants in a systematic and continuous manner. This heterogeneity hinders the comparison of results among different initiatives and compromises the consolidation of more consistent public training policies. In addition, institutional fragmentation contributes to the dispersion of efforts and to the implementation of one-off actions, often disconnected from broader people management strategies.

From a methodological point of view, it is observed that a large part of the analysed studies adopts predominantly quantitative approaches, with emphasis on surveys and statistical analyses, as verified in Hussain *et al.* (2025). Although these methods are important for identifying relationships among variables, they present limitations in the in-depth understanding of the subjective and organisational processes that mediate the effects of training. Moreover, there is a significant gap in longitudinal studies that allow assessing the impacts of training over time, especially with regard to the sustainability of the results and the evolution of the professional trajectories of civil servants.

These limitations indicate the need for more integrated and qualitative approaches, capable of capturing the complexity of the relationships between training, satisfaction, and well-being in the public sector. The absence of analyses that consider the institutional context, management practices, and the perceptions of civil servants over time restricts the understanding of the real effects of training policies, reinforcing the importance of future research that advances in this direction.

In view of the above, it becomes possible to integrate the discussed findings and resume the central objective of this study, which consists of analysing the contribution of training actions to promoting job satisfaction and well-being among public servants. The analysis evidenced that training plays a relevant role in this process, but its effects are neither direct nor automatic, being mediated by organisational, psychosocial, and institutional factors, such as recognition, career progression, motivation, work values, meaning attributed to the activities, and conditions of the organisational environment.

Thus, it is concluded that training only constitutes an effective instrument for promoting satisfaction and well-being when integrated into a strategic people management, capable of articulating professional development, appreciation of the civil servant, and improvement of working conditions. When treated in isolation, training tends to present limited impact; on the other hand, when inserted into structured policies aligned with institutional objectives, it becomes a fundamental element for strengthening public administration and for the construction of healthier, more productive, and more meaningful organisational environments for civil servants.

5 FINAL CONSIDERATIONS

The final considerations of this article reinforce that training in the public sector, although widely recognised as a strategic instrument for institutional development, does not produce direct and automatic effects on the satisfaction and well-being of civil servants. Throughout the analysis, it was evidenced that its contribution occurs in a manner mediated by organisational, psychosocial, and institutional factors, such as professional recognition, career progression opportunities, motivation, the meaning of work, organisational climate, and working conditions.

In this sense, it is concluded that training, when treated in isolation, tends to present limited impact, being frequently perceived merely as a formal requirement, without significant repercussions on the work experience of civil servants. On the other hand, when integrated into a strategic people management, which articulates professional development, appreciation of the civil servant, and improvement of working conditions, training assumes a central role in promoting healthier, more productive, and more meaningful organisational environments.

In addition, the study evidences the need to overcome weaknesses still present in the literature and in practice, such as the fragmentation of training policies, the absence of standardisation, the predominance of quantitative studies, and the scarcity of longitudinal analyses. Such limitations indicate the importance of theoretical-methodological advances

that enable understanding, in a more in-depth manner, the impacts of training over time and in different institutional contexts.

Finally, it is highlighted that the effectiveness of training in the public sector depends on its insertion into structured, continuous policies aligned with institutional objectives. Only from this integration will it be possible to enhance its effects, contributing not only to the improvement of organisational performance, but also to the promotion of job satisfaction and well-being, consolidating a public management oriented both towards results and towards the appreciation of people.

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INVESTIGATION OF ACCESS TO OPHTHALMIC CARE IN CEARÁ: WHAT ARE THE MAIN BARRIERS AND HOW TO INTERVENE?

INVESTIGAÇÃO DE ACESSO AO CUIDADO OFTALMOLÓGICO NO CEARÁ: QUAIS OS PRINCIPAIS ENTRAVES E COMO INTERVIR?

INVESTIGACIÓN DEL ACCESO A LA ATENCIÓN OFTALMOLÓGICA EN CEARÁ: ¿CUÁLES SON LAS PRINCIPALES BARRERAS Y CÓMO INTERVENIR?



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ABSTRACT

In Brazil, many patients still face restricted access to ophthalmic treatment services, particularly within the public health system. The aim of this study was to characterise the obstacles faced by individuals in obtaining eye care in the state of Ceará. This cross-sectional study was conducted at the Instituto Cearense de Oftalmologia (ICO) in Fortaleza, from August 2024 to February 2025. A total of 116 SUS users were interviewed to better characterise their profiles, how they perceive vision loss, how it interferes with or impacts their daily lives, and to explore barriers to accessing care. The majority of participants were women (68.1%), with an average age of approximately 64 years. More than half (56.9%) reported transportation difficulties, and 52.6% indicated that cost was a challenge. Most participants acknowledged experiencing vision loss, with 80.1% reporting awareness of it, ranging from less than one year to more than five years. Furthermore, 54.3% had to stop performing important activities such as working, walking alone, or reading. Regarding waiting times, 18.1% of participants waited 12 to 24 months for their first consultation, and 32.1% waited 3 to 6 months after diagnosis to undergo surgery. Among those with an ocular condition, 83.6% required surgical intervention. Additional barriers included fear of surgically induced injuries, the need for multiple pre-procedure visits for examinations, and long waiting lists for surgeries, particularly in the public system. SUS users in Ceará, particularly older adults and women with lower educational levels, face limitations in accessing healthcare due to waiting times, costly care, and interruptions to daily life. The findings highlight the critical importance of developing public policies that increase access to ophthalmic care.

Keywords: Access to Health. Ophthalmology. Public Health System. Access Barriers. Quality of Life.

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RESUMO

No Brasil, muitos pacientes ainda enfrentam acesso restrito aos serviços de tratamento oftalmológico, particularmente na rede pública. O objetivo deste estudo foi caracterizar os obstáculos enfrentados pelos indivíduos no cuidado com a visão no estado do Ceará. O presente estudo foi transversal e foi realizado no Instituto Cearense de Oftalmologia (ICO), situado em Fortaleza, de agosto de 2024 a fevereiro de 2025. Um total de 116 usuários do SUS foram entrevistados para ajudar a caracterizar melhor seu perfil, como eles veem a perda de visão, como isso interfere ou impacta sua vida diária, além de explorar barreiras para ter acesso ao cuidado. A maioria dos entrevistados era mulher (68,1%) com idade média em torno de 64 anos. Mais da metade, 56,9 por cento, disseram ter problemas de transporte, e 52,6 por cento disseram que o custo é uma dificuldade. A grande maioria reconheceu que estava perdendo a visão, 80,1% disseram estar cientes disso, o que variou de menos de um ano atrás a mais de cinco anos atrás, 54,3% tiveram que parar de fazer coisas importantes como trabalhar, andar sozinhos ou ler. Em termos de espera, 18,1% dos participantes esperaram de 12 a 24 meses para a primeira consulta, e 32,1% esperaram de 3 a 6 meses após o diagnóstico para realizar a cirurgia. Daqueles que tinham alguma doença ocular, 83,6 por cento necessitaram de cirurgia. Barreiras adicionais foram o medo de lesões induzidas cirurgicamente, ter que fazer múltiplas visitas pré-procedimento para exames, e listas de espera para cirurgias, especialmente na saúde pública. Usuários do SUS no Ceará, particularmente os idosos e as mulheres com pouca escolaridade, têm sua demanda por cuidados de saúde limitada pelo tempo de espera, cuidado custoso e interrupções na vida diária. Os achados sugerem quão crítico pode ser o desenvolvimento de políticas públicas que aumentem a capacidade de acesso ao cuidado oftalmológico.

Palavras-chave: Acesso à Saúde. Oftalmologia. Rede Pública. Barreiras de Acesso. Qualidade de Vida.

RESUMEN

En Brasil, muchos pacientes aún enfrentan acceso restringido a los servicios de tratamiento oftalmológico, particularmente en el sistema de salud pública. El objetivo de este estudio fue caracterizar los obstáculos enfrentados por los individuos en la obtención de atención oftalmológica en el estado de Ceará. Este estudio transversal se realizó en el Instituto Cearense de Oftalmologia (ICO) en Fortaleza, de agosto de 2024 a febrero de 2025. Se entrevistó a un total de 116 usuarios del SUS para caracterizar mejor sus perfiles, cómo perciben la pérdida de visión, cómo interfiere o impacta en su vida diaria, y explorar barreras para acceder a la atención. La mayoría de los participantes eran mujeres (68,1%), con una edad promedio de aproximadamente 64 años. Más de la mitad (56,9%) reportó dificultades de transporte, y el 52,6% indicó que el costo fue un desafío. La mayoría de los participantes reconocieron la pérdida de visión, con el 80,1% reportando conocimiento de la misma, que osciló entre menos de un año y más de cinco años. Además, el 54,3% tuvo que dejar de realizar actividades importantes como trabajar, caminar solo o leer. Con respecto a los tiempos de espera, el 18,1% de los participantes esperó de 12 a 24 meses para su primera consulta, y el 32,1% esperó de 3 a 6 meses después del diagnóstico para someterse a una cirugía. Entre aquellos con una condición ocular, el 83,6% requirió intervención quirúrgica. Las barreras adicionales incluyeron miedo a lesiones inducidas quirúrgicamente, la necesidad de múltiples visitas preoperatorias para exámenes, y largas listas de espera para cirugías, particularmente en el sistema público. Los usuarios del SUS en Ceará, particularmente los adultos mayores y las mujeres con niveles educativos más bajos, enfrentan limitaciones para acceder a la atención médica debido a los tiempos de espera, atención costosa e interrupciones en la vida diaria. Los hallazgos destacan la importancia crítica de desarrollar políticas públicas que aumenten el acceso a la atención oftalmológica.



Palabras clave: Acceso a la Salud. Oftalmología. Sistema de Salud Pública. Barreras de Acceso. Calidad de Vida.

1 INTRODUCTION

Caring for eye health is crucial for the well-being of all, as it impacts quality of life and daily activities. **Today, more than 2.2 billion people worldwide have some form of vision problem or blindness, and almost half of these cases could have been prevented or can be successfully treated if detected early.** A large portion of this number is comprised of people living in low- and middle-income countries, where rates of vision loss are up to eight times higher than in wealthier nations.

Refractive errors (myopia and hypermetropia), cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy are the main causes of visual problems, most of which are preventable or treatable by simple approaches, such as the use of corrective glasses and cataract surgery, which are generally effective and accessible, according to the World Health Organization (2019).

In Brazil, spending on eye health is guaranteed by the SUS (Unified Health System) and offers visual care to all; however, much inequality persists, mainly between regions and social classes. Most specialised services and specialists are located in large cities such as São Paulo, which hinders access for people from inland areas. More recently, it was shown that **14.7% of the population using the SUS has never visited an ophthalmologist**, compared with **4.8% of those who have a private health insurance plan** (SILVA *et al.*, 2023). Almost half of those accessing the public health system consulted an ophthalmologist in the last year, compared to 71.7% in the private network. This disparity is even greater among older adults, women, individuals with lower educational attainment, and residents in the North and Northeast regions, thus imposing additional difficulties to these segments (IBGE, 2020).

The state of Ceará, for example, provides a perfect example of such contrasts. Despite high levels of poverty and **problems of accessibility to services in regions outside the capital**, there are few ophthalmic centres outside the capital, long waiting lists for elective surgeries, very few specialists available, and a fragile hierarchical continuity of care structure. Most eye surgeries in the region take place in the city of Fortaleza, which means that many people from inland areas arrive many days before their surgeries, often without assistance in terms of transport and accommodation (BARRETO *et al.*, 2021).

Beyond structural challenges, **indirect expenses**, such as transport, food, and the need for accompanying persons, are major barriers to eye care services. All of the above aspects are predominantly faced by the most vulnerable, who depend exclusively on the SUS and who not only face difficulty in accessing healthcare, but also face problems with information, time, and continuity of treatment (MORAIS *et al.*, 2018; NUNES *et al.*, 2021).

The absence of health information is another obstacle, with most users seeking treatment only when visual symptoms have already developed, thus preventing the prognostic phase and early intervention. Few educational campaigns, the lack of articulation between primary and specialised care, and the absence of system control are other weaknesses in this landscape of silent neglect of eye health (SANTOS *et al.*, 2020).

In this context, we need to study in the population of the state of Ceará what are **the factors that limit access to ophthalmic services**, from **the perception of symptoms to referral to specialist centres for treatment in specialised services** (cases that should be submitted to surgical management). There is no regional information on the pathway that users take within the public network and on access barriers, and this research once again highlights the need for local studies, capable of guiding more equitable public policies.

As a result, the aim of the present study was **to analyse the main obstacles to ophthalmic care in the state of Ceará** from the perspective of SUS users. The study aims to reveal what are the challenges of the care pathway – from the first complaint through diagnosis and surgery.

2 MATERIALS AND METHODS

From **August 2024 to February 2025**, a survey was conducted at the ICO (Instituto Cearense de Oftalmologia) located in the capital of the state of Ceará, in a descriptive, exploratory, and cross-sectional manner, with qualitative and quantitative approaches.

This study involved **116 patients** who received ophthalmic care and met the following inclusion criteria: being a SUS patient, being in follow-up at the ICO, responding immediately to the questionnaire, and the patient and/or legal guardian being 18 years of age or older. Private patients were excluded from the research, as well as those who refused to participate, did not respond immediately to the questionnaire, or refused to sign the Informed Consent Form (ICF).

Data were collected at the ICO through a questionnaire using Google Forms, which included identification information, sociodemographic data, ophthalmic data, and factors that interfere with access to ophthalmic care, in order to verify which possible barriers exist to obtain specialised treatment for eye problems in the state health system in the state of Ceará and how users themselves perceive these barriers. The interviews were conducted by medical students.

The variables of interest were:

- Sociodemographic variables (such as age, sex, and educational level), general characteristics of the person surveyed and their family (for example, number of years in

current residence or whether they have any relatives suffering from a particular type of disease);

- Ophthalmic clinical variables [changes in visual acuity, ocular symptoms, severity], family history, previous eye surgeries, use of glasses, knowledge about the disease;
- Quality of life variables (adapted from the National Eye Institute VFQ-25).

The questionnaire contains 25 items, took on average about 15 minutes to be completed in an interview model format, and included the following:

- **General assessment of health and vision (9 items),**
- **Need for correction for near vision (1 item),**
- **Difficulty with distance vision (1 item),**
- **Limitations in autonomy caused by visual disability or prevented participation (9 items),**
- **Patient expectations regarding their future vision (2 items),**
- **Difficulties with mobility and transport (4 items),**
- **Pain or discomfort experienced (2 items);**
- **Access to diagnosis and surgical treatment (6 items).**

The 25 items can be divided into objective and subjective items – with 22 objective and 3 subjective items.

The research project was approved by the Research Ethics Committee with Human Subjects of the Faculty of Medicine of Centro Universitário Christus in Fortaleza, Ceará, Brazil, No. 692 5355, CAAE: 80441224.2.0000.5049.

3 RESULTS

A total of 116 interviewees aged 23 years or older who use public health systems were available for this investigation. Age ranged from 23 to 84 years, with **67.2% of subjects falling in the 60 to 77 years age group**. On average, 63.85 years, of which only 116 years. 95% were married; **68.1% of people were women**.

6% of interviewees were illiterate or had not completed primary school, 34.4% had completed primary school, whilst 52.5% were educated to secondary school level or had completed two-year technical courses. In response to the question 'Are you literate?', almost 90% said yes.

Furthermore, **42.2% were retired**; 78.4% of interviewees were unemployed. **56.9% said that transport was a problem**. The average cost to reach the clinic was **R\$20.66**.

Regarding patients' perception of travel costs, **52.6% considered it a prohibitive factor for scheduling their appointment**. **About 71% reside in Fortaleza**.

Only 14.7% of interviewees said they had eye pain. As for interviewees who received ophthalmic care as part of treatment for chronic diseases, 48.3% were receiving attention.

When asked about the period in which their vision worsened (80%), the majority experienced a decline between one and five years ago or more than 5 years ago. With their vision in decline, **54.3% of participants said that this prevented them from doing something they did regularly**. The activities they stopped doing were **mainly work** (39.7%), walking alone, and reading newspapers or magazines (38.1%).

Approximately 69% of interviewees used prescription glasses for refractive correction, and 98.7% of interviewees who did so knew which professional had prescribed the glasses. Of these, 63.3% by an ophthalmologist and the remainder by an optometrist. 95.7% had undergone a previous ophthalmic examination – as they themselves reported.

Of the interviewees, 95.6% agreed to report why they went to an ophthalmic consultation, the main reasons being **post-operative care** (46.8%) and ophthalmic review consultation (21.6%). As for the time the patient waited for treatment, the main responses consisted of: between 1 and 3 months (37.9%), 3–6 months (19.8%), and 12–24 months (18.1%).

The individual was diagnosed with ocular diseases requiring surgery in approximately 83.6% of those surveyed.

4 DISCUSSION

The present research included a sample of 116 individuals, aged 23 years or older, covered by the SUS, with a mean age of 63.85 years. The majority of participants were comprised of women (68.1%), with various educational levels: illiterate (6%), incomplete primary education (34.4%), and complete primary or secondary education (52.5%). The self-reported literacy rate was high ($\approx 90\%$).

Furthermore, 42.2% of participants were economically inactive and 78.4% were unemployed. Notably, ocular pain was reported by only 14.7% of individuals, and 48.3% were in ophthalmic follow-up for systemic diseases. Eighty per cent reported visual deterioration over 1–5 years, and 54.3% reported having stopped daily activities, including working, walking alone, or reading. The mean waiting time for the first ophthalmic examination was 1–3 months (37.9%), 3–6 months (19.8%), and 12–24 months (18.1%).

The present findings confirm that the prevalence of visual impairment in older Brazilian adults is high, especially among those with **limited formal education and those in more advanced age groups** (HOLZ *et al.*, 2009). The sociodemographic characteristics of the study – **older individuals, low educational attainment, female over-representation**

– are similar to the profile of individuals more vulnerable to vision loss, as reported in national and international literature (VISION LOSS EXPERT GROUP OF GBD STUDY; GBD 2019 COLLABORATORS, 2024; LEASHER *et al.*, 2019).

The findings of this study demonstrate that, despite the majority of subjects living in Fortaleza (71.6%), transport expenses remain a barrier to access to ophthalmic care, cited as a limiting factor by more than half of the interviewees (52.6%). Although the average reported expenditure (R\$20.66) may be substantial for the average person, it is significant, considering that the majority of the population served by the SUS has low family income, predominantly comprised of pensioners and the unemployed. This result confirms, in part, those found in other studies conducted in Brazil, in which the indirect cost of travel to the health service is identified as a significant barrier to adherence to treatment, especially to the use of pre-operative examinations (SILVA *et al.*, 2004).

It is also notable the comprehensive dependence on application-based transport (58%) rather than private vehicles (28.6%). This information may be related to the ease of use and the option of a door-to-door service, which is important for older patients with visual disability. However, it exposed dependence on a paid resource, reflecting the financial burden on the population studied.

The disruption of daily activities, such as working, moving about, or reading, mentioned by more than half of respondents, underscores the high functional cost of visual disability. Furthermore, the fact that the presence of a correlated risk factor for depression among older adults residing in China is the limitation of daily activities may also indicate that this relationship is repeated in Brazil (LIU *et al.*, 2023).

Another relevant factor relates to the characteristics of people who prescribe glasses. 63.3% and 36.7% were prescribed by ophthalmologists and optometrists, respectively. These data open the way for debate regarding the regulation of optometrist practice in Brazil and its relationship with ophthalmology. The nearly 40% of prescriptions issued by optometrists shows that a significant portion of the population resorts to this professional in search of quicker care and perhaps due to difficulty in accessing the specialist in the SUS.

Furthermore, the high percentage of patients who had a previous ophthalmic evaluation (95.7%) and the fact that almost half of the patients had their follow-up after surgery (46.8%) indicate that, after an initial screening, when included in the 'specialised care pathway', the patient becomes accustomed to the connection with the service. These data have practical importance, as they support the adoption of strategies that promote patient entry into the network, such as the expansion of primary care with specialised ophthalmology structure, periodic screening, and decentralisation of specialised consultation.

The waiting time experienced (up to 2 years for 18.1% of the sample) confirms the long waiting times witnessed in the literature. Research conducted in the Metropolitan Health Region of Espírito Santo (RSM-ES) estimated the average waiting time from January 2014 to December 2016 as 419 days in 2014, 687 days in 2015, and 1077 days in 2016 (FARIAS *et al.*, 2019). This sluggishness is due to the lack of structure in the SUS, including fragmented control of waiting lists and inadequate resources.

The WHO and international research have highlighted that long waiting times are measures of low quality in health service and can affect the prognosis of chronic and elective diseases. For these cases, risk prioritisation, clinical regulation tools, telehealth, and articulation between Primary Healthcare (PHC) and Specialised Outpatient Care (SAC) are suggested (GIANNOTTI *et al.*, 2025).

Despite its small sample size ($n = 116$) and local character, the study generated important findings about the profile of ophthalmic patients in the SUS in Fortaleza, as it strengthened the relationship between low educational attainment, advanced age, long waiting times, and significant functional impact. These findings are consistent with national epidemiological studies and emphasise the need for policies aimed at increasing access, including queue management, telehealth, and case screening.

5 CONCLUSION

Regarding the results of the study on access to ophthalmology services in Ceará, it is noted that users of the Unified Health System (SUS) in the state of Ceará face multiple and different barriers that affect the comprehensiveness and effectiveness of services.

The waiting times listed for the first consultation (up to 24 months for almost one-fifth of participants) and for surgery (up to 9 months for more than 12% of patients), direct and indirect costs (i.e., transport, multiple visits to the service for pre-operative examinations, which represent significant financial barriers), and the direct functional impact of restricted vision on daily routine activities – particularly among older adults and women with lower educational level – were some of the barriers.

The cost of consultations, failed attempts to seek help, fear of surgery, and lack of money, low effectiveness in the public system, all of this represents evidence of a persistent gap between need and effective access to treatment.

The high need for surgical management (83.6%) in the presence of such obstacles is a reflection of the serious policy and management countermeasures needed.

It is recommended that measures be taken for the optimisation of queue control, use of tele-ophthalmology to increase access, effectively integrate levels of assistance,

prioritising cases at higher risk, humanising care and ensuring all citizens the right to health, including the continuation of community campaigns for the access and treatment of vulnerable patients.

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NEW GUIDELINES FOR PULP TREATMENT WITH BIODENTINE

NOVAS DIRETRIZES PARA O TRATAMENTO PULPAR COM BIODENTINE

NUEVAS DIRECTRICES PARA EL TRATAMIENTO PULPAR CON BIODENTINE



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ABSTRACT

The protection of the dentine-pulp complex is achieved through pulp therapy, which is a procedure aimed at maintaining the health of the pulp or its revitalisation by means of direct or indirect treatments, the former being applied directly to the pulp and the latter to the dentine-pulp complex. The aim of this literature review is to compare the effectiveness and behaviour of Calcium Hydroxide (CH), Mineral Trioxide Aggregate (MTA) and Biodentine (BD) in pulp therapy; to this end, the methodology used was a bibliographic survey of the following bibliographic databases: Scielo, Bireme, PubMed and CrossRef. CH has high bacteriostatic and bactericidal power, an alkaline pH, easy handling and low cost, but is limited with regard to marginal adaptation to dentine, solubility over time and resorption of the deciduous tooth. On the other hand, MTA has an alkaline pH, significantly greater mechanical strength than calcium hydroxide-based materials, low solubility and high marginal sealing power; however, it is difficult to handle, has a long setting time and, after acid etching, its compressive strength is compromised. Lastly, BD has high biocompatibility, low risk of pulp reaction and shorter working time; despite these advantages, it has a high cost, since the package contains 5 capsules. The final considerations showed positive results for BD, which may be considered a material of choice for pulp therapies.

Keywords: Calcium Hydroxide. Biodentine. Pulp Therapy.

RESUMO

A proteção do complexo dentino-pulpar ocorre por meio da terapia pulpar que é um procedimento que visa a sanidade da polpa ou sua revitalização por meio de tratamentos diretos ou indiretos, sendo o primeiro aplicado diretamente sobre polpa e o segundo, sobre o complexo dentino-pulpar. O Objetivo desta revisão literária é comparar a efetividade e o comportamento do Hidróxido de Cálcio (HC), Mineral Trióxido Agregado (MTA) e do Biodentine (BD) na terapia pulpar e, para isso, a metodologia utilizada foi um levantamento bibliográfico das seguintes bases bibliográficas Scielo, Bireme, PubMed e CrossRef. O HC possui alto poder bacteriostático e bactericida, pH alcalino, fácil manuseio e baixo custo, mas

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limitante quanto a adaptação marginal à dentina, solubilidade com o tempo e reabsorção do dente decíduo. Por outro lado, o MTA possui pH alcalino, resistência mecânica significativamente maior do que materiais a base de hidróxido de cálcio, baixa solubilidade e alto poder selador marginal, no entanto, é de difícil manuseio, possui longo tempo de endurecimento e, após condicionamento ácido, tem sua resistência a compressão comprometida. Por último, o BD possui alta biocompatibilidade, baixo risco de reação pulpar e menor tempo de trabalho apesar destas vantagens possui alto custo, uma vez que a embalagem contém 5 cápsulas. As considerações finais mostraram resultados positivos para o BD, podendo ser considerado um material de eleição para as terapias pulpares.

Palavras-chave: Hidróxido de Cálcio. Biodentine. Terapia Pulpar.

RESUMEN

La protección del complejo dentino-pulpar se realiza mediante la terapia pulpar, que es un procedimiento que busca la salud de la pulpa o su revitalización por medio de tratamientos directos o indirectos, siendo el primero aplicado directamente sobre la pulpa y el segundo sobre el complejo dentino-pulpar. El objetivo de esta revisión literaria es comparar la efectividad y el comportamiento del Hidróxido de Calcio (HC), Mineral Trióxido Agregado (MTA) y del Biodentine (BD) en la terapia pulpar y, para ello, la metodología utilizada fue un levantamiento bibliográfico de las siguientes bases bibliográficas Scielo, Bireme, PubMed y CrossRef. El HC posee alto poder bacteriostático y bactericida, pH alcalino, fácil manejo y bajo costo, pero limitante en cuanto a la adaptación marginal a la dentina, solubilidad con el tiempo y reabsorción del diente decíduo. Por otro lado, el MTA posee pH alcalino, resistencia mecánica significativamente mayor que los materiales a base de hidróxido de calcio, baja solubilidad y alto poder sellador marginal; sin embargo, es de difícil manejo, posee largo tiempo de endurecimiento y, tras el acondicionamiento ácido, tiene su resistencia a la compresión comprometida. Por último, el BD posee alta biocompatibilidad, bajo riesgo de reacción pulpar y menor tiempo de trabajo; a pesar de estas ventajas posee alto costo, ya que el envase contiene 5 cápsulas. Las consideraciones finales mostraron resultados positivos para el BD, pudiendo ser considerado un material de elección para las terapias pulpares.

Palabras clave: Hidróxido de Calcio. Biodentine. Terapia Pulpar.

1 INTRODUCTION

Within the specialities of Dentistry, Operative Dentistry is responsible for the therapeutic, preventive, semiological, operative and educational procedures that aim to preserve and restore the aesthetic, functional and structural functions of the tooth (MONDELLI, 2017). Pulp therapy acts as an intermediary to maintain or preserve the healthy state of the damaged tooth, its objective being the formation of reparative dentine through stimuli, first biological and then restorative (PESTANA, 2016). The loss of the dentinal substrate implies the need for restoration of the tooth by means of a biostimulating material between the dentine and the provisional restorative material, since this loss indicates an injury to the dentine-pulp complex (SILVA, 2019).

The dentine-pulp complex is the name given to the pulp and dentine unit. The composition of dentine of 70% inorganic material (hydroxyapatite crystals), 18% organic material (collagen fibres) and 12% water confers permeability upon it (SILVA, 2019), and its tubules present variation in thickness as they move away from the pulp with 0.7 μm and as they approach it with 2.6 μm . The dental pulp is composed of amorphous ground substance, cells (undifferentiated mesenchymal and defence cells, odontoblasts and fibroblasts) and a vasculo-nervous bundle (CONCEIÇÃO, 2018). Dentine is dependent on the pulp for its formation, just as the pulp is dependent on the protection offered by dentine and enamel; therefore, when there is aggression to any of these structures, it is likely to be reflected in the other tissue at different levels (HARGREAVES, 2017).

The forms of aggression of the dentine-pulp complex may be caries, trauma, anatomical anomalies and incorrect cavity preparations. Caries attacks the dentine-pulp complex through the diffusion of toxic substances through the dentinal tubules. The production of reparative dentine and sclerotic dentine, the former in response to the attack on primary dentine and the latter with filling of hydroxyapatite crystals in the dentinal tubules, are the forms of reaction to the aggression (CONCEIÇÃO, 2018). Aggression by trauma may occur through accidents, food intake or congenitally, through hemifacial atrophy or hypertrophy. Anatomical anomalies are individual to each patient. Lack of care regarding the forms of resistance, contour and convenience, the use of inadequate instruments, non-cutting burs, interrupted movements, removal of remaining dentine and cleaning, both performed inadequately, are aggressions related to cavity preparation (MONDELLI, 2017). As there are various forms of injury to the dentine-pulp complex, there is an increasing search for ways to protect this complex (PESTANA, 2016).

The protection of the dentine-pulp complex through restorative processes may be achieved by direct and indirect pulp protection and should be indicated when the pulp

presents reversible pulpitis or when a part is inflamed but is capable of creating a hard-tissue barrier that protects the pulp from future attacks (HARGREAVES, 2017). For these therapies, protective or bioactive materials are used, which must have characteristics such as non-irritation of the pulp, the capacity to protect the dentine-pulp complex, bactericidal and/or bacteriostatic action, stimulation of the formation of tertiary dentine or reparation, maintenance of pulp vitality, biocompatibility, low cost, easy handling and remineralisation of the affected or decalcified dentine (PESTANA, 2016).

The main materials employed for the revitalisation of the dentine-pulp complex are presented below, namely Calcium Hydroxide (CH), Mineral Trioxide Aggregate (MTA) and Biodentine® (BD). This work will be carried out through a bibliographic survey of the following databases: Scielo, Bireme, PubMed and CrossRef, the objective of which is to compare the effectiveness and behaviour of each of the aforementioned materials in pulp treatment.

2 METHODOLOGY

The present study is characterised as a narrative literature review, developed with the objective of analysing and comparing the scientific evidence available on the use of Calcium Hydroxide, Mineral Trioxide Aggregate (MTA) and Biodentine in pulp treatment, emphasising their biological properties, clinical indications, advantages and limitations.

The search for studies was carried out in the PubMed/MEDLINE database, using descriptors related to the topic, such as “pulp therapy”, “Biodentine”, “calcium hydroxide” and “mineral trioxide aggregate”, combined by means of the Boolean operators AND and OR, in accordance with the Medical Subject Headings (MeSH) terminology. The inclusion criteria considered complete scientific articles, published in peer-reviewed journals, available in full and that directly addressed the use of these biomaterials in direct or indirect pulp therapies. Duplicate articles, studies that had no direct relation to the proposed theme, opinion publications and works with insufficiently described methodology were excluded.

The selection of the articles occurred in two stages: initially, the titles and abstracts were read to verify their suitability for the proposed theme, and subsequently, the full texts were analysed to confirm eligibility. After selection, the relevant data were organised descriptively, considering aspects such as year of publication, type of study, objectives, methodology employed, main results and conclusions, allowing the performance of a comparative qualitative analysis between the materials studied.

3 RESULTS AND DISCUSSION

The protection of the dentine-pulp complex is achieved through pulp treatments, either directly or indirectly, and its objective is to create a mineralised barrier over the pulp (GIANI e CEDRÉS, 2017). Direct pulp therapy consists of covering the exposed pulp directly (SILVA, 2019). On the other hand, indirect pulp therapy is used when there is no pulp exposure; therefore, the material is placed above the already existing dentinal structure (PEREIRA, 2014). Direct pulp treatment may be subdivided into direct pulp capping, pulpotomy and pulpectomy. In direct pulp capping (DPC), the material is placed over the exposure and then the tooth is restored permanently (KUNERT, 2020). In pulpotomy, the pulp present in the pulp chamber is removed, either totally or partially, preceded by the placement of a bioactive material and a provisional restoration. In pulpectomy, the entire pulp is removed and a filling of the root canals is performed (SILVA, 2019).

Calcium Hydroxide (CH) has been considered the gold standard in pulp treatments in general, mainly when taking into account the long-term clinical observations, with publications present between 1934 and 1941 affirming the success of this material (KUNERT, 2020). Its positive characteristics are high bacteriostatic and bactericidal power, high alkaline pH causing necrosis by superficial coagulation, it neutralises acidic pH, promotes mechanisms of repair and defence of the pulp tissue, easy handling and low cost (HARGREAVES, 2017). However, its disadvantages remain inadequate adhesion to dentine, poor sealing and high solubility (GIANI e CEDRÉS, 2017; KUNERT, 2020). For this reason, this material has been replaced by other calcium silicate-based cements, such as MTA and Biodentine. Its presentation may be in powder, paste or cement form (NIEDERMAIER, 2014).

MTA is composed of a base of hydrated calcium silicate powder and oxides of calcium, iron, silicon, sodium and potassium, magnesium and aluminium (HARGREAVES, 2017) and is presented in a powder and liquid version that must be spatulated for 40 s on a glass plate with a sterile spatula. The initial setting time is 70 minutes and the final setting time is 175 minutes (MANDEEP KAPUR *et al.*, 2017). Its advantages are high clinical efficiency guaranteed by its high biocompatibility, calcium release and antimicrobial activity (BAGATOLI, 2018; PEREIRA, 2014). On the other hand, its disadvantages are colour alteration, difficult manipulation and handling technique and, after acid conditioning, its compressive strength is compromised (PESTANA, 2016).

Biodentine (BD) aims, in its composition, at the absence of any calcium sulphate and aluminate and a high level of purity of calcium silicate in the final product (SEPTODONT, St Maur-des-Fossés, France). The presentation of this material is powder and liquid, the powder being placed inside a capsule and the liquid in a pipette. For its manipulation, it is necessary

to add the liquid to the capsule and insert it into an amalgamator (GIANI e CEDRÉS, 2017). The initial setting time is 6 minutes and the final is 12 minutes (MANDEEP KAPUR *et al.*, 2017); however, the final set has been demonstrated after 45 minutes (KUNERT, 2020). Its advantages are easy manipulation, high biocompatibility, low risk of pulp or tissue reaction, shorter working time, effective and durable sealing and a radiopacity of 3.5 mm in aluminium. However, it has as a disadvantage the high cost, since the package contains 5 capsules.

In DPC, it is expected that the capping materials present characteristics such as non-toxicity, non-irritation of the pulp, avoidable infiltration and an adequate response with regard to the dental pulp (PRECZEWSKI, 2016). The indications for this procedure are trauma or iatrogenic exposures; however, high success rates have been found in teeth in which DPC was performed due to exposure by dental caries (PARINYAPROM, 2018; PAULA, 2019). Based on these aforementioned characteristics, a comparison between the materials CH, MTA and BD in DPC will be made.

With the objective of broadening the comparative analysis between the biomaterials used in vital pulp therapies, Table 1 presents a synthesis of recent clinical studies that evaluated the performance of Biodentine, MTA and calcium hydroxide in different therapeutic approaches, including direct and indirect pulp capping, pulpotomy and vital pulp therapies. The selected studies mainly include randomised clinical trials and systematic reviews, evidencing high rates of clinical and radiographic success for calcium silicate-based materials. This compilation allows an integrated visualisation of the main clinical findings, methodological objectives and relevant conclusions, strengthening the discussion presented in this study.

Table 1

Table 1 – Clinical studies on Biodentine, MTA and calcium hydroxide in vital pulp therapies

Reference	Model	Objective	Intervention	Result	Conclusion
Rahman; Goswami, 2021	Randomized clinical trial; Comparative clinical study; 24-month follow-up; Sample: 60 young permanent molars with deep carious lesions in healthy children	To compare the clinical and radiographic efficacy of three materials used in indirect pulp therapy (IPT) in young permanent molars: TheraCal LC, Biodentine, Dycal	Selective caries removal (retaining affected dentin close to the pulp). Application of one of the three tested materials over the remaining dentin. Coverage with glass ionomer. Definitive restoration with	TheraCal LC: 100% success; Biodentine: 94.4% success; Dycal: 77.8% success.	TheraCal LC and Biodentine demonstrated a high success rate in indirect pulp therapy in young permanent molars, being superior alternatives to traditional

Reference	Model	Objective	Intervention	Result	Conclusion
			composite resin. Periodic clinical and radiographic evaluations up to 24 months.		Dycal. TheraCal LC showed the best clinical and radiographic performance after 24 months
Taha et al., 2024	Randomized, double-blind, controlled clinical trial. Comparison between two caries removal techniques in mature permanent teeth with reversible pulpitis.	To compare pulp survival and postoperative treatment needs between: Selective caries removal (SCR) Total caries removal (TCR) in mature permanent teeth diagnosed with reversible pulpitis.	SCR (Selective Caries Removal): caries removal down to firm dentin followed by application of Biodentine and composite restoration. TCR (Total Caries Removal): complete caries removal down to hard dentin; in cases of pulp exposure, immediate vital pulp therapy (VPT) with Biodentine was performed. Clinical and radiographic follow-up after 6 and 12 months.	A total of 124 teeth with reversible pulpitis were treated: 63 in the SCR group; 61 in the TCR group. Pulp exposure occurred in 17/61 (28%) in the TCR group and was successfully treated with VPT. Pulp survival: TCR: 100 % at 6 months and 98.4 % at 12 months; SCR: 93.65 % at 6 months and 82.5 % at 12 months.	Total caries removal down to hard dentin, accompanied by vital pulp therapy when pulp exposure occurs, resulted in greater pulp survival over 12 months than selective caries removal in mature permanent teeth with reversible pulpitis.
Taha; Abuzaid; Khader, 2023	Randomized clinical trial; sample of 60 mature permanent molars with caries-induced pulp exposure and diagnosis of irreversible pulpitis; two groups (n =	To compare the clinical outcome, quality of life (QOL), and patient satisfaction after full pulpotomy and conventional root canal treatment (RCT) in mature permanent teeth with irreversible	The 60 mature permanent molars were randomly divided into two groups: Group 1: Full pulpotomy using Biodentine (Septodont, France). Group 2: Conventional root canal treatment (RCT). Pain	The clinical and radiographic success rate was 93% in both groups (27/29). Pulpotomy showed lower pain intensity on the first postoperativ	Full pulpotomy can be considered an alternative to conventional root canal treatment in mature permanent teeth with caries-induced pulp

Reference	Model	Objective	Intervention	Result	Conclusion
	30); 12-month clinical and radiographic follow-up; additional assessment of quality of life (QOL) and patient satisfaction.	pulpitis.	levels were recorded preoperatively and at 1, 2, 3, 5, and 7 days. Clinical and radiographic evaluations were performed at 6 and 12 months. Quality of life was assessed using the Oral Health Impact Profile questionnaire and patient satisfaction using semantic differential scales.	e day ($P = 0.037$) and lower need for analgesics ($P = 0.028$), with faster pain relief compared to RCT. Both treatments promoted significant improvement in quality of life after 12 months, with no statistical difference between the groups. Patient satisfaction was significantly higher in the pulpotomy group ($P < 0.05$).	exposure and symptomatic irreversible pulpitis, presenting similar clinical and radiographic success rates, in addition to greater patient satisfaction.
Srinivasan et al., 2025	Randomized clinical trial with split-mouth design.	To evaluate and compare the clinical, radiographic, and histological outcomes of indirect pulp therapy using Silver Diamine Fluoride (SDF) and Biodentine in primary molars with deep carious lesions close to the pulp.	After partial caries removal: Group 1: Application of SDF. Group 2: Application of Biodentine. The teeth were restored and followed up clinically and radiographically at 3, 6, and 9 months.	Clinical success at 9 months: Biodentine (85.3%) superior to SDF (77.9%). Radiographic success: Biodentine (83.8%) superior to SDF (70.6%). Histological evaluation showed better pulp response and greater reparative dentin formation in	Both materials were effective in indirect pulp therapy in primary teeth; however, Biodentine showed superior performance in clinical, radiographic, and biological terms.

Reference	Model	Objective	Intervention	Result	Conclusion
				the Biodentine group.	
Jassal et al., 2023	Randomized, single-center clinical trial with two parallel groups.	To evaluate and compare the clinical and radiographic outcomes of partial pulpotomy versus full pulpotomy in mature molar teeth with carious exposure and symptoms suggestive of irreversible pulpitis, using the biomaterial Biodentine.	The teeth were randomly assigned to two groups: Partial pulpotomy: removal of the exposed pulp tissue to a depth of 2-3 mm. Full pulpotomy: removal of the entire coronal pulp to the level of the root canal orifices. In both groups, the pulp capping material used was Biodentine.	Both groups showed a high success rate after 12 months ($\approx 88\%$ in partial pulpotomy and $\approx 91.6\%$ in full pulpotomy), with no statistically significant difference between them. There was a significant reduction in postoperative pain in both groups.	Partial pulpotomy with Biodentine showed results comparable to full pulpotomy with Biodentine, both clinically and radiographically, in mature teeth with carious exposure and signs of irreversible pulpitis. If long-term results are similar, partial pulpotomy can be considered a viable alternative to full pulpotomy in this clinical scenario
Selvendran et al., 2022	Randomized in vivo clinical trial comparing three vital therapy materials in permanent molars with deep caries.	To evaluate and compare the clinical and radiographic outcomes of partial pulpotomy versus full pulpotomy in mature molar teeth with carious exposure and symptoms suggestive of irreversible pulpitis, using the biomaterial Biodentine.	The teeth were randomly assigned to two groups: Partial pulpotomy: removal of the exposed pulp tissue to a depth of 2-3 mm. Full pulpotomy: removal of the entire coronal pulp to the level of the root canal orifices. In	Biodentine and MTA showed higher clinical success rates ($\approx 91.6\%$ and 83.3%) compared to calcium hydroxide ($\approx 58.3\%$).	Calcium silicate-based materials, such as Biodentine and MTA, showed better clinical performance in indirect pulp capping than calcium hydroxide.

Reference	Model	Objective	Intervention	Result	Conclusion
			both groups, the pulp capping material used was Biodentine.		
Abuarqoub et al., 2022	Experimental in vitro study with human cells (THP-1-derived macrophages and dental pulp stem cells).	To investigate the immunomodulatory and regenerative effects of Biodentine on inflammatory cells and dental pulp stem cells.	Cells were stimulated with lipopolysaccharide (LPS) to induce inflammation and subsequently treated with Biodentine. Inflammatory cytokines, cell migration, and macrophage polarization were evaluated.	Biodentine reduced pro-inflammatory markers, increased anti-inflammatory cytokines, promoted stem cell migration, and favored macrophage polarization toward the reparative phenotype (M2).	Biodentine presents anti-inflammatory properties and regenerative potential, contributing to the repair and regeneration of the dentin-pulp complex.
Chhabra et al., 2025	Comparative randomized clinical trial with children aged 4 to 9 years with carious primary molars and no signs of irreversible pulpitis, followed for 18 months.	To compare the clinical and radiographic success of Biodentine versus Mineral Trioxide Aggregate (MTA) as indirect pulp capping materials in primary molars with reversible pulpitis.	Children with bilateral molars were divided into two groups: Group 1 received Biodentine; Group 2 received MTA: Both underwent indirect pulp treatment followed by stainless steel crowns, with clinical and radiographic evaluations at 3, 6, 12, and 18 months.	Of the 68 initial participants, 50 completed the 18 months, resulting in the analysis of 100 molars. The treatment success rates were: Biodentine: 96% MTA: 94%	Biodentine and MTA showed similar clinical and radiographic success after 18 months, indicating that both are effective as materials for indirect pulp capping in primary molars.

Reference	Model	Objective	Intervention	Result	Conclusion
Abuelniel et al., 2021	Randomized controlled clinical trial with split-mouth design in immature permanent molars with caries-induced pulp exposure.	To compare the efficacy of Biodentine and Mineral Trioxide Aggregate (MTA) as pulpotomy materials in immature permanent molars with carious pulp exposure.	Immature teeth with carious exposure were treated by coronal pulpotomy. The pulp tissues were amputated and covered with: Biodentine and MTA. The teeth were restored and followed up clinically and radiographically at 6, 12, and 18 months.	Both materials demonstrated high clinical and radiographic success rates over 18 months. There was no statistically significant difference between Biodentine and MTA	Biodentine and MTA were equally effective as pulpotomy agents in immature permanent molars with carious pulp exposure, with no significant differences between them in clinical and radiographic success after 18 months.
Mangat et al., 2025	Randomized controlled clinical trial with 12-month follow-up.	To compare the clinical and radiographic success rates of Biodentine and light-curable MTA when used as indirect pulp capping materials in teeth with deep carious lesions.	Patients were divided into two groups: Group 1: capping with Biodentine; Group 2: capping with light-curable MTA. Both were evaluated clinically and radiographically at intervals over 1 year.	There was no statistically significant difference between the two materials. The overall clinical and radiographic success rate after 1 year was approximately 93.33% in both groups.	Both Biodentine and light-curable MTA showed similar clinical and radiographic results as indirect pulp capping agents, with no significant difference between them over 12 months of follow-up.
Gabriel et al., 2024	Randomized controlled clinical trial, with clinical and radiographic follow-up.	To evaluate the clinical and radiographic success of Biodentine in vital pulp therapy, comparing it with conventional bioceramic material in teeth with carious pulp exposure.	The included teeth underwent pulpotomy/vital pulp therapy and were randomly divided into two groups: Group treated with Biodentine; Group treated with comparative material (bioceramic/MTA); Patients were followed up periodically for clinical and radiographic	Both groups showed high success rates, with maintenance of pulp vitality and absence of pathological clinical or radiographic signs. There was no statistically significant difference between the materials.	Biodentine proved to be an effective material for vital pulp therapy, presenting performance similar to the comparative material in clinical and radiographic follow-up.

Reference	Model	Objective	Intervention	Result	Conclusion
			evaluation.		
Hatipoğlu; Varlı Tekingür; Pertek Hatipoğlu, 2025	Systematic review with network meta-regression (network meta-analysis) of randomized clinical trials comparing direct pulp capping materials	To evaluate and compare the clinical efficacy of different materials used in direct pulp capping in permanent teeth, taking into account the follow-up duration	21 randomized clinical trials were included that compared at least two pulp capping agents (such as Biodentine, MTA, and calcium hydroxide), with a minimum follow-up of 3 months.	Biodentine and MTA showed higher clinical success rates than calcium hydroxide in direct pulp capping. In the success probability ranking, Biodentine showed the highest probability, followed by MTA, with calcium hydroxide having the lowest probability of success.	Calcium silicate-based materials, such as Biodentine and MTA, were associated with better clinical outcomes in direct pulp capping than calcium hydroxide. However, due to the heterogeneity of the studies and low certainty of evidence, it is not possible to state with absolute certainty the definitive superiority of one material.
Taha; Abdulkhader, 2018	Prospective clinical study with clinical and radiographic follow-up.	To evaluate the success of full pulpotomy with Biodentine in young permanent teeth with carious exposure and pulpal symptoms.	Performance of full pulpotomy, application of Biodentine as pulp capping material, and definitive restoration, with periodic follow-up.	High clinical and radiographic success rate, with maintenance of pulp vitality and absence of pathological signs in most of the evaluated cases.	Full pulpotomy with Biodentine proved to be an effective alternative to conventional root canal treatment in symptomatic young permanent teeth, preserving pulp vitality.
Tungjitphanpong et al., 2024	Randomized controlled clinical trial with clinical and radiographic follow-up for 6–24 months.	To compare the success rate of partial pulpotomy in primary molars with deep carious lesions using three different materials (MTA, Biodentine, and acemannan).	Primary molars of children (3–8 years) were randomized into three groups (30 teeth each): Group 1: pulpotomy with MTA; Group 2: pulpotomy with Biodentine;	After 24 months, the clinical and radiographic success rates were; MTA: 83.3%; Biodentine: 76.9%; Acemannan:	There was no significant difference in the efficacy of partial pulpotomy between MTA, Biodentine, and acemannan after 24 months,

Reference	Model	Objective	Intervention	Result	Conclusion
			Group 3: pulpotomy with acemannan; All were restored with stainless steel crowns and followed up for up to 24 months.	74.1%; There was no statistically significant difference in success rates between the groups.	indicating that the three materials are comparable in the management of deep lesions in primary molars
Singh et al., 2026	Randomized controlled clinical trial, with parallel-group analysis and comparison of rinsing solutions before direct pulp capping	To evaluate whether irrigation with different solutions influences the clinical/radiographic success rate and postoperative pain in permanent teeth with carious exposure treated with direct pulp capping.	Adults with permanent teeth with carious pulp exposure (preserved vitality) participated. After hemostasis, the cavities were randomized into 4 rinsing groups before capping: SS (sterile saline); 2.5% NaOCl (sodium hypochlorite); 12% EDTA; 2.5% NaOCl followed by 12% EDTA (NaOCl/EDTA). After rinsing, the tissue was covered with Biodentine, followed by liner and definitive restoration. Clinical and radiographic follow-up was performed at 6 and 12 months and pain was recorded during the first 7 days with a visual analog scale (VAS).	Overall clinical and radiographic success rate at 12 months: 86.9%. By group: SS: 71.9%; NaOCl: 90.6%; EDTA: 87.9%; NaOCl/EDTA: 97.0%	The use of irrigation with NaOCl and NaOCl/EDTA before pulp capping with Biodentine increased the clinical success rate and reduced postoperative pain in permanent teeth with carious pulp exposure, compared to rinsing with saline.

Reference	Model	Objective	Intervention	Result	Conclusion
Wadhwa et al., 2025	Prospective randomized controlled clinical trial.	To evaluate the impact of age on the success of direct pulp capping with two bioceramic materials (MTA and Biodentine) in teeth with deep caries and reversible pulpitis.	174 patients with permanent (mandibular) teeth with deep caries were divided by age: Group 1: young (18–40 years) – 87 patients; Group 2: middle-aged (41–60 years) – 87 patients; Within each age range, they were randomized to receive MTA or Biodentine as pulp capping material after preparation and hemostasis. Clinical and radiographic evaluation was performed up to 12 months of follow-up.	Overall success rate at 12 months: 96% (168/174) retrievability; Success by age: young (95.2%) > middle-aged (85.7%) — By material: MTA = 91.6% and Biodentine = 89.4% at 12 months	Age influenced the outcomes of direct pulp capping, with higher success rates in younger patients. Both MTA and Biodentine showed comparable and predictable performance for treatment in teeth with carious exposure and reversible pulpitis.

Source: prepared by the authors.

The findings presented in Table 1 corroborate the previously discussed literature, demonstrating that bioactive calcium silicate-based materials present better biological and clinical responses when compared to calcium hydroxide, especially in terms of dentinal barrier formation, maintenance of pulp vitality and reduction of inflammatory processes.

According to Niedermaier (2014), who carried out a comparative study between CH and BD by means of a randomised clinical trial, it was concluded that both were tolerable to the pulp tissue; however, the inflammatory response of the latter was of lesser intensity than that of the former, whereby a favouring of pulp regeneration can be obtained, and this occurrence suggests the level of biocompatibility. As regards the formation of the mineralising barrier, BD had a complete or almost complete mineralised barrier over the pulp exposure, whereas CH presented failures in this barrier. However, according to Bayerl and colleagues (2023), who carried out two clinical cases of indirect pulp capping employing the bioceramic material Biodentine, a significant improvement was observed in both cases, in which the patients reported total remission of the symptoms noted before the intervention, reverting the clinical condition of reversible pulpitis to a normal pulp. The results of the research by VEGAS

MSV e DIAZ JAR in 2023 indicated that Biodentine has anti-inflammatory properties and helps in dentinal regeneration, influencing cell differentiation and mineralisation. It also showed broad reparative potential in vital pulp therapies in permanent teeth, reducing pulp inflammation, great cellular biocompatibility, differentiation and high dentine quality. Similar results were observed in recent clinical studies, which demonstrated high rates of clinical and radiographic success with the use of Biodentine in vital pulp therapies, reinforcing its clinical predictability and its capacity to maintain pulp vitality (RAHMAN; GOSWAMI, 2021; SELVENDRAN *et al.*, 2022; GABRIEL *et al.*, 2024; MANGAT *et al.*, 2025; SINGH *et al.*, 2026).

As regards the histological evaluation in DPC, Preczevski (2016), when evaluating the inflammatory process, found that CH presented pulp necrosis and that MTA and BD presented moderate chronic inflammatory processes. As regards the dentinal barrier, CH again proved to be porous, whereas the other two materials presented a continuous barrier with obliteration of the root canal with the characteristics of an atubular dentine, the BD barrier being superior to the MTA barrier. From this obliteration, it is possible to affirm that there is a correct sealing of the pulp, which will prevent infiltrations of microorganisms or restorative materials. No type of pulp inflammation was found when the exposure was treated with BD and MTA, and the barrier formed was thick, continuous and excellent, whereas that of CH was porous and presented empty spaces. The three materials induced the differentiation of cells similar to odontoblasts and foci of mineralisation with the dentinal morphology were observed. Jalan (2017). A comparison between ProRoot MTA and BD by Parinyaprom (2018), in a randomised controlled study, concluded that success in DPC for both materials is quite similar, with rates of 92% and 96%. This demonstrates that there was no significant difference between the materials. More recent studies also confirm similar results between MTA and Biodentine, demonstrating comparable clinical success rates in different pulp capping and pulpotomy protocols (ABUELNIEL *et al.*, 2021; CHHABRA *et al.*, 2025; WADHWA *et al.*, 2025).

For pulpotomy in deciduous teeth, the treatment consists of the surgical removal of the coronal pulp with the objective of maintaining a vital root canal and the functionality of the tooth until its exfoliation. The material suggested for pulpotomy must have certain characteristics such as being bactericidal, harmless to the pulp and promoting the regeneration of the radicular pulp, not inhibiting the physiological resorptions of the canal and preserving the pulp in such a way that it does not cause any clinical or radiological symptom. The material considered the gold standard in pulpotomy was formocresol, but its characteristics with toxic and carcinogenic potential make this material limiting. Although there is no consensus regarding the most indicated material for pulpotomy, studies suggest

that MTA may be the most indicated for pulpotomy of deciduous teeth (COSTA e SILVA *et al.*, 2019; CARTI e OZNURHAN, 2017). Another randomised controlled study analysed CH in different viscosities and MTA for pulpotomy in deciduous teeth. MTA obtained superior results when compared with CH, regardless of the viscosity (COSTA e SILVA *et al.*, 2019). MTA and BD were compared for pulpotomy in deciduous teeth. Although they are materials with high success rates, MTA was considered superior to BD, both radiographically and clinically, with 80% and 96% for MTA and 60% and 96% for BD, respectively. This was in agreement with the survey previously conducted by the authors; the clinical consideration regarding the superiority of MTA was suggested by its high biocompatibility and sealing capacity, by the pH of 11-12 and better radiopacity (CARTI e OZNURHAN, 2017). Additional clinical evidence demonstrates that pulpotomy with Biodentine presents predictable results comparable to conventional endodontic treatments in certain cases, and may represent a viable conservative alternative (TAHA; ABUZAID; KHADER, 2023; JASSAL *et al.*, 2023; TAHA *et al.*, 2024).

Through a literature review, the authors Borges e Arid (2023) concluded that when a comparison is made between the materials used for pulp protection and pulpotomy and the evolution of dentistry over the years, nowadays Biodentine is the best material to be used for these purposes in Paediatric Dentistry.

The biocompatibility of a material is of extreme importance, given that it is in direct contact with the dental tissues (SULTANA *et al.*, 2018; HATIPOĞLU *et al.*, 2025). A study analysed the effect of CH, MTA and BD on undifferentiated cells from exfoliated deciduous teeth at 1, 3, 5 and 7 days, and the results demonstrated that in the first 24 hours, the cellular proliferation of CH was equal to the positive control group and that of BD equal to the negative control group, and only MTA had the lowest proliferation rate. On days 3 and 5, CH and BD presented similar proliferations that were greater than MTA, and on day 7, CH was superior to BD and MTA; and when analysing the cytotoxicity of these materials, it was observed that at 1 mg/mL, all the materials are non-cytotoxic, in addition to being biocompatible (ARAÚJO *et al.*, 2018; ARAÚJO, 2014). Other studies confirmed this non-cytotoxicity (CORNÉLIO, 2015; TOMÁS-CATALÁ *et al.*, 2018) and the biocompatibility of the materials (SULTANA *et al.*, 2018; SOUZA, 2018; SARMIENTO, 2019; PETTA *et al.*, 2020). Furthermore, experimental studies demonstrate that Biodentine has immunomodulatory properties and regenerative potential, promoting a reduction of inflammatory markers and favouring cell differentiation related to pulp repair (ABUARQOUB *et al.*, 2022; SRINIVASAN *et al.*, 2025).

4 CONCLUSION

The conclusion of an article should synthesise the main findings of the study succinctly, highlighting the significant contributions to the field of research. It should reiterate the objectives of the study and summarise the most important findings, emphasising their relevance and practical or theoretical implication. Based on the analysis of the reviewed literature, it was possible to observe that the bioactive materials used in pulp therapies, especially Biodentine, present promising clinical and biological results, standing out for their high biocompatibility, capacity to induce mineralisation, adequate marginal sealing and lesser inflammatory response when compared to the materials traditionally used such as Calcium Hydroxide and, in some aspects, results similar to Mineral Trioxide Aggregate (MTA). These findings reinforce the potential of Biodentine as a material of choice in procedures such as direct pulp capping, pulpotomy and other therapies conservative of pulp vitality.

However, despite the favourable results, certain limitations must be considered. There is still a relatively limited number of long-term clinical studies, in addition to the methodological heterogeneity between the works analysed, mainly with regard to the clinical protocols, follow-up times and criteria of clinical and histological evaluation. Furthermore, part of the available studies still concentrate on laboratory or experimental models, which evidences the need for a greater number of randomised clinical trials and longitudinal studies that allow a more consistent evaluation of the clinical predictability of these materials.

As future perspectives, it is recommended that research be developed to evaluate the behaviour of Biodentine in different clinical conditions, including different age groups, types of pulp exposure and associated restorative protocols. Studies investigating the interaction of this material with new adhesive techniques and restorative biomaterials are also relevant, as well as research evaluating biological markers of pulp regeneration and the molecular mechanisms involved in the process of tissue repair.

Additionally, it is suggested that future investigations seek the standardisation of the methodological criteria, including larger samples, more extensive follow-up periods and well-defined comparative methodologies between the available biomaterials. In vivo studies with combined clinical, radiographic and histological evaluation may also contribute significantly to strengthening the level of scientific evidence in this area.

Although Biodentine presents characteristics that position it as a highly promising material in pulp therapy, the continuity of research is fundamental to consolidate its clinical indication, establish better-defined protocols and broaden the predictability of the therapeutic results, thus contributing to the evolution of conservative therapies in operative dentistry and endodontics. In general, recent evidence from randomised clinical trials and systematic

reviews suggests that bioactive materials such as Biodentine and MTA present clinical performance that is superior or equivalent to calcium hydroxide in different modalities of vital pulp therapies, with emphasis on their biocompatibility, sealing capacity and potential for tissue regeneration.

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THE CONNECTION BETWEEN ALZHEIMER'S DISEASE AND PERIODONTITIS: A RELATIONSHIP THAT GOES BEYOND THE ORAL CAVITY

A CONEXÃO ENTRE A DOENÇA DE ALZHEIMER E A PERIODONTITE: UMA RELAÇÃO QUE VAI ALÉM DA CAVIDADE ORAL

LA CONEXIÓN ENTRE LA ENFERMEDAD DE ALZHEIMER Y LA PERIODONTITIS: UNA RELACIÓN QUE VA MÁS ALLÁ DE LA CAVIDAD ORAL



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ABSTRACT

Periodontitis and Alzheimer's disease have been extensively investigated due to growing evidence that inflammatory and infectious processes may connect oral health to cognitive function. This study aimed to understand how periodontitis can influence the development or progression of Alzheimer's disease through systemic and local mechanisms. The general objective was to analyze this relationship, while the specific objectives focused on explaining the biological mechanisms involved, gathering recent scientific evidence, and identifying clinical implications for dental practice in elderly care. This bibliographic research used recent studies retrieved from SciELO, Google Scholar, and BVS, based on the keywords "periodontitis," "Alzheimer's disease," and "systemic inflammation." The findings demonstrated that inflammatory mediators released in periodontitis can cross the blood-brain barrier, that oral pathogens can reach brain tissue, and that oral dysbiosis contributes to neurodegenerative processes. It was also observed that adequate periodontal treatment can reduce inflammatory markers and support the maintenance of overall health in older adults. It is concluded that oral health plays a significant role in the prevention and management of Alzheimer's disease, highlighting the need for broader and integrated clinical approaches.

Keywords: Periodontitis. Alzheimer's Disease. Systemic Inflammation. Elderly Health. Neurodegeneration.

RESUMO

A periodontite e a doença de Alzheimer têm sido amplamente estudadas devido à crescente evidência de que processos inflamatórios e infecciosos conectam a saúde bucal às funções cognitivas. O problema central deste trabalho consistiu em compreender de que maneira a periodontite pode influenciar o desenvolvimento ou a progressão do Alzheimer, considerando mecanismos sistêmicos e locais. O objetivo geral foi analisar essa relação, enquanto os objetivos específicos buscaram explicar os mecanismos biológicos envolvidos, reunir evidências científicas recentes e identificar implicações clínicas para a prática odontológica no cuidado ao paciente idoso. A pesquisa, de caráter bibliográfico, utilizou estudos recentes obtidos nas bases SciELO, Google Acadêmico e BVS, com foco nas palavras-chave "periodontite", "Alzheimer" e "inflamação sistêmica". Os resultados da análise demonstraram que mediadores inflamatórios liberados na periodontite podem atravessar a barreira hematoencefálica, que patógenos orais são capazes de alcançar o tecido cerebral e que a disbiose oral contribui para processos neurodegenerativos. Verificou-se também que o tratamento periodontal adequado pode reduzir marcadores inflamatórios e favorecer a manutenção da saúde global do idoso. Conclui-se que a saúde bucal representa um fator

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relevante na prevenção e no manejo do Alzheimer, reforçando a necessidade de abordagens clínicas ampliadas e integradas.

Palavras-chave: Periodontite. Doença de Alzheimer. Inflamação Sistêmica. Saúde do Idoso. Neurodegeneração.

RESUMEN

La periodontitis y la enfermedad de Alzheimer han sido ampliamente estudiadas debido a la creciente evidencia de que los procesos inflamatorios e infecciosos conectan la salud bucal con las funciones cognitivas. El problema central de este trabajo consistió en comprender de qué manera la periodontitis puede influir en el desarrollo o la progresión del Alzheimer, considerando mecanismos sistémicos y locales. El objetivo general fue analizar esta relación, mientras que los objetivos específicos buscaron explicar los mecanismos biológicos implicados, reunir evidencias científicas recientes e identificar implicaciones clínicas para la práctica odontológica en el cuidado del paciente anciano. La investigación, de carácter bibliográfico, utilizó estudios recientes obtenidos en las bases SciELO, Google Académico y BVS, con foco en las palabras clave “periodontitis”, “Alzheimer” e “inflamación sistémica”. Los resultados del análisis demostraron que los mediadores inflamatorios liberados en la periodontitis pueden atravesar la barrera hematoencefálica, que los patógenos orales son capaces de alcanzar el tejido cerebral y que la disbiosis oral contribuye a los procesos neurodegenerativos. Se verificó también que el tratamiento periodontal adecuado puede reducir los marcadores inflamatorios y favorecer el mantenimiento de la salud global del anciano. Se concluye que la salud bucal representa un factor relevante en la prevención y el manejo del Alzheimer, reforzando la necesidad de abordajes clínicos ampliados e integrados.

Palabras clave: Periodontitis. Enfermedad de Alzheimer. Inflamación Sistémica. Salud del Anciano. Neurodegeneración.

1 INTRODUCTION

Alzheimer's disease has become established as one of the greatest challenges for global public health, affecting millions of people and profoundly impacting the quality of life of individuals, families and healthcare systems. In the field of Dentistry, periodontitis has likewise gained prominence owing to its high prevalence and its chronic inflammatory nature, which affects not only the oral cavity but the entire organism.

In view of this emerging evidence, the central problem of this research arises: in what way can periodontitis be associated with the development or progression of Alzheimer's disease, considering the infectious and inflammatory processes involved?

The relevance of this research is justified by the need to broaden the understanding of how oral diseases can have repercussions beyond the oral cavity, contributing to serious systemic conditions such as Alzheimer's disease. By deepening this relationship, the study contributes to preventive dental practice, to interdisciplinary action in the health of older adults and to the advancement of scientific knowledge regarding modifiable factors that may influence neurodegeneration.

The general objective of this work is to analyse the relationship between periodontitis and Alzheimer's disease, identifying the main mechanisms that connect both conditions. In a complementary manner, the specific objectives seek to discuss the biological mechanisms that link periodontitis to neurodegeneration, to present recent scientific evidence on the association between the two diseases and to examine the clinical implications for dental professionals in the care of elderly patients.

2 METHODOLOGY

The present research is characterised as bibliographic research, grounded in recent perspectives on the relationship between periodontitis and Alzheimer's disease. According to Gil (2019), bibliographic research enables the researcher to gather, analyse and interpret theoretical contributions that have already been published.

The inclusion criteria adopted were: articles published within the last five years, written in the Portuguese language and directly addressing the research question, dealing with the possible relationship between periodontitis, systemic inflammation and Alzheimer's disease.

The exclusion criteria involved articles considered outdated (published more than five years ago), materials that did not engage with the guiding question and duplicate studies found in more than one database. The keywords applied in the searches were: "periodontitis", "Alzheimer's disease" and "systemic inflammation", allowing the selection of studies aligned with the proposed objective.

The searches were carried out in the SciELO, Google Scholar and BVS databases, ensuring access to relevant, contemporary scientific production consistent with the established methodological scope. The final analysis was constructed on the basis of a critical and interpretative reading of the selected materials, making it possible to map biological mechanisms, epidemiological evidence and clinical contributions relating to oral health and neurodegeneration.

3 BIOLOGICAL MECHANISMS LINKING PERIODONTITIS TO ALZHEIMER'S DISEASE

3.1 BIOLOGICAL MECHANISMS CONNECTING PERIODONTITIS TO ALZHEIMER'S DISEASE

Xie *et al.*, (2025) explain that periodontitis generates a persistent inflammatory environment characterised by the release of cytokines such as IL-1 β , IL-6 and TNF- α , which are capable of crossing physiological barriers and exerting a direct impact on the central nervous system. In a complementary manner, Tostes, Villela and Mitidieri (2025) emphasise that this prolonged inflammation compromises neural defence mechanisms and intensifies neuroinflammation, creating conditions favourable to the advance of Alzheimer's disease.

Monteiro *et al.*, (2025) describe that *Porphyromonas gingivalis*, a key bacterium of chronic periodontitis, has the capacity to migrate from the oral cavity to the brain by means of haematogenic routes. Arruda *et al.*, (2024), for their part, state that the gingipains produced by *P. gingivalis* are highly neurotoxic and induce the exacerbated formation of β -amyloid, a classic marker of Alzheimer's disease.

In addition to direct infection, oral dysbiosis stands out as a relevant mechanism. Arruda *et al.*, (2024) explain that the imbalance of the oral microbiome generates systemic immune hyperactivation, affecting microglial cells responsible for cerebral defence. Conceição *et al.*, (2023) add that this dysregulated activation favours the release of pro-inflammatory substances in neural tissue, contributing to progressive damage.

According to Conceição *et al.*, (2023), the chronic inflammation resulting from periodontal disease increases the permeability of this barrier, facilitating the entry of toxins and pathogens into the brain. Tostes, Villela and Mitidieri (2025) observe that this loss of biological selectivity exposes neural tissue to circulating inflammatory mediators, intensifying vulnerability to neurodegenerative lesions.

More recent research explores how periodontal interventions can modulate these pathological mechanisms. Shao *et al.*, (2025) demonstrated that advanced therapies — such as the use of stem cells in periodontal regeneration — significantly reduce systemic inflammatory markers. Xie *et al.*, (2025), for their part, state that the clinical control of

periodontitis reduces the inflammatory burden and, consequently, the stimulus to neurodegenerative processes.

3.2 RECENT SCIENTIFIC EVIDENCE ON THE RELATIONSHIP BETWEEN PERIODONTITIS AND ALZHEIMER'S DISEASE

Siqueira, Vincis and Guimarães (2021), in an integrative review, highlight that several longitudinal studies point to greater cognitive decline in older adults with severe periodontitis. In a complementary manner, Rosa and Silva Junior (2024) emphasise that the presence of chronic periodontal inflammation is associated with a significantly increased risk of neurodegenerative alterations.

Athayde *et al.*, (2021) describe that DNA fragments of *Porphyromonas gingivalis* were found in post-mortem analyses of patients with Alzheimer's disease, indicating possible bacterial migration. Facchini and Bona (2024) reinforce this finding by discussing studies that demonstrate the presence of bacterial lipopolysaccharides in the central nervous system, contributing to neuroinflammation.

Parreira and Santos (2025) state that patients with Alzheimer's disease present elevated levels of systemic cytokines when associated with periodontitis, indicating pathological synergy between oral and cerebral inflammation. In line with this, Siqueira, Vincis and Guimarães (2021) report that the increase in IL-1 β and TNF- α is directly associated with the progression of cognitive dysfunction.

The evidence from interventions also strengthens the relationship between periodontal health and cognition. Shao *et al.*, (2025), in a meta-analysis, showed that advanced periodontal therapies, including techniques involving stem cells, reduce systemic inflammatory markers and promote significant tissue regeneration. Rosa and Silva Junior (2024) add that conventional periodontal treatment is already capable of improving inflammatory parameters and, potentially, positively influencing cognition in older adults.

The integration of the results presented by the studies demonstrates that the relationship between periodontitis and Alzheimer's disease is not incidental but multifactorial and supported by robust evidence. Athayde *et al.*, (2021) reinforce that the association between periodontal inflammation and neurodegeneration is consistent across different types of study, including clinical, laboratory and epidemiological ones. Facchini and Bona (2024) conclude that, although absolute causality still requires further study, the body of evidence points to a solid connection that justifies clinical and scientific attention.

3.3 CLINICAL IMPLICATIONS FOR DENTAL PRACTICE IN THE CARE OF THE ELDERLY PATIENT

Arruda *et al.*, (2024) emphasise that periodontal health should be treated as an integral part of systemic health, especially in individuals with cognitive decline. In this same sense, Conceição *et al.*, (2023) demonstrate that uncontrolled periodontal inflammation contributes to aggravating neurodegenerative conditions, making dental intervention strategic in the prevention of complications.

Monteiro *et al.*, (2025) stress that the progression of the disease compromises the patient's capacity to perform adequate oral hygiene, increasing the risk of bacterial accumulation and inflammation. Siqueira, Vincis and Guimarães (2021) add that the loss of functional autonomy demands adapted dental strategies, including regular appointments and simplified maintenance plans.

The involvement of caregivers in the process of maintaining oral health also proves indispensable. Parreira and Santos (2025) emphasise that appropriately instructed caregivers contribute significantly to reducing the progression of periodontal disease in older adults with Alzheimer's disease. Arruda *et al.*, (2024) add that the training of these carers promotes greater adherence to oral hygiene routines, preventing infectious aggravations.

Shao *et al.*, (2025) demonstrate that regenerative therapies, such as the use of stem cells, promote significant periodontal improvement, positively impacting the systemic inflammatory response. Complementing this perspective, Monteiro *et al.*, (2025) observe that even more traditional interventions, when applied early, are already capable of reducing bacterial load and modulating inflammation.

The clinical implications of this relationship reinforce the importance of multiprofessional action. Conceição *et al.*, (2023) state that comprehensive care for the older adult with Alzheimer's disease must involve collaboration between dentistry, geriatrics, neurology and support teams. Likewise, Siqueira, Vincis and Guimarães (2021) highlight that the integration between specialties allows the construction of effective therapeutic plans, considering both oral health and cognitive status.

4 FINAL CONSIDERATIONS

The relationship between periodontitis and Alzheimer's disease proved to be grounded in inflammatory and infectious mechanisms capable of directly connecting oral health to brain health. The delimiting question — in what way can periodontitis influence the development and progression of Alzheimer's disease — was able to be answered on the basis of the analysis of the biological processes shared between both conditions. It was observed that

systemic inflammation, the presence of periodontal pathogens in cerebral regions and the alteration of the oral microbiome exert a significant impact on neurodegeneration, reinforcing that periodontal health extends beyond the limits of the oral cavity. In this way, the interconnection between oral inflammation and cognitive decline proves to be consistent and reinforces the need for broader attention in the care of the older adult.

On the basis of the synthesis presented, it is concluded that the specific objectives were fully addressed, making it possible to understand the biological mechanisms involved, analyse the recent scientific evidence and identify clinical implications relevant to dental practice. The general objective was also achieved, showing that periodontitis can, indeed, contribute to the worsening of Alzheimer's disease and that adequate periodontal care assumes a significant preventive role. Thus, the importance of integrated approaches and of valuing oral health as an essential component of the promotion of the older adult's global health is highlighted.

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PROSTHODONTIC REHABILITATION IN PATIENTS WITH BRUXISM: CLINICAL CHALLENGES AND THERAPEUTIC STRATEGIES

REABILITAÇÃO PROTÉTICA EM PACIENTES COM BRUXISMO: DESAFIOS CLÍNICOS E ESTRATÉGIAS TERAPÊUTICAS

REHABILITACIÓN PROTÉSICA EN PACIENTES CON BRUXISMO: DESAFÍOS CLÍNICOS Y ESTRATEGIAS TERAPÉUTICAS

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ABSTRACT

Bruxism is a masticatory muscle activity characterized by clenching, grinding of the teeth, or mandibular bracing, which may occur during sleep or wakefulness. Due to its potential to cause tooth wear, restorative fractures, muscular alterations, and functional impairment of the stomatognathic system, this condition represents a significant challenge for restorative and rehabilitative dentistry. The present study aimed to review the scientific literature regarding the main clinical challenges involved in prosthodontic rehabilitation of patients with bruxism and to analyze the therapeutic strategies employed to increase treatment longevity. This narrative literature review was conducted through searches in the PubMed/MEDLINE, SciELO, Google Scholar, and ScienceDirect databases, including studies published between 2016 and 2026. The findings demonstrated that patients with bruxism are at greater risk of severe tooth wear, mechanical complications in restorations and prostheses, and increased susceptibility to failures in implant-supported rehabilitations. The literature also highlights the importance of careful selection of restorative materials, appropriate occlusal planning, the use of stabilization occlusal splints, and periodic clinical follow-up as key strategies to minimize the effects of parafunctional activity. It can be concluded that a multidisciplinary and individualized approach is essential to promote greater clinical predictability, functional stability, and longevity of prosthodontic rehabilitations in patients with bruxism.

Keywords: Bruxism. Prosthodontic Rehabilitation. Dental Prosthesis. Occlusal Splints. Clinical Longevity.

RESUMO

O bruxismo é uma atividade dos músculos mastigatórios caracterizada pelo apertamento, ranger dos dentes ou tensionamento mandibular, podendo ocorrer durante o sono ou em estado de vigília. Devido ao seu potencial de provocar desgaste dentário, fraturas restauradoras, alterações musculares e comprometimento funcional do sistema estomatognático, essa condição representa um importante desafio para a Odontologia restauradora e reabilitadora. O presente estudo teve como objetivo revisar a literatura científica acerca dos principais desafios clínicos envolvidos na reabilitação protética de pacientes com bruxismo e analisar as estratégias terapêuticas empregadas para aumentar a longevidade dos tratamentos. Trata-se de uma revisão narrativa da literatura realizada por meio de buscas nas bases de dados PubMed/MEDLINE, SciELO, Google Scholar e ScienceDirect, contemplando estudos publicados entre 2016 e 2026. Os resultados demonstraram que pacientes bruxômanos apresentam maior risco de desgaste dentário severo, complicações mecânicas em restaurações e próteses, além de maior suscetibilidade a falhas em reabilitações implantossuportadas. A literatura também evidencia a importância da seleção criteriosa dos materiais restauradores, do adequado planejamento oclusal, do uso de placas oclusais estabilizadoras e do acompanhamento clínico periódico como estratégias fundamentais para minimizar os efeitos da atividade parafuncional. Conclui-se que a abordagem multidisciplinar e individualizada é essencial para promover maior previsibilidade clínica, estabilidade funcional e longevidade das reabilitações protéticas em pacientes com bruxismo.

Palavras-chave: Bruxismo. Reabilitação Protética. Prótese Dentária. Placas Oclusais. Longevidade Clínica.

RESUMEN

El bruxismo es una actividad de los músculos masticatorios caracterizada por el apretamiento, rechinamiento de los dientes o tensión mandibular, que puede ocurrir durante

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el sueño o en estado de vigilia. Debido a su potencial para provocar desgaste dental, fracturas restauradoras, alteraciones musculares y compromiso funcional del sistema estomatognático, esta condición representa un importante desafío para la Odontología restauradora y rehabilitadora. El presente estudio tuvo como objetivo revisar la literatura científica sobre los principales desafíos clínicos involucrados en la rehabilitación protésica de pacientes con bruxismo y analizar las estrategias terapéuticas empleadas para aumentar la longevidad de los tratamientos. Se trata de una revisión narrativa de la literatura realizada mediante búsquedas en las bases de datos PubMed/MEDLINE, SciELO, Google Scholar y ScienceDirect, contemplando estudios publicados entre 2016 y 2026. Los resultados demostraron que los pacientes con bruxismo presentan mayor riesgo de desgaste dental severo, complicaciones mecánicas en restauraciones y prótesis, además de mayor susceptibilidad a fallos en rehabilitaciones implantosoportadas. La literatura también evidencia la importancia de la selección criteriosa de los materiales restauradores, de la adecuada planificación oclusal, del uso de férulas oclusales estabilizadoras y del seguimiento clínico periódico como estrategias fundamentales para minimizar los efectos de la actividad parafuncional. Se concluye que el abordaje multidisciplinario e individualizado es esencial para promover mayor previsibilidad clínica, estabilidad funcional y longevidad de las rehabilitaciones protésicas en pacientes con bruxismo.

Palabras clave: Bruxismo. Rehabilitación Protésica. Prótesis Dental. Férulas Oclusales. Longevidad Clínica.

1 INTRODUCTION

Bruxism is currently defined as a masticatory muscle activity characterized by clenching, grinding of the teeth, bracing or thrusting of the mandible, with these manifestations occurring either in isolation or in association during sleep or wakefulness. In recent decades, the understanding of this condition has undergone important conceptual transformations, no longer being considered exclusively a disorder but rather a behaviour that may act as a risk factor or a protective factor for different clinical outcomes, depending on the intensity, frequency and context in which it manifests. In addition, bruxism has a multifactorial aetiology, involving neurological, behavioural, psychological and physiological factors, which contributes to its high prevalence and diagnostic complexity (LOBBEZOO *et al.*, 2018).

Among the main clinical consequences associated with bruxism, the following stand out: progressive tooth wear, fractures of dental structures, hypersensitivity, muscle fatigue, temporomandibular alterations and functional impairment of the stomatognathic system. In more severe cases, continuous parafunctional activity may result in significant loss of dental structure and reduction of the vertical dimension of occlusion, requiring complex restorative and rehabilitative interventions. In this context, the literature shows that patients with bruxism frequently require individualized prosthodontic approaches for the re-establishment of masticatory function, aesthetics and occlusal stability (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016).

Prosthodontic rehabilitation in individuals with bruxism represents an important clinical challenge due to the high occlusal loads generated during episodes of clenching and grinding of the teeth. These forces may compromise the longevity of direct and indirect restorations, fixed prostheses, removable prostheses and implant-supported rehabilitations. Recent studies demonstrate that patients with bruxism are at greater risk of mechanical complications, including ceramic fractures, loosening of prosthetic screws, accelerated wear of restorative materials and failures in prosthetic components, requiring careful planning and continuous monitoring (MELO *et al.*, 2019; SHAFIEE; NOURIZADEH, 2025).

In view of these challenges, different therapeutic strategies have been proposed with the aim of increasing the predictability and durability of prosthodontic rehabilitations. Among the most widely used approaches, the following stand out: the use of stabilization occlusal splints, the careful selection of restorative materials with high mechanical resistance, appropriate occlusal adjustment, the balanced distribution of masticatory loads and the implementation of periodic clinical follow-up protocols. Recent evidence suggests that the use of occlusal splints constitutes one of the most effective interventions to reduce the deleterious effects of bruxism on dental structures and prosthodontic rehabilitations, contributing to a

better distribution of occlusal forces and protection of restorative components (MINAKUCHI *et al.*, 2022; AINOOSAH *et al.*, 2024).

Considering the high prevalence of bruxism and its significant impact on the longevity of restorative and prosthodontic treatments, it becomes essential to understand the main clinical challenges related to the rehabilitation of these patients, as well as the therapeutic strategies currently available to minimize complications and optimize clinical outcomes. Thus, the present study aims to review the scientific literature regarding the challenges of prosthodontic rehabilitation in patients with bruxism and to analyze the main therapeutic approaches employed to promote greater predictability, functional stability and longevity of oral rehabilitations.

2 METHODOLOGY

This is a narrative literature review developed with the aim of analyzing the clinical challenges and therapeutic strategies related to prosthodontic rehabilitation in patients with bruxism, emphasizing the impacts of parafunctional activity on teeth, restorations, conventional prostheses and implant-supported rehabilitations.

The bibliographic search was carried out in internationally recognized scientific databases, including PubMed/MEDLINE, SciELO and ScienceDirect, considered relevant sources for scientific production in the dental field. Studies published between January 2016 and June 2026 were selected, encompassing the last ten years of scientific production on the diagnosis, clinical repercussions and therapeutic approaches aimed at the management of bruxism in patients undergoing oral rehabilitation.

For the search strategy, descriptors in Portuguese and English related to the topic were used, including the terms: “bruxismo”, “reabilitação protética”, “prótese dentária”, “próteses sobre implantes”, “placas oclusais”, “desgaste dentário”, “Bruxism”, “Prosthetic Rehabilitation”, “Dental Prosthesis”, “Implant-Supported Prosthesis”, “Occlusal Splints” and “Tooth Wear”. The descriptors were combined using the Boolean operators AND and OR, allowing the sensitivity and specificity of the search to be broadened.

Original articles, systematic reviews, narrative reviews, international consensuses and clinical studies that directly addressed the relationship between bruxism and prosthodontic rehabilitation were included, as well as strategies aimed at the prevention of complications and the increase in the longevity of restorative treatments. Duplicate studies, works published outside the established period, abstracts from scientific events, letters to the editor, dissertations, theses and publications that did not present a direct relationship with the objective of the review were excluded.

The selection of studies occurred through the analysis of titles, abstracts and full texts, considering the methodological relevance and scientific contribution of each publication to the understanding of the topic. After the critical reading of the selected articles, the information was organized and synthesized descriptively, encompassing aspects related to the current concepts of bruxism, the impacts on dental and prosthetic structures, the risk factors for restorative and implant failures, as well as the main therapeutic strategies employed to optimize the predictability, functional stability and longevity of prosthodontic rehabilitations.

3 RESULTS AND DISCUSSION

3.1 CURRENT CONCEPTS AND EPIDEMIOLOGICAL ASPECTS OF BRUXISM

The understanding of bruxism has undergone important transformations in recent decades as a result of the advancement of knowledge about its pathophysiology. For many years, the condition was associated mainly with occlusal interferences and mechanical imbalances of the masticatory system. However, more recent evidence has demonstrated that this interpretation is insufficient to explain the complexity of the mechanisms involved in its occurrence. Currently, bruxism is defined as a masticatory muscle activity characterized by clenching, grinding of the teeth, bracing or thrusting of the mandible, which may occur during sleep or wakefulness. In addition, it has come to be understood as a behaviour that may act as a risk factor or a protective factor for different clinical outcomes, depending on its intensity, frequency and context of occurrence (LOBBEZOO *et al.*, 2018).

Contemporary literature recognizes two distinct manifestations of the condition: sleep bruxism and awake bruxism. Although both share similar clinical characteristics, the evidence suggests important differences in their pathophysiological mechanisms. Sleep bruxism presents a greater association with neurophysiological phenomena related to micro-arousals and autonomic activation, whereas awake bruxism demonstrates a more consistent relationship with emotional, behavioural and psychosocial factors, especially stress and anxiety. This distinction has clinical relevance, as it reinforces the need for individualized diagnostic and therapeutic approaches for each manifestation (LOBBEZOO *et al.*, 2018; MELO *et al.*, 2019; LAL; SANKARI; WEBER, 2024).

From an epidemiological point of view, bruxism presents a wide variation in prevalence among the available studies. High-level evidence demonstrates that awake bruxism affects approximately 22% to 30% of adults, whereas sleep bruxism presents an estimated prevalence between 1% and 15% (MELO *et al.*, 2019). However, the interpretation of these data requires caution, since the literature still presents important methodological heterogeneity. The use of different diagnostic criteria, varying between self-report, clinical

examination, electromyography and polysomnography, makes direct comparisons between studies difficult and constitutes one of the main limitations for determining the real magnitude of the condition (LOBBEZOO *et al.*, 2018; MELO *et al.*, 2019).

Another widely accepted aspect refers to the multifactorial nature of bruxism. Factors such as alcohol consumption, smoking, caffeine, use of psychotropic medications, sleep alterations, stress and anxiety have been consistently associated with parafunctional activity. However, the literature demonstrates that these associations should not be interpreted in isolation, since the development of bruxism results from the interaction between biological, neurological, behavioural and environmental factors. This understanding has contributed to the progressive abandonment of aetiological models centred exclusively on occlusal factors and has favoured more comprehensive approaches to the clinical management of the condition (MELO *et al.*, 2019; LAL; SANKARI; WEBER, 2024).

From the perspective of prosthodontic rehabilitation, the early recognition of bruxism plays a fundamental role, since excessive muscle activity may generate mechanical overloads capable of accelerating tooth wear, compromising restorations and reducing the longevity of conventional and implant-supported prostheses. Thus, an adequate understanding of the conceptual and epidemiological aspects of the condition constitutes an essential step for the planning of preventive and therapeutic strategies aimed at the preservation of masticatory function, occlusal stability and the durability of rehabilitative treatments (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016).

3.2 IMPACTS OF BRUXISM ON THE TEETH AND THE STOMATOGNATHIC SYSTEM

Bruxism is associated with a series of functional and structural alterations capable of compromising the integrity of the stomatognathic system. The excessive and repetitive muscle activity characteristic of the condition promotes an increase in the occlusal loads applied to teeth, periodontium, masticatory muscles and temporomandibular joints, favouring the development of different clinical manifestations. However, the magnitude of these effects varies considerably among individuals, being influenced by the intensity, frequency and duration of parafunctional activity, as well as by the adaptive capacity of the tissues involved (MELO *et al.*, 2019; LAL; SANKARI; WEBER, 2024).

Among the repercussions most frequently associated with bruxism, progressive tooth wear stands out. In more severe cases, the continuous loss of dental structure may compromise the occlusal anatomy, favour dentine exposure, reduce the vertical dimension of occlusion and generate complex rehabilitative demands. However, although tooth wear is frequently related to parafunctional activity, the literature demonstrates that its occurrence

has a multifactorial character, also involving erosive factors, dietary habits and systemic conditions. Thus, the presence of wear should not be interpreted in isolation as definitive evidence of bruxism, requiring a comprehensive clinical assessment for the adequate determination of its aetiology (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; MELO *et al.*, 2019).

In addition to the damage to dental tissues, bruxism has been associated with muscular and articular manifestations, including muscle fatigue, orofacial pain, mandibular stiffness and functional limitation. Although studies demonstrate a frequent association between bruxism and signs or symptoms related to temporomandibular disorders, the current literature has not yet established a consensus on the existence of a direct causal relationship between these conditions. High-level evidence suggests that the association is plausible, but remains limited by the methodological heterogeneity of the studies and by the difficulties inherent to the precise diagnosis of bruxism. This limitation reinforces the need for caution in the interpretation of clinical findings and in the attribution of causality between parafunctional activity and temporomandibular disorders (MELO *et al.*, 2019).

The repercussions of bruxism assume even greater importance when analyzed from the restorative and prosthodontic perspective. The increase in mechanical loads may favour fractures of restorations, accelerated wear of restorative materials, decementation of prostheses and failures in prosthetic components. Although the literature presents heterogeneous results regarding the impact of bruxism on different types of restorations, there is consensus that parafunctional activity represents a relevant clinical factor in the assessment of the risk of mechanical complications, especially in patients undergoing extensive rehabilitations (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; MELO *et al.*, 2019).

In implant-supported rehabilitations, the available evidence demonstrates even greater concern regarding the effects of parafunctional overloads. The absence of the periodontal ligament reduces the physiological capacity to dissipate masticatory forces, favouring the direct transmission of loads to the implant-bone interface and to the prosthetic components. Recent reviews indicate an increased risk of mechanical complications, including screw loosening, fractures of components and prosthetic failures in patients with bruxism. However, the strength of this association is still limited by the absence of uniform diagnostic criteria and by the heterogeneity of the available studies. Despite these limitations, the body of evidence supports the need to consider bruxism as an important risk factor during the planning and follow-up of implant-supported rehabilitations (SHAFIEE; NOURIZADEH, 2025; WANDEKOKEN *et al.*, 2024).

3.3 CHALLENGES OF PROSTHODONTIC REHABILITATION IN PATIENTS WITH BRUXISM

The prosthodontic rehabilitation of patients with bruxism represents one of the greatest challenges of contemporary restorative dentistry, mainly due to the high mechanical loads generated by parafunctional activity. Unlike physiological masticatory forces, which have an intermittent character and relatively balanced distribution, the forces associated with bruxism tend to occur in a repetitive, prolonged and frequently non-axial manner. This condition significantly increases the stress applied to teeth, restorations, prostheses and implants, requiring careful planning to minimize the risk of mechanical and biological complications over time (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; SHAFIEE; NOURIZADEH, 2025).

One of the main clinical challenges is related to the predictability of rehabilitative outcomes. Although bruxism is widely recognized as a risk factor for prosthetic failures, the literature still presents important limitations regarding the precise quantification of this impact. Evidence reviews point to a consistent association between parafunctional activity and an increased occurrence of restorative fractures, accelerated wear of materials, retention failures and mechanical complications in implant-supported prostheses. However, the heterogeneity of the diagnostic methods employed in the studies makes it difficult to determine the real magnitude of these risks, making the cautious interpretation of the available results necessary (MELO *et al.*, 2019; SHAFIEE; NOURIZADEH, 2025).

Another relevant aspect refers to the structural impairment frequently observed in these patients. Cases of advanced tooth wear may result in significant loss of coronal structure, reduction of the available prosthetic space and alterations of the vertical dimension of occlusion, making restorative planning more complex. In these situations, rehabilitation is not limited to the replacement of lost tissues but requires the functional reconstruction of the stomatognathic system, considering occlusal, aesthetic and biomechanical aspects capable of withstanding the functional and parafunctional demands present in the long term (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016).

In implant-supported rehabilitations, the challenges become even more evident due to the absence of the periodontal ligament, the structure responsible for the physiological dissipation of masticatory loads in natural teeth. Recent evidence indicates that patients with bruxism present greater susceptibility to mechanical complications, including screw loosening, fractures of prosthetic components and structural failures of the rehabilitations. In addition, systematic reviews suggest an increased risk of implant loss in individuals with

intense parafunctional activity, although the strength of this association is still limited by the methodological variability of the available studies. Thus, the recognition of bruxism as a risk factor becomes fundamental for the definition of clinical protocols aimed at reducing overloads and increasing the longevity of implant-supported treatments (SHAFIEE; NOURIZADEH, 2025; WANDEKOKEN *et al.*, 2024).

In view of this scenario, the success of prosthodontic rehabilitation in patients with bruxism depends on the integration of multiple factors, including adequate diagnosis, careful selection of restorative materials, individualized biomechanical planning and continuous clinical monitoring. Rather than contraindicating certain treatments, current evidence suggests that the early identification of risk factors allows the adoption of preventive strategies capable of minimizing complications and providing predictable clinical results, even in individuals subjected to high functional demands (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; WANDEKOKEN *et al.*, 2024; SHAFIEE; NOURIZADEH, 2025).

3.4 SELECTION OF RESTORATIVE AND PROSTHETIC MATERIALS IN PATIENTS WITH BRUXISM

The selection of restorative materials constitutes a fundamental step in the planning of the prosthodontic rehabilitation of patients with bruxism, since the high mechanical loads generated by parafunctional activity significantly increase the risk of structural failures. In this context, the choice of material should not be based exclusively on aesthetic criteria but also on biomechanical properties capable of withstanding repetitive and intense forces over time. The literature demonstrates that the longevity of restorations is directly related to the adequate combination between mechanical resistance, functional behaviour and the individual clinical characteristics of the patient (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016).

Historically, highly aesthetic restorative materials were frequently prioritized in extensive rehabilitations. However, current evidence suggests that patients with bruxism require a more careful assessment of the relationship between aesthetics and mechanical resistance. Although ceramic materials present excellent optical properties and high biocompatibility, their use in individuals subjected to occlusal overloads requires special attention due to the potential risk of chipping, fractures or accelerated wear in certain clinical situations. Thus, the choice of material should consider not only its isolated properties but also factors such as the extent of the rehabilitation, occlusal pattern, intensity of parafunctional activity and location of the restoration in the dental arch (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016).

Another widely discussed aspect refers to the capacity of restorative materials to absorb and distribute functional loads. Although there is no absolute consensus on an ideal material for all patients with bruxism, the literature demonstrates that clinical success depends more on the adequate application of biomechanical principles than exclusively on the choice of restorative material. This observation reinforces that prosthetic failures frequently result from the interaction between material, restorative design, occlusal planning and the intensity of parafunctional forces, and not only from the intrinsic properties of the materials used (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; MELO *et al.*, 2019).

In implant-supported rehabilitations, the selection of materials assumes even greater relevance due to the absence of the periodontal ligament and the consequent reduction of the physiological capacity to cushion loads. Recent reviews indicate that prosthetic planning should prioritize strategies capable of reducing excessive stress concentrations on implants and prosthetic components, considering characteristics such as the type of framework, the restorative material employed and the distribution of occlusal loads. In this scenario, the selection of materials should integrate a global biomechanical planning aimed at reducing the risk of mechanical complications and increasing the longevity of the rehabilitation (WANDEKOKEN *et al.*, 2024; SHAFIEE; NOURIZADEH, 2025).

Thus, current evidence indicates that there is no single material capable of eliminating the risks associated with bruxism. Restorative success depends on the combination of careful selection of materials, adequate occlusal planning, control of risk factors and periodic clinical follow-up. This integrated approach makes it possible to maximize the durability of rehabilitations and minimize the occurrence of failures in patients subjected to high functional and parafunctional demands (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; SHAFIEE; NOURIZADEH, 2025).

3.5 OCCLUSAL SPLINTS AS A STRATEGY FOR PROTECTION AND CONTROL OF BRUXISM

Occlusal splints constitute one of the most widely used interventions in the clinical management of bruxism, especially in patients undergoing restorative and prosthodontic treatments. Their wide use is related to their capacity to promote the mechanical protection of dental and restorative structures against the excessive loads generated by parafunctional activity. However, although their use is widely accepted in clinical practice, the literature demonstrates that their benefits are more related to the reduction of the consequences of

bruxism than to the definitive elimination of the muscle activity responsible for the condition (MINAKUCHI *et al.*, 2022; CERÓN *et al.*, 2023).

The available evidence indicates that occlusal splints may contribute to the reduction of the damage associated with clenching and grinding of the teeth, minimizing tooth wear, restorative fractures and mechanical overloads on prostheses and implants. Recent systematic reviews demonstrate that different types of splints present favourable results regarding the protection of oral structures and the improvement of symptoms reported by patients. However, the magnitude of these benefits varies among studies, reflecting methodological differences, diagnostic criteria and characteristics of the interventions evaluated (AINOOSAH *et al.*, 2024; MINAKUCHI *et al.*, 2022).

Despite the favourable results observed in several studies, the literature still presents important limitations regarding the determination of the superiority of a specific type of occlusal splint. Evidence suggests that adjustable devices and certain modalities of biofeedback may present superior performance in some clinical outcomes, especially in the reduction of episodes of sleep bruxism and in the improvement of patients' quality of life. However, the results remain heterogeneous, preventing the establishment of definitive recommendations on which device should be considered standard for all clinical situations. This variability reinforces the need for individualization of treatment according to the characteristics of each patient (AINOOSAH *et al.*, 2024).

Another relevant aspect refers to the quality of the available evidence on the different therapeutic modalities for the control of bruxism. Critical assessments of systematic reviews demonstrate that a large part of the studies presents important methodological limitations, including reduced samples, short follow-up periods and high risk of bias. Consequently, although occlusal splints remain among the approaches most supported by the literature, the strength of the evidence is still insufficient to affirm absolute superiority in relation to other therapeutic modalities. In addition, the benefits observed are predominantly concentrated on the protection of oral structures and the reduction of the clinical impacts of the condition, and not necessarily on the definitive resolution of bruxism (CERÓN *et al.*, 2023; MINAKUCHI *et al.*, 2022).

From the perspective of prosthodontic rehabilitation, occlusal splints assume a strategic role in the preservation of the longevity of the treatments performed. In patients undergoing extensive or implant-supported rehabilitations, their use may contribute to a better distribution of occlusal loads and to the reduction of the risk of mechanical complications associated with parafunctional activity. Thus, although they do not represent a cure for bruxism, current evidence supports their use as an important auxiliary tool in the

control of the deleterious effects of the condition and in the protection of restorations, prostheses and implants over time (SHAFIEE; NOURIZADEH, 2025; WANDEKOKEN *et al.*, 2024; AINOOSAH *et al.*, 2024).

3.6 STRATEGIES FOR INCREASING THE LONGEVITY OF PROSTHODONTIC REHABILITATIONS IN PATIENTS WITH BRUXISM

The longevity of prosthodontic rehabilitations in patients with bruxism depends on a multifactorial approach that transcends the simple replacement of lost dental structures. Considering that parafunctional activity imposes mechanical loads greater than those observed under physiological conditions, clinical success is directly related to the integration between adequate diagnosis, individualized biomechanical planning and periodic follow-up. In this context, current evidence suggests that the early identification of risk factors constitutes one of the main strategies for reducing mechanical complications and increasing the predictability of rehabilitative treatments (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; SHAFIEE; NOURIZADEH, 2025).

Occlusal planning represents one of the fundamental pillars for the preservation of restorations and prostheses in patients with bruxism. Although there is no absolute consensus on an ideal occlusal scheme for all clinical situations, the literature demonstrates that the adequate distribution of masticatory and parafunctional loads contributes to reducing excessive stress concentrations on teeth, restorations and prosthetic components. Thus, the control of occlusal contacts and the pursuit of greater functional balance remain relevant measures in the prevention of failures related to mechanical overload (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; WANDEKOKEN *et al.*, 2024).

In implant-supported rehabilitations, strategies aimed at reducing biomechanical stress assume an even more relevant role. Recent evidence indicates that factors such as adequate positioning of the implants, careful distribution of the prosthetic elements, use of favourable prosthetic designs and continuous monitoring may contribute to minimizing complications associated with bruxism. Although none of these measures is capable of completely eliminating the risks arising from parafunctional activity, their joint application seems to favour greater clinical stability and better performance of the rehabilitations over time (SHAFIEE; NOURIZADEH, 2025; WANDEKOKEN *et al.*, 2024).

Another aspect widely highlighted in the literature refers to the importance of the longitudinal follow-up of these patients. Considering the dynamic character of bruxism and the possibility of alterations in the intensity of muscle activity throughout life, periodic assessments allow the early identification of signs of wear, restorative failures, loosening of

prosthetic components and other mechanical complications. In addition, the use of occlusal splints as a complementary protective measure may contribute to reducing the deleterious effects of parafunctional activity, especially in patients undergoing extensive or implant-supported rehabilitations (AINOOSAH *et al.*, 2024; MINAKUCHI *et al.*, 2022).

Thus, the available evidence indicates that the success of prosthodontic rehabilitations in patients with bruxism does not depend on a single isolated intervention, but on the combination of different preventive and therapeutic strategies. The association between careful planning, adequate selection of materials, occlusal control, mechanical protection and continuous clinical follow-up represents the most consistent approach to minimizing complications and increasing the longevity of rehabilitative treatments in individuals exposed to high functional and parafunctional demands (MENGATTO; COELHO-DE-SOUZA; SOUZA JUNIOR, 2016; SHAFIEE; NOURIZADEH, 2025).

4 CONCLUSION

The present literature review made it possible to analyze the main challenges involved in the prosthodontic rehabilitation of patients with bruxism. The available evidence indicates that parafunctional activity is associated with an increased risk of tooth wear, restorative failures, prosthetic complications and impairment of the longevity of rehabilitative treatments.

It was observed that the clinical predictability of these treatments depends on the integration between adequate diagnosis, individualized biomechanical planning, careful selection of restorative materials and periodic follow-up. In addition, occlusal splints stand out as an important auxiliary strategy in the protection of dental and prosthetic structures, contributing to minimizing the effects of mechanical overloads associated with bruxism.

Thus, it can be concluded that the success of prosthodontic rehabilitation in patients with bruxism depends on an individualized and multidisciplinary approach. However, the heterogeneity of the available evidence reinforces the need for studies with greater methodological rigour to broaden the knowledge about the most effective strategies for increasing the longevity of rehabilitative treatments.

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RETATRUTIDE USE IN THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND OBESITY: AN INTEGRATIVE REVIEW

USO DA RETATRUTIDA NO TRATAMENTO DA ESTEATOSE HEPÁTICA E OBESIDADE: REVISÃO INTEGRATIVA

USO DE LA RETATRUTIDA EN EL TRATAMIENTO DE LA ESTEATOSIS HEPÁTICA Y LA OBESIDAD: REVISIÓN INTEGRADORA

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ABSTRACT

Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) are major global public health challenges, being associated with increased morbidity, mortality, and healthcare costs. In this context, novel pharmacological therapies have been developed to promote significant weight reduction and improve metabolic and hepatic outcomes. Retatrutide, a triple agonist of the GLP-1, GIP, and glucagon receptors, has emerged as an innovative therapeutic approach due to its ability to simultaneously target multiple pathways involved in energy metabolism regulation. The aim of this study was to analyze the available scientific evidence regarding the use of retatrutide in the treatment of obesity and MASLD. This integrative literature review included studies published between 2016 and 2026, identified through searches in the MEDLINE/PubMed and ScienceDirect databases. Clinical trials, prospective studies, systematic reviews, and relevant publications addressing the topic were included. The analyzed evidence demonstrated that retatrutide promotes weight reductions exceeding 24%, in addition to significant improvements in metabolic, glycemic, and cardiovascular parameters. In patients with MASLD, substantial reductions in liver fat content, exceeding 80% at higher doses, were observed, along with high rates of normalization of hepatic fat levels. Compared with previously established incretin-based therapies, such as semaglutide and tirzepatide, retatrutide showed particularly promising results. In conclusion, retatrutide represents one of the most innovative pharmacological approaches currently under development for the treatment of obesity and MASLD, although long-term studies are still required to confirm its sustained efficacy and clinical safety.

Keywords: Retatrutide. Obesity. MASLD. Weight Loss. Incretin Therapy.

RESUMO

A obesidade e a doença hepática gordurosa associada à disfunção metabólica (Metabolic Dysfunction-Associated Steatotic Liver Disease – MASLD) representam importantes desafios de saúde pública mundial, estando associadas ao aumento da morbimortalidade e a elevados custos assistenciais. Nesse contexto, novas terapias farmacológicas têm sido desenvolvidas com o objetivo de promover redução ponderal significativa e melhora dos desfechos metabólicos e hepáticos. A retatrutida, um agonista triplo dos receptores de GLP-1, GIP e glucagon, surge como uma abordagem inovadora devido à sua capacidade de atuar simultaneamente sobre múltiplas vias envolvidas na regulação do metabolismo energético. O objetivo deste estudo foi analisar as evidências científicas disponíveis acerca do uso da retatrutida no tratamento da obesidade e da MASLD. Trata-se de uma revisão integrativa da literatura realizada a partir de estudos publicados entre 2016 e 2026, identificados nas bases MEDLINE/PubMed e ScienceDirect. Foram incluídos ensaios clínicos, estudos prospectivos, revisões sistemáticas e artigos relevantes relacionados à temática. As evidências analisadas demonstraram que a retatrutida promove perdas ponderais superiores a 24%, além de melhorias significativas em parâmetros metabólicos, glicêmicos e cardiovasculares. Em pacientes com MASLD, observou-se redução expressiva da gordura hepática, superior a 80% nas maiores doses avaliadas, acompanhada de elevadas taxas de normalização do conteúdo lipídico hepático. Em comparação com terapias incretínicas previamente estabelecidas, como semaglutida e tirzepatida, a retatrutida apresentou resultados particularmente promissores. Conclui-se que a retatrutida representa uma das abordagens farmacológicas mais inovadoras atualmente em desenvolvimento para o tratamento da obesidade e da MASLD, embora estudos de longo prazo ainda sejam necessários para confirmar sua eficácia sustentada e segurança clínica.

Palavras-chave: Retatrutida. Obesidade. MASLD. Perda de Peso. Terapia Incretínica.

RESUMEN

La obesidad y la enfermedad hepática grasa asociada a la disfunción metabólica (Metabolic Dysfunction-Associated Steatotic Liver Disease – MASLD) representan importantes desafíos de salud pública mundial, estando asociadas al aumento de la morbilidad y a elevados costes asistenciales. En este contexto, nuevas terapias farmacológicas han sido desarrolladas con el objetivo de promover una reducción ponderal significativa y la mejora de los desenlaces metabólicos y hepáticos. La retatrutida, un agonista triple de los receptores de GLP-1, GIP y glucagón, surge como un abordaje innovador debido a su capacidad de actuar simultáneamente sobre múltiples vías implicadas en la regulación del metabolismo energético. El objetivo de este estudio fue analizar las evidencias científicas disponibles acerca del uso de la retatrutida en el tratamiento de la obesidad y de la MASLD. Se trata de una revisión integradora de la literatura realizada a partir de estudios publicados entre 2016 y 2026, identificados en las bases MEDLINE/PubMed y ScienceDirect. Se incluyeron ensayos clínicos, estudios prospectivos, revisiones sistemáticas y artículos relevantes relacionados con la temática. Las evidencias analizadas demostraron que la retatrutida promueve pérdidas ponderales superiores al 24%, además de mejoras significativas en parámetros metabólicos, glucémicos y cardiovasculares. En pacientes con MASLD, se observó una reducción expresiva de la grasa hepática, superior al 80% en las mayores dosis evaluadas, acompañada de elevadas tasas de normalización del contenido lipídico hepático. En comparación con terapias incretínicas previamente establecidas, como semaglutida y tirzepatida, la retatrutida presentó resultados particularmente prometedores. Se concluye que la retatrutida representa uno de los abordajes farmacológicos más innovadores actualmente en desarrollo para el tratamiento de la obesidad y de la MASLD, aunque aún son necesarios estudios de largo plazo para confirmar su eficacia sostenida y seguridad clínica.

Palabras clave: Retatrutida. Obesidad. MASLD. Pérdida de Peso. Terapia Incretínica.

1 INTRODUCTION

Obesity currently represents one of the greatest challenges to global public health, being recognised as a chronic, multifactorial, and progressive disease associated with important metabolic, cardiovascular, and inflammatory repercussions. In recent decades, the marked increase in its prevalence has been accompanied by the growth of various chronic non-communicable conditions, including type 2 diabetes mellitus, systemic arterial hypertension, dyslipidaemias, and metabolic liver diseases. In addition to significantly compromising the quality of life of affected individuals, obesity is associated with increased morbidity and mortality and with rising healthcare-related costs, constituting a condition of high epidemiological and clinical relevance. In this scenario, the search for therapeutic strategies capable of promoting sustained weight loss and overall improvement of the metabolic profile has become one of the main priorities of contemporary medicine (WILDING *et al.*, 2021; JASTREBOFF *et al.*, 2022).

Among the main complications associated with excess adiposity is metabolic dysfunction-associated steatotic liver disease (MASLD), the terminology currently adopted to replace the former designation of non-alcoholic fatty liver disease. Considered one of the most prevalent chronic liver diseases in the world, MASLD is characterised by the excessive accumulation of fat in the liver in individuals with underlying metabolic alterations, presenting a close relationship with obesity, insulin resistance, and metabolic syndrome. Disease progression may culminate in metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Prospective evidence demonstrates that the severity of fibrosis constitutes the main prognostic determinant of the disease, being associated with a substantial increase in the risk of hepatic complications and mortality, which reinforces the need for effective therapeutic interventions capable of acting on the pathophysiological mechanisms involved in its progression (SANYAL *et al.*, 2021).

Although lifestyle changes remain the cornerstone of the treatment of obesity and MASLD, achieving and maintaining clinically significant weight loss continues to represent an important challenge in clinical practice. In recent years, advances in the understanding of incretin physiology have driven the development of pharmacological therapies capable of acting simultaneously on multiple metabolic pathways involved in the regulation of body weight and energy homeostasis. In this context, glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated expressive results in reducing body weight and improving cardiometabolic parameters. Studies conducted with semaglutide showed relevant weight losses, accompanied by consistent metabolic benefits, while investigations in patients with steatohepatitis demonstrated a significant increase in the rates of resolution of liver disease,

consolidating the role of this therapeutic class in the management of metabolic diseases associated with obesity (WILDING *et al.*, 2021; NEWSOME *et al.*, 2021).

Subsequently, the development of dual GIP and GLP-1 receptor agonists further broadened the therapeutic perspectives in this area. Tirzepatide stood out for promoting weight reductions greater than those observed with isolated GLP-1 agonists, establishing a new paradigm for the pharmacological treatment of obesity. Building on these advances, retatrutide (LY3437943) emerged, an innovative molecule that combines the activation of the GLP-1, GIP, and glucagon receptors in a single pharmacological structure. Experimental evidence demonstrated that the combination of these three mechanisms promotes complementary effects on satiety, food intake, glycaemic control, lipid metabolism, and energy expenditure. Recent clinical studies revealed weight losses exceeding 24% after 48 weeks of treatment, in addition to substantial improvements in multiple metabolic markers, results that position retatrutide among the most promising therapies currently under development for the treatment of obesity (COSKUN *et al.*, 2022; JASTREBOFF *et al.*, 2023).

In addition to its effects on body weight, recent evidence suggests that retatrutide may exert a direct impact on the pathophysiology of MASLD. In patients with metabolic dysfunction-associated steatotic liver disease, treatment was associated with expressive reductions in hepatic fat, with decreases exceeding 80% at some evaluated doses, as well as high rates of normalisation of hepatic lipid content. These findings indicate that the benefits of the therapy may transcend isolated weight loss, contributing to the improvement of the metabolic and hepatic environment underlying disease progression. Considering the growing relevance of obesity and MASLD as public health problems and the emergence of recent evidence on the efficacy of retatrutide, it becomes essential to gather and critically analyse the available knowledge regarding this new therapeutic approach. Thus, the present study aims to conduct an integrative literature review on the use of retatrutide in the treatment of hepatic steatosis and obesity, synthesising the evidence related to its mechanisms of action, clinical efficacy, metabolic impact, and potential future perspectives.

2 METHODOLOGY

This is an integrative literature review, developed with the aim of gathering, analysing, and critically synthesising the available scientific evidence regarding the use of retatrutide in the treatment of obesity and metabolic dysfunction-associated steatotic liver disease (MASLD). The integrative review was chosen because it allows the incorporation of studies with different methodological designs, enabling a broad and up-to-date understanding of the investigated topic.

The bibliographic search strategy was carried out in the PubMed/MEDLINE and ScienceDirect databases and in electronic libraries linked to the international biomedical literature, covering publications available between January 2016 and June 2026. Descriptors in English combined by the Boolean operators AND and OR were used, including the terms: “retatrutide”, “LY3437943”, “obesity”, “weight loss”, “metabolic dysfunction-associated steatotic liver disease”, “MASLD”, “nonalcoholic fatty liver disease”, “NAFLD”, “metabolic dysfunction-associated steatohepatitis”, “MASH”, “GLP-1 receptor agonist”, “GIP”, and “glucagon receptor agonist”. The search strategies were adapted according to the specificities of each database consulted.

The following inclusion criteria were established: original scientific articles, randomised clinical trials, prospective studies, observational studies, and systematic reviews published in indexed and peer-reviewed journals; studies made fully available in the English language; research directly addressing the use of retatrutide or discussing its therapeutic role in the context of obesity, MASLD, and associated metabolic diseases. As exclusion criteria, editorials, letters to the editor, conference abstracts, research protocols, experimental studies without direct clinical applicability, duplicate publications, and articles unrelated to the proposed objective were considered.

After applying the eligibility criteria and critically reading the identified studies, the final sample comprised nine publications considered relevant to answering the guiding question of the review. Studies addressing the mechanism of action of retatrutide, its efficacy in the treatment of obesity, its impact on hepatic fat in patients with MASLD, as well as investigations involving related incretin therapies, used for the contextualisation and comparison of the observed clinical results, were included. The sample encompassed studies published in journals of high scientific impact, including the New England Journal of Medicine, Nature Medicine, Cell Metabolism, Baylor University Medical Center Proceedings, and Biomolecules.

Data analysis was carried out in a descriptive and comparative manner, considering methodological characteristics, study population, interventions employed, main clinical outcomes, and observed results. The selected studies were organised into thematic categories related to the pathophysiological mechanisms of retatrutide, the effects on body weight loss, the impact on the reduction of hepatic fat, and future therapeutic perspectives. The synthesis of the findings was conducted in a narrative manner, seeking to identify convergences, divergences, and existing gaps in the current scientific literature regarding the use of retatrutide in the treatment of obesity and hepatic steatosis.

3 RESULTS AND DISCUSSION

3.1 MECHANISMS OF ACTION OF RETATRUTIDE AND ITS METABOLIC RELEVANCE

Analysis of the included studies shows that the main innovation of retatrutide lies in the simultaneous activation of the GLP-1, GIP, and glucagon receptors, a characteristic that distinguishes it from conventional incretin therapies. This multimodal action allows interference in different mechanisms related to the control of body weight, glycaemic homeostasis, and energy metabolism, broadening the therapeutic potential of the molecule in the treatment of obesity and associated metabolic diseases (COSKUN *et al.*, 2022; KATSI *et al.*, 2025).

The effects mediated by the GLP-1 receptors are related mainly to increased satiety, reduced food intake, and improved glycaemic control. In parallel, activation of the GIP receptors potentiates insulin secretion and contributes to the enhancement of energy metabolism. Clinical evidence demonstrated that the combination of these two pathways promotes benefits superior to those observed with isolated GLP-1 agonists, a fact initially evidenced by the results obtained with tirzepatide in the treatment of obesity (WILDING *et al.*, 2021; JASTREBOFF *et al.*, 2022).

The main differential of retatrutide, however, lies in the incorporation of agonist activity on the glucagon receptors. Although traditionally associated with the regulation of glycaemia, glucagon also plays a relevant role in the elevation of energy expenditure and in the oxidation of fatty acids. Thus, the simultaneous activation of the three receptors favours not only the reduction of caloric intake but also the increase in energy consumption, resulting in a more pronounced negative energy balance and potentiating the weight loss observed in the clinical studies (COSKUN *et al.*, 2022).

The clinical relevance of this mechanism becomes particularly important in the context of obesity and MASLD, conditions that share insulin resistance, metabolic inflammation, and alterations in lipid metabolism. By acting simultaneously on these pathophysiological processes, retatrutide has the potential to promote broad metabolic benefits, contributing both to the reduction of body weight and to the improvement of the hepatic fat accumulation observed in the most recent studies (SANYAL *et al.*, 2024; KATSI *et al.*, 2025).

3.2 EFFICACY OF RETATRUTIDE IN THE TREATMENT OF OBESITY

Analysis of the included studies demonstrates that retatrutide represents one of the most promising advances in the pharmacotherapy of obesity. Its mechanism of action combines the activation of the GLP-1, GIP, and glucagon receptors, promoting complementary effects on satiety, glycaemic control, and energy expenditure. This

multifactorial action has aroused great scientific interest, especially due to its potential to produce weight reductions greater than those observed with previously available incretin therapies (COSKUN *et al.*, 2022; KATSI *et al.*, 2025).

The most expressive clinical results were observed in a randomised clinical trial involving individuals with obesity or overweight associated with comorbidities. After 48 weeks of treatment, participants who received retatrutide at doses of 8 mg and 12 mg showed mean weight reductions of 22.8% and 24.2%, respectively, demonstrating a clear dose-response relationship and efficacy superior to that observed in the placebo group. Furthermore, most patients achieved weight losses exceeding 10% and 15% of the initial body weight, results considered highly relevant for reducing cardiometabolic risk (JASTREBOFF *et al.*, 2023).

When compared with other incretin therapies, retatrutide showed a particularly expressive performance. Semaglutide promoted a mean reduction of approximately 14.9% of body weight, while tirzepatide achieved losses close to 20.9%. Although both represent important therapeutic advances, the results obtained with retatrutide suggest potential superiority regarding the magnitude of weight loss, possibly as a result of the additional activation of the glucagon receptors and the consequent increase in energy expenditure (WILDING *et al.*, 2021; JASTREBOFF *et al.*, 2022; JASTREBOFF *et al.*, 2023).

In addition to the reduction of body weight, significant improvements were observed in several metabolic parameters, including waist circumference, glycaemia, glycated haemoglobin, and blood pressure. These benefits reinforce that the effects of the therapy go beyond isolated weight loss, contributing to the overall improvement of the cardiometabolic profile of patients with obesity. Recent reviews corroborate these findings and highlight that retatrutide presents an acceptable safety profile and the potential to become established as one of the main pharmacological strategies for the treatment of obesity and its metabolic complications (ABOUELMAGD *et al.*, 2025; KATSI *et al.*, 2025).

Overall, the available evidence indicates that retatrutide establishes a new level of efficacy in the pharmacological treatment of obesity. However, studies with longer follow-up periods are still necessary to confirm the maintenance of the observed benefits and to evaluate their effects on long-term clinical outcomes, especially cardiovascular and metabolic ones (ABOUELMAGD *et al.*, 2025).

3.3 IMPACT OF RETATRUTIDE ON METABOLIC DYSFUNCTION-ASSOCIATED HEPATIC STEATOSIS (MASLD)

MASLD constitutes one of the main metabolic complications associated with obesity and insulin resistance, being currently considered the most prevalent form of chronic liver

disease in the world. Its progression may culminate in steatohepatitis, advanced fibrosis, cirrhosis, and increased mortality related to hepatic complications. In this context, therapies capable of promoting significant weight loss and sustained metabolic improvement have been considered fundamental strategies for the control of the disease and the prevention of its progression (SANYAL *et al.*, 2021).

The most relevant results on the use of retatrutide in patients with MASLD demonstrated expressive reductions in hepatic fat, exceeding 80% at the highest doses evaluated after 24 weeks of treatment. In addition, a significant proportion of participants reached levels considered normal for hepatic fat, suggesting an important regression of steatosis. These findings indicate that the benefits of the therapy are not restricted to the reduction of body weight but also directly reach one of the main markers related to the activity of metabolic liver disease (SANYAL *et al.*, 2024).

The mechanisms responsible for these results appear to be related to the simultaneous activation of the GLP-1, GIP, and glucagon receptors, which promote reduced food intake, increased energy expenditure, and improved insulin sensitivity. Consequently, there is a decrease in the supply of fatty acids to the liver and a reduction in hepatic lipotoxicity, factors directly involved in the pathophysiology of MASLD. These effects distinguish retatrutide from conventional therapies and help to explain the magnitude of the reductions observed in hepatic fat (COSKUN *et al.*, 2022).

When compared with other incretin therapies, retatrutide presents particularly promising results. Studies with semaglutide demonstrated benefits in the resolution of steatohepatitis, while more recent therapies, such as tirzepatide, reinforced the importance of weight loss in the control of metabolic liver disease. Retatrutide broadens this strategy by incorporating the activation of the glucagon receptors, potentiating its effects on energy and hepatic metabolism. Although long-term studies are still necessary to confirm impacts on fibrosis and more robust clinical outcomes, current evidence positions the molecule as one of the most promising pharmacological approaches for the treatment of obesity-associated MASLD (NEWSOME *et al.*, 2021; JASTREBOFF *et al.*, 2022; ABOUELMAGD *et al.*, 2025; KATSI *et al.*, 2025).

3.4 COMPARISON OF RETATRUTIDE WITH OTHER INCRETIN THERAPIES

The evolution of incretin therapies has progressively broadened the efficacy of the pharmacological treatment of obesity and associated metabolic diseases. GLP-1 receptor agonists represented an important advance by promoting significant reductions in body weight and improved glycaemic control. In this context, semaglutide became established as

one of the main therapeutic options by demonstrating a mean weight loss of approximately 14.9%, in addition to relevant metabolic and hepatic benefits in patients with metabolic dysfunction-associated steatotic liver disease (WILDING *et al.*, 2021; NEWSOME *et al.*, 2021).

Subsequently, the development of tirzepatide introduced the simultaneous activation of the GIP and GLP-1 receptors, resulting in weight losses of up to 20.9% and establishing a new level of therapeutic efficacy. These results reinforced the importance of acting on multiple metabolic pathways in promoting weight loss and improving the cardiometabolic profile, serving as a basis for the development of even more complex molecules (JASTREBOFF *et al.*, 2022).

In this scenario, retatrutide emerges as an evolution of this strategy by combining the activation of the GLP-1, GIP, and glucagon receptors. The available studies demonstrated weight losses exceeding 24%, accompanied by expressive reductions in hepatic fat, results that surpass those observed with the previously evaluated incretin therapies. Although direct comparative studies and long-term follow-up are still necessary, current evidence suggests that retatrutide may represent the most advanced stage in the evolution of incretin therapies, offering simultaneous benefits on obesity, glucose metabolism, and metabolic dysfunction-associated steatotic liver disease (JASTREBOFF *et al.*, 2023; SANYAL *et al.*, 2024; KATSI *et al.*, 2025).

3.5 FUTURE PERSPECTIVES AND LIMITATIONS OF CURRENT EVIDENCE

Although the results obtained so far are highly promising, the evidence related to retatrutide still presents limitations that must be considered in the interpretation of the findings. Most of the available data derive from phase 2 studies, with relatively short follow-up periods when compared with the chronic nature of obesity and metabolic dysfunction-associated steatotic liver disease. Thus, studies with prolonged follow-up are still necessary to evaluate the maintenance of the observed benefits and their impact on relevant clinical outcomes, including cardiovascular morbidity and mortality, progression of liver disease, and patients' quality of life (JASTREBOFF *et al.*, 2023; SANYAL *et al.*, 2024).

Another aspect that deserves attention concerns the understanding of the effects of retatrutide on the evolution of MASLD and its histological outcomes. Although current studies demonstrate expressive reductions in hepatic fat, the evidence related to the regression of fibrosis, prevention of cirrhosis, and reduction of long-term hepatic complications remains limited. Furthermore, issues related to prolonged safety, therapeutic adherence, and cost-

effectiveness still require additional investigation before the widespread incorporation of the therapy into clinical protocols (ABOUELMAGD *et al.*, 2025).

Even so, the current literature points to a consensus regarding the potential of retatrutide as one of the most innovative pharmacological approaches for the treatment of metabolic diseases. The combination of expressive effects on weight loss, glycaemic control, and reduction of hepatic fat suggests a strategy capable of acting simultaneously on different pathophysiological mechanisms of obesity and MASLD. In this scenario, the results of ongoing studies may definitively consolidate the role of retatrutide in clinical practice, broadening the available therapeutic options and contributing to reducing the impact of these conditions on global public health (KATSI *et al.*, 2025).

4 CONCLUSION

The present integrative review allowed the analysis of the available scientific evidence regarding the use of retatrutide in the treatment of obesity and metabolic dysfunction-associated steatotic liver disease (MASLD). The evaluated studies demonstrated that the molecule presents high efficacy in promoting weight loss, with results superior to those observed in previously established incretin therapies, in addition to relevant metabolic benefits related to glycaemic control, reduction of body adiposity, and improvement of cardiometabolic risk factors. Additionally, an important reduction in hepatic fat was observed in patients with MASLD, suggesting therapeutic potential not only for the management of obesity but also for the treatment of the hepatic alterations associated with metabolic syndrome.

In general, the analysed evidence indicates that retatrutide represents one of the most promising pharmacological approaches currently under development for complex metabolic diseases. Its simultaneous action on the GLP-1, GIP, and glucagon receptors provides broad benefits on multiple pathophysiological mechanisms involved in obesity and MASLD. However, despite the highly favourable results, long-term studies are still necessary to confirm the maintenance of the observed efficacy, to evaluate its prolonged safety, and to determine its effects on more robust clinical outcomes. Even so, the current data suggest that retatrutide has the potential to transform the therapeutic management of these conditions and to significantly broaden the options available in clinical practice.

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THE RELATIONSHIP BETWEEN ORAL CAVITY BACTERIA AND CANCER DEVELOPMENT: MICROBIOLOGICAL EVIDENCE, PATHOGENIC MECHANISMS AND CLINICAL IMPLICATIONS

A RELAÇÃO ENTRE BACTÉRIAS DA CAVIDADE ORAL E O DESENVOLVIMENTO DE CÂNCER: EVIDÊNCIAS MICROBIOLÓGICAS, MECANISMOS PATOGENICOS E IMPLICAÇÕES CLÍNICAS

LA RELACIÓN ENTRE LAS BACTERIAS DE LA CAVIDAD ORAL Y EL DESARROLLO DEL CÁNCER: EVIDENCIAS MICROBIOLÓGICAS, MECANISMOS PATOGENICOS E IMPLICACIONES CLÍNICAS



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ABSTRACT

Cancer is one of the main global public health challenges, characterized by uncontrolled cell growth and metastatic potential. In recent years, the human microbiota, particularly the oral microbiota, has been increasingly investigated as a relevant factor in carcinogenesis. The oral cavity harbors a complex microbial community that contributes to homeostasis under balanced conditions; however, disturbances in this balance, known as dysbiosis, may promote chronic inflammation and the development of diseases, including cancer. This study aimed to analyze the relationship between oral bacteria and cancer development, highlighting microbiological evidence, pathogenic mechanisms, and clinical implications. This is a descriptive literature review conducted between December 2025 and February 2026, using databases such as PubMed, Scopus, Web of Science, BVS, LILACS, and SciELO, with

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descriptors in Portuguese and English. Articles published between 2015 and 2025 were included. The findings indicate a significant association between oral bacteria, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, and the development of various cancers, including oral, gastrointestinal, and pancreatic cancers. The main mechanisms involved include chronic inflammation, immune response modulation, production of carcinogenic metabolites, DNA damage, and inhibition of apoptosis. It is concluded that the oral microbiota plays an important role in carcinogenesis and may serve as a biomarker and target for prevention strategies, early diagnosis, and targeted therapies.

Keywords: Oral Bacteria. Oral Microbiota. Oral Cancer. Mouth Neoplasms. Dysbiosis.

RESUMO

O câncer constitui um dos principais desafios de saúde pública mundial, sendo caracterizado pelo crescimento celular desordenado e potencial metastático. Nos últimos anos, a microbiota humana, especialmente a microbiota oral, tem sido investigada como um fator relevante na carcinogênese. A cavidade oral abriga uma comunidade microbiana complexa que, em condições de equilíbrio, contribui para a homeostase; entretanto, alterações nesse equilíbrio, conhecidas como disbiose, podem favorecer processos inflamatórios crônicos e o desenvolvimento de doenças, incluindo o câncer. O presente estudo teve como objetivo analisar a relação entre bactérias da cavidade oral e o desenvolvimento de neoplasias, destacando evidências microbiológicas, mecanismos patogênicos e implicações clínicas. Trata-se de uma revisão de literatura descritiva, realizada entre dezembro de 2025 e fevereiro de 2026, com busca nas bases PubMed, Scopus, Web of Science, BVS, LILACS e SciELO, utilizando descritores em português e inglês. Foram incluídos artigos publicados entre 2015 e 2025. Os resultados indicam associação significativa entre bactérias orais, como *Porphyromonas gingivalis* e *Fusobacterium nucleatum*, e o desenvolvimento de diferentes tipos de câncer, incluindo oral, gastrointestinal e pancreático. Os principais mecanismos envolvidos incluem inflamação crônica, modulação da resposta imune, produção de metabólitos carcinogênicos, danos ao DNA e inibição da apoptose. Conclui-se que a microbiota oral desempenha papel importante na carcinogênese, podendo atuar como biomarcador e alvo para estratégias de prevenção, diagnóstico precoce e terapias direcionadas.

Palavras-chave: Bactérias Orais. Microbiota Oral. Câncer Oral. Disbiose Oral.

RESUMEN

El cáncer constituye uno de los principales desafíos de salud pública mundial, caracterizado por el crecimiento celular descontrolado y el potencial metastático. En los últimos años, la microbiota humana, especialmente la microbiota oral, ha sido investigada como un factor relevante en la carcinogénesis. La cavidad oral alberga una comunidad microbiana compleja que, en condiciones de equilibrio, contribuye a la homeostasis; sin embargo, alteraciones en ese equilibrio, conocidas como disbiosis, pueden favorecer procesos inflamatorios crónicos y el desarrollo de enfermedades, incluido el cáncer. El presente estudio tuvo como objetivo analizar la relación entre las bacterias de la cavidad oral y el desarrollo de neoplasias, destacando evidencias microbiológicas, mecanismos patogénicos e implicaciones clínicas. Se trata de una revisión de literatura descriptiva, realizada entre diciembre de 2025 y febrero de 2026, con búsqueda en las bases PubMed, Scopus, Web of Science, BVS, LILACS y SciELO, utilizando descriptores en portugués e inglés. Se incluyeron artículos publicados entre 2015 y 2025. Los resultados indican una asociación significativa entre bacterias orales, como *Porphyromonas gingivalis* y *Fusobacterium nucleatum*, y el desarrollo de diferentes tipos de cáncer, incluidos el oral, el gastrointestinal y el pancreático. Los principales mecanismos implicados incluyen la inflamación crónica, la modulación de la respuesta inmune, la producción de metabolitos carcinogénicos, daños al ADN y la inhibición de la

apoptosis. Se concluye que la microbiota oral desempeña un papel importante en la carcinogénesis, pudiendo actuar como biomarcador y objetivo para estrategias de prevención, diagnóstico precoz y terapias dirigidas.

Palabras clave: Bacterias Orales. Microbiota Oral. Cáncer Oral. Disbiosis Oral.

1 INTRODUCTION

Cancer constitutes one of the main global public health challenges, being characterised by uncontrolled cell proliferation, tissue invasion capacity and metastatic potential. Although genetic, environmental and behavioural factors are widely recognised as important determinants in carcinogenesis, recent scientific evidence indicates that microorganisms also play a relevant role in this process. In this context, the human microbiota has been increasingly investigated as a possible modulating factor in the development and progression of different types of cancer (Nikolai *et al.*, 2025).

The oral cavity harbours a highly complex microbiota, composed of hundreds of bacterial species that coexist in balance with the host. This microbial ecosystem performs important functions in maintaining oral homeostasis; however, disturbances in this balance, known as oral dysbiosis, may favour the growth of pathogenic microorganisms and trigger chronic inflammatory processes. Recent studies suggest that this dysbiosis may contribute to the development of several systemic diseases, including different types of cancer (Nikolic *et al.*, 2025).

Several studies have demonstrated an association between oral cavity bacteria and the development of neoplasms, especially oral, gastrointestinal and pancreatic cancer. Among the most frequently investigated microorganisms, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* stand out, having been identified in tumour tissues and associated with tumour progression. These pathogens may influence different biological processes related to carcinogenesis, including persistent inflammation, modulation of the immune response and alterations in cell proliferation (Reitano *et al.*, 2021).

In addition, molecular mechanisms such as the production of carcinogenic metabolites, DNA damage, activation of cell signalling pathways and inhibition of apoptosis have been described as possible ways in which oral bacteria contribute to malignant transformation and tumour progression. Experimental evidence also indicates that certain bacteria, such as *Fusobacterium nucleatum*, may act directly in promoting tumour growth and in modulating the tumour microenvironment (Yamamoto *et al.*, 2023).

In view of this scenario, understanding the relationship between the oral cavity microbiota and cancer development becomes fundamental to broadening knowledge about the pathogenic mechanisms involved in carcinogenesis. Thus, the present study emphasises that this understanding may contribute to the identification of microbiological biomarkers and to the development of new strategies for prevention, early diagnosis and targeted therapies.

2 METHODOLOGY

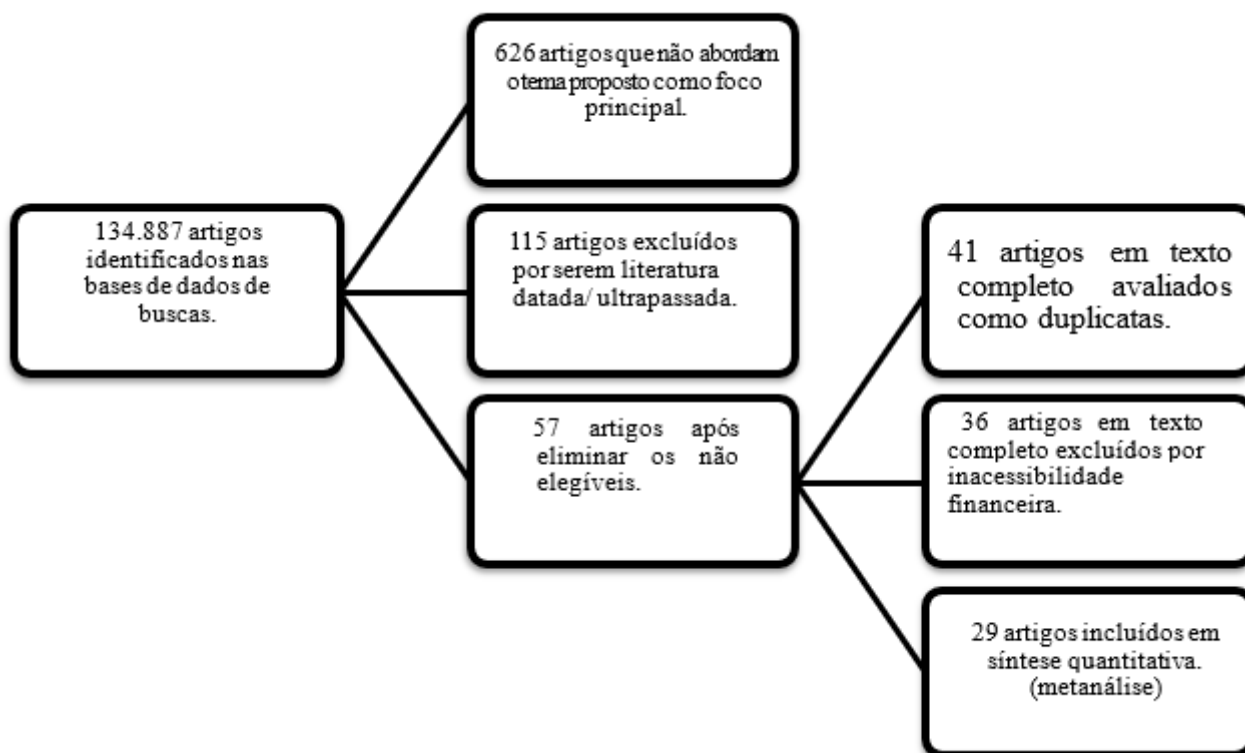
This is a descriptive literature review study aimed at approaching the subject in an impartial manner, yet encompassing all its diverse aspects, providing broader information on the subject and synthesising the results obtained in previous research on the topic.

The study was developed during the second semester of 2025. Data collection was carried out from December 2025 to February 2026 through the databases: PubMed, Scopus, Web of Science, BVS, LILACS and SciELO. It was conducted in Juazeiro do Norte, CE, through the use of keywords such as “Oral Bacteria”, “Oral microbiota”, “Oral Cancer”, “Mouth Neoplasms”, “Dysbiosis” in English, and “Bactérias Orais”, “Microbiota Oral”, “Câncer Oral” and “Disbiose Oral” in Portuguese.

The text includes articles published between 2015 and 2025 in English and Portuguese, with duplicate articles or those outside the stipulated time period being discarded, as well as articles with paid access in foreign currency. Furthermore, articles that, upon reading the title and abstract, did not address the theme of the effect of the oral microbiota on oral or systemic cancer were discarded.

Figure 1

Article selection using inclusion and exclusion criteria



Source: Autoria própria, 2026.

Table 1*Articles selected for synthesis*

Author/Year	Objectives	Main findings	Conclusion
Huang et al., (2025)	To assess the existence of a causal relationship between the oral and gut microbiota and the risk of developing lung cancer, using a two-sample Mendelian randomization approach.	The results of the two-sample Mendelian randomization study indicated that certain taxa of the oral and gut microbiota show causal associations with lung cancer risk. The analyses demonstrated that some microorganisms were associated with an increased risk, while others showed a protective effect, suggesting a bidirectional relationship between the microbiota and lung carcinogenesis.	The results of this study suggest a possible causal relationship between distinct oral and gut microbial communities and lung cancer risk, offering valuable information on microbial candidates that may serve as targets for future diagnostic innovations.
Kashima et al., (2025)	The study aimed to examine the relationships between oral bacterial composition, clinicopathological factors, and tumor-infiltrating immune cells in patients with oral squamous cell carcinoma (OSCC), and to investigate whether interventions targeting the local microbiota and the tumor immune microenvironment may contribute to improvements in OSCC prognosis.	The investigation showed that specific taxa of the oral microbiota exhibited a significant causal association with lung cancer, reinforcing the hypothesis that changes in the oral cavity microbiota may influence pulmonary pathological processes. Likewise, components of the gut microbiota were also identified as causally associated with disease risk, supporting the role of the gut–lung axis.	This is the first study to demonstrate a direct relationship between the predominance of intratumoral anaerobic bacteria and CD8 ⁺ T-cell exhaustion in oral squamous cell carcinoma (OSCC), suggesting a mechanism of immune dysfunction and disease progression dependent on the microbiota. The bacterial scoring system has potential as a prognostic marker and a guide for microbiota-targeted therapies aimed at enhancing antitumor immunity.
Kiss et al., (2025)	The aim of this study was to assess the spectrum of pathogenic microorganisms and the antimicrobial resistance rates of clinical isolates from head and neck infections in the Hungarian population.	The study demonstrated that patients with oral cancer showed a greater abundance of bacteria of the order Enterobacterales compared to individuals without cancer. Among the clinical isolates obtained from head and neck infections, Enterobacterales were frequently identified as relevant pathogens.	The study also showed that the antimicrobial resistance profile varies among the different isolated pathogens, reinforcing the need for continuous microbiological monitoring and the adaptation of therapeutic strategies based on local resistance data.
Meurman; Bascones-Martínez, (2020)	To review and discuss the available evidence on the relationship between the oral microbiota and	The oral microbiota may act as a contributing factor in carcinogenesis, interacting with classic risk factors such as smoking and alcohol consumption. The article also	The study concludes that the oral microbiota plays a relevant role in the carcinogenesis process, especially in oral cancer, acting through

	cancer development, addressing the possible biological mechanisms involved, such as chronic inflammation, bacterial infections, and their implications in oral and systemic carcinogenesis.	suggests that specific microorganisms may serve as potential biomarkers for early detection and monitoring of cancer.	mechanisms such as chronic inflammation, modulation of the immune response, and production of potentially carcinogenic metabolites. The evidence indicates that changes in the oral microbial balance may contribute to tumor initiation and progression.
Amaral et al., (2023)	O objetivo foi apresentar nesta revisão narrativa de literatura a correlação entre o câncer bucal e os possíveis micro-organismos que podem estar presentes na cavidade oral.	O tabaco e o álcool são os fatores de risco mais importantes. Junto a isso, soma-se a exposição solar excessiva sem a devida proteção, o HPV, dieta e ocupação, onde estudados com provam suas implicações na carcinogênese bucal. No que tange às condições sociais, nota-se que estas devem ser incluídas como determinantes no processo saúde-doença. Logo, torna-se necessário um olhar ampliado sobre essa neoplasia, no sentido de verificar os fatores relacionados.	Conclui-se que o câncer bucal pode estar relacionado com os microrganismos da cavidade oral frente a alterações que modifiquem sua composição, que somadas a fatores de risco culminem entre si favorecendo a ação dos pró- carcinogênicos. Contudo, sua relação ainda não se apresenta devidamente definida na literatura. O estudo dos microrganismos que compõe a microbiota oral é de suma importância para o conhecimento, diagnóstico e tratamento das patologias orais, sobretudo o câncer de boca.
Pares et al., (2023)	O presente estudo teve como objetivo caracterizar os microrganismos da cavidade oral e orofaringe de pacientes acometidos pelo Câncer de Cabeça e Pescoço (CCP) em tratamento com antineoplásicos, atendidos em um Centro Odontológico localizado no Agreste Pernambucano.	O gênero <i>Candida</i> esteve presente em todos os pacientes incluídos na amostra, sendo a espécie <i>C. albicans</i> a mais prevalente, como também é descrito em outros estudos, principalmente seu aumento ocasionado pela imunossupressão da terapia antineoplásica. Já entre as <i>Candida</i> não <i>albicans</i> , as três espécies isoladas no GE foram também isoladas em um estudo que identificou a predominância de <i>C. glabrata</i> , <i>C. tropicalis</i> e <i>C. krusei</i> em pacientes com carcinoma de células escamosas na cavidade oral.	As alterações microbiológicas na cavidade oral e orofaringe dos participantes do presente estudo indicam aumento de prevalência de <i>Enterobacteriales</i> e <i>Enterococcus</i> spp., além do isolamento de <i>Pseudomonas</i> spp. e <i>Staphylococcus</i> spp., sendo identificada a multi-resistência de bactérias oportunistas a várias classes de antibióticos, como aminoglicosídeos, carbapenêmicos, cefalosporinas, fluoroquinolonas, glicopeptídeos, macrolídeos e

			penicilinas. Houve também diminuição considerável de <i>Streptococcus viridans</i> no GE em comparação ao GC.
Leão et al., (2021)	O objetivo deste artigo foi realizar uma revisão narrativa de literatura sobre a relação entre ambas as doenças.	This study showed that there is a relationship between PD and both oral and systemic cancer. The overall understanding of this association remains evolving, meaning that the mechanisms of cancer induction and progression by periodontal disease have not yet been fully elucidated. Based on the epidemiological results combined with the epigenetic understanding, it was observed that periodontopathogens and the inflammatory state directly contribute to strengthening this association.	Epidemiological studies point to an association of periodontal disease with cancer, highlighting sites of greater likelihood, mainly those closer to the oral cavity. Although many mechanisms remain uncertain, epigenetic events, the inflammatory process, and the action of periodontal bacteria appear to exert influence on carcinogenesis, cellular transformation, and tumor progression.
Oliveira et al., (2020)	Realizar uma revisão da literatura, abordando a utilização de bactérias orais como biomarcadores do câncer de pâncreas, descrevendo assim, a relevância do diagnóstico açodado dos tumores pancreáticos.	A presença de algumas bactérias periodontopatogênicas pode relacionada com mutação do gene do Tumor P53 e por serem tóxicas para as células circulantes, instigando a mutação de genes supressores de tumores.	Em suma, os estudos têm apontado a presença algumas espécies de bactérias no microbioma oral de pacientes com câncer pancreático. A bactéria citada com maior frequência é a <i>Granulicatella adiacens</i> , entretanto, faz-se necessária a realização de mais estudos sobre as temáticas abordadas, bem como a elaboração de testagens bioquímicas, por colorimetria, de fácil e rápida execução para a indicação da presença dessas bactérias, o que facilitará a indução de um paciente com histórico familiar da doença, por exemplo, para exames mais específicos e confirmatórios, além de estudos epidemiológicos longitudinais que comprovem tal associação.
Peres et al., (2022)	To systematically review studies on the impact caused by antineoplastic treatment on the oral and	In the present study, it is observed that male patients are more affected by head and neck cancer, in agreement with worldwide statistics ²² . Among the histopathological profiles,	After analyzing the selected articles, the authors reported the presence of pathological processes, such as mucositis and dental

	oropharyngeal microbiota in patients with head and neck cancer.	most studies pointed to squamous cell carcinoma as the most prevalent, a finding in accordance with the scientific literature 23,24. Radiotherapy was the most used therapy for the treatment of cancers affecting the head and neck region; this finding corroborates most worldwide antineoplastic treatment protocols	caries, in a large proportion of the patients involved in their research, these being caused by microorganisms present in the oral and oropharyngeal microbiota, with the most frequently reported being: bacteria of the species <i>Streptococcus</i> spp. and fungi of the species <i>Candida</i> spp.
Sun et al., (2020)	To discuss the role of oral bacteria and their influence on the emergence of neoplasms in the oral cavity.	Anaerobic oral bacteria with pathogenic potential, especially <i>Fusobacterium nucleatum</i> and <i>Porphyromonas gingivalis</i> , are closely related to several types of carcinomas. Some aerobic bacteria, such as <i>Parvimonas</i> , are also linked to tumorigenesis. In addition, human papillomavirus, oral fungi, and parasites are closely associated with oropharyngeal carcinoma. Microbial dysbiosis, colonization, and translocation of the oral microbiota are necessary for the implementation of carcinogenic functions.	In line with the article, the abundance of oral bacteria specifically associated with cancer appears to be a clinical biomarker to a certain extent, although further exploration is still needed. The detection rates of changes in the oral microbiota may be used to predict various global health problems, since the oral cavity could act as a window toward deeper areas of the human body.
Montero et al., (2015)	To present the relationship between the effect of smoking and alcohol on the oral cavity, regarding the emergence of oral neoplasms.	In the study cited, it is revealed that squamous cell carcinoma (SCC) is the most common cancerous tumor condition in the oral cavity and the main etiological factors are the use of tobacco and alcohol. It also addresses the treatment and prevention of this type of oral cancer.	According to the article, primary and secondary prevention of oral cancer requires better education on lifestyle-related risk factors, as well as greater awareness and tools for early diagnosis.
Zhang et al., (2019)	Identificar os gêneros e espécies bacterianas predominantes em casos de neoplasmas bucais.	According to the study, cancerous tissues were found to be enriched in six families (<i>Prevotellaceae</i> , <i>Fusobacteriaceae</i> , <i>Flavobacteriaceae</i> , <i>Lachnospiraceae</i> , <i>Peptostreptococcaceae</i> , and <i>Campylobacteraceae</i>) and 13 genera, including <i>Fusobacterium</i> , <i>Alloprevotella</i> , and <i>Porphyromonas</i> . At the species level, the abundances of <i>Fusobacterium nucleatum</i> , <i>Prevotella intermedia</i> , <i>Aggregatibacter</i> , <i>Segnis</i> , <i>Capnocytophaga leadbetteri</i> , <i>Peptostreptococcus stomatis</i> , were also seen as prevalent in cancerous tissue.	Os tecidos cancerígenos exibiram uma Microbiota única em comparação com o normal contralateral dos Tecidos. A partir das descobertas, propõe-se que a recolonização De bactérias podem perturbar o equilíbrio entre a Microbiota oral residente e o hospedeiro. Isso pode ser uma Ligação chave através da qual as bactérias orais comensais promovem o câncer oral.

Pignatelli et al., (2022)	To compare the oral microbiota of an individual with adequate oral health and an individual with carcinoma in the oral cavity.	Changes in microbial biomass in the oral cavity depend on the interaction between different microbial species in the biofilm. The oral biofilm matures through interactions between early colonizing and later colonizing microorganisms via various mechanisms, including coaggregation, metabolic exchange, communication mediated by small-molecule signals, and exchange of genetic material. The numerous bacteria in the oral cavity are not evenly distributed across all surfaces but proliferate differently in ecological niches depending on their metabolism in a healthy oral cavity.	Based on the review carried out in the article, it is clear that several risk factors are implicated in the development of oral cancer, the most common and established being smoking and areca nut consumption, in addition to alcoholism. However, many patients are diagnosed with oral cancer despite abstaining from known lifestyle- or environment-related risk factors, where factors such as genetic susceptibility are considered causative. Therefore, the patient's habits should be considered by health professionals when examining the possibility of oral carcinomas.
Kumar et al., (2016)	To correlate a diet deficient in essential micronutrients with the emergence of oral neoplasms.	O estudo aponta que, a relação entre dieta e nutrição e o risco de câncer existe, entretanto não é amplamente discutido. O grupo de trabalho da Agência Internacional de Pesquisa sobre o Câncer afirmou que a baixa ingestão de frutas e vegetais predispõe ao aumento do risco do desenvolvimento do câncer. Consumo mais frequente de frutas e vegetais, particularmente de cenouras, tomates e pimentas verdes foram associadas à redução do risco de câncer oral e Câncer de faringe. Alimentos e grupos alimentares que não sejam frutas e vegetais crus que têm um efeito protetor são, por exemplo, peixes, azeite, pão, cereais, legumes, proteína, gordura, carne fresca, frango, fígado, camarão, lagosta e fibras.	The results show that diet is related to cancer risk, although this subject is still not much discussed. Low intake of fruits and vegetables may increase this risk, while frequent consumption of these foods, such as carrots, tomatoes, and green peppers, helps protect against some types of cancer. Other foods, such as fish, cereals, fresh meats, and fiber, also have a protective effect. Thus, maintaining a varied and balanced diet is important for cancer prevention.
Pereira et al., (2025)	To assess oral pathology in a population observed in oral cancer screening activities in Portugal, analyzing the prevalence of benign lesions, oral potentially malignant disorders, and	A total of 2,674 participants were screened, of whom 83.4% presented some alteration of the oral mucosa. Benign lesions and non-pathological conditions were the most frequent, highlighting Fordyce granules (16.3%) and hairy tongue (11.04%). Oral potentially malignant disorders (OPMDs) were identified in 6.3% of participants, with leukoplakia being the most	The study concludes that, although benign lesions are the most prevalent, a clinically relevant proportion of the population presented potentially malignant disorders and lesions suspicious of oral cancer. The oral cancer screening activities carried out proved effective in the

	malignant lesions, as well as their possible association with sociodemographic variables and tobacco and alcohol habits.	frequent OPMD (43.58%), followed by oral lichen planus/lichenoid lesions. A statistically significant association was observed between leukoplakia and tobacco and alcohol consumption, both individually and in combination.	early identification of OPMDs and oral cancer, through intraoral visual examination.
Wang et al., (2024)	To analyze the oncogenic potential of changes in the oral microbiota, investigating its role as a causal factor and biomarker of oral cancer, as well as to discuss the possibility of therapeutic strategies based on reversing oral microbiota dysbiosis.	The article demonstrates that oral microbiota dysbiosis is strongly associated with the development and progression of oral cancer, especially oral squamous cell carcinoma. Changes in the microbial balance favor a conducive tumor microenvironment through multiple biological mechanisms. Among the main mechanisms identified are the production of carcinogenic metabolites (such as acetaldehyde, nitrosamines, and sulfides), the induction of chronic inflammation, oxidative stress, inhibition of apoptosis, suppression of the immune response, and facilitation of tumor invasion and migration.	The article concludes that the oral microbiota plays a fundamental role in maintaining homeostasis, and that changes in its composition are directly related to oral carcinogenesis. Evidence indicates significant differences between the microbiota of healthy individuals and patients with oral cancer, reinforcing its relevance in the tumor process.
Karpinski; Tomasz, (2019)	To present and discuss potentially oncogenic oral bacteria and the possible mechanisms by which the oral microbiota participates in the carcinogenesis process in human cells, focusing on oral cancer and neoplasms of the gastrointestinal tract.	Among the most frequently associated microorganisms are Porphyromonas gingivalis and Fusobacterium nucleatum, considered the periopathogens with the strongest evidence of carcinogenic effect, in addition to Streptococcus spp., Peptostreptococcus spp., Prevotella spp., and Capnocytophaga gingivalis.	The study concludes that bacteria of the oral cavity play an important role in cancer development, not only locally but also in distant organs, such as the colon and pancreas. The oncogenic effects of the oral microbiota occur mainly through chronic inflammation, antiapoptotic activity, and the production of carcinogenic substances.

Source: Authorship, 2026.

The oral microbiota is intrinsically related to the development of carcinogenesis, since it is composed of a diversity of microorganisms that, under conditions of health, maintain bacterial homeostasis; however, in oncological patients, the occurrence of oral dysbiosis is observed, characterised by an increase in opportunistic pathogens and a deficit of commensal microorganisms. Studies based on next-generation sequencing demonstrate significant differences in the composition of the oral microbiota between healthy individuals

and patients with various types of cancer, indicating the potential for these microorganisms to be used as biomarkers for diagnosis and therapeutic strategies (Sun *et al.*, 2023).

From this perspective, in healthy individuals, the bacterial microbiota is mostly composed of genera such as *Streptococcus*, *Neisseria*, *Veillonella*, *Actinomyces* and *Prevotella*, which establish a commensal relationship with the organism and are frequently associated with oral health, directly influencing prevention against opportunistic pathogens and performing immunomodulatory functions that assist in the control of inflammation (Lamont *et al.*, 2018).

However, there are microorganisms that may cause disadvantages to the organism; certain bacteria associated with periodontal conditions, such as *Escherichia coli* and other microorganisms with genotoxic potential, may act through mutagenic mechanisms, causing DNA damage and favouring the formation of an inflammatory microenvironment. This environment contributes to the intensification of oncogenic mutations and to tumour progression (Amaral *et al.*, 2023).

In addition, bacteria that are frequently associated with periodontal diseases, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, have been present in greater abundance in tumour tissues and oral samples of patients with oral cancer. These are microorganisms that may influence oxidative stress and carcinogenesis (Han *et al.*, 2015).

Beyond the alterations present in specific taxa, cancer patients present in the constitution of their oral microbiota a bacterial profile distinct from that of healthy individuals, with a reduction of microorganisms associated with homeostasis and an enrichment of gram-negative bacteria. Thus, these are alterations that reflect bacterial adaptations to the tumour environment (Mohapatra *et al.*, 2025).

Evidence confirmed in studies indicates that certain oral bacteria are also enriched in tumour tissues when compared to adjacent non-tumour tissues. In this way, there is a greater abundance of periodontopathogenic bacteria in tumour samples of oral squamous cell carcinoma, strengthening the hypothesis of a direct interaction between the neoplastic tissue and microorganisms (Mohapatra *et al.*, 2025).

The identification of specific bacterial signatures has been an important tool for developing studies that associate the oral microbiota with the risk of carcinogenesis, since certain oral bacterial profiles are demonstrating a strong link with the development of head and neck cancer, independent of known factors such as smoking and excessive alcohol consumption. In summary, this demonstrates a finding that reinforces the potential of the oral microbiota as a biological indicator of risk (Hayes *et al.*, 2018).

The human microbiota comprises the set of microorganisms, including bacteria, archaea and viruses, that inhabit the organism and perform functions essential for the maintenance of homeostasis and for the proper development of the immune system. This microbiota establishes continuous interactions with the host's innate and adaptive immune systems, contributing to immune training and to the induction of tolerance towards commensal and potentially pathogenic microorganisms. Furthermore, the communication between the microbiota and the immune system proves to be fundamental for the development and maturation of immune cell populations and lymphoid organs (Moreno *et al.*, 2023).

From this perspective, periodontitis is associated with different systemic conditions, such as gestational complications, cardiovascular and pulmonary diseases, inflammatory bowel disease, cancer and type 2 diabetes mellitus. Evidence indicates that *Porphyromonas gingivalis*, an important periodontal pathogen, may be related to Alzheimer's disease. In addition, studies demonstrate that the ectopic colonisation of the oral microbiota, especially by species of the genus *Klebsiella*, contributes to Th1 polarisation and to intestinal inflammation, evidencing the influence of oral dysbiosis on the modulation of the systemic immune response (Wang *et al.*, 2024).

In view of this scenario, chronic inflammatory processes resulting from infections, such as chronic periodontitis, or from trauma may generate important clinical repercussions, since the continuous release of inflammatory mediators contributes to tissue damage and increases the risk of conditions such as hypertension, hyperglycaemia, type 2 diabetes mellitus, chronic kidney disease, depression, neurodegenerative diseases and different types of cancer (Rashid *et al.*, 2025).

In this context, oral dysbiosis and chronic inflammation present relevant implications in neurodegenerative diseases, such as Alzheimer's disease. Evidence indicates that chronic periodontitis is positively associated with this condition, since it induces the release of inflammatory mediators, such as C-reactive protein and interleukin-6, capable of compromising the blood-brain barrier and favouring processes of neuroinflammation (Moreno *et al.*, 2023).

Cancer immunoediting refers to the ambiguous action of the immune system, which exerts both antitumour surveillance functions and contributes to tumour progression. Although the immune system is capable of recognising and eliminating tumour cells, neoplastic cells develop evasion mechanisms, such as the recruitment of immunosuppressive cells and the release of inhibitory factors, resulting in the formation of an

immunosuppressive tumour microenvironment and in the progressive suppression of the immune response (Wang *et al.*, 2024).

Therefore, despite the central role of cytotoxic CD8⁺ T cells in tumour control, these cells frequently enter a state of functional exhaustion, which compromises their capacity to contain cancer progression. Tumour-specific exhausted T cells present characteristics associated with immunotolerance and tumour immunosuppression, making their understanding essential for the development of antitumour therapeutic strategies (Jiang *et al.*, 2021).

The influence of the oral microbiota on carcinogenesis has been an increasing focus of research, and recent reviews highlight that, in addition to traditional risk factors such as alcohol and tobacco, oral bacterial dysbiosis contributes directly to tumour-initiating and tumour-promoting processes. Oral microorganisms may interfere with key cellular pathways, including the production of carcinogenic compounds, the induction of oxidative stress with DNA damage, the modulation of programmed cell death and the alteration of tumour suppressor genes (Nikolic *et al.*, 2025).

Several bacteria present in the oral cavity possess enzymes capable of converting common substances such as ethanol and nitrates into metabolites with carcinogenic potential. The production of acetaldehyde from ethanol through the activity of bacterial alcohol dehydrogenase is an important example: species such as *Streptococcus*, *Neisseria* and other microorganisms have demonstrated a high capacity to form acetaldehyde in the oral environment, increasing the probability of DNA adducts and genetic mutations, as observed in reviews on the role of the oral microbiome in carcinogenesis. Furthermore, the same study observes that certain periods of compromised oral health result in higher concentrations of genotoxic compounds such as acetaldehyde (Karpnski, 2019).

Another group of relevant metabolites are the nitrosamines and volatile sulphur compounds (VSC), including hydrogen sulphide (H₂S), which act as cytotoxic agents and facilitators of chronic inflammation. Studies point out that these compounds are generated by periodontal pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, being able to induce tissue oxidative stress and sustained inflammation, factors associated with oral and systemic carcinogenesis. In addition, the bacterial production of VSC, including H₂S and methyl mercaptan, was associated with direct cellular damage and genomic instability, suggesting an important role of these metabolites in the tumour microenvironment (data from other reviews on compounds produced by oral microorganisms) (Semiz; Aksoy; Altun, 2025).

The prolonged immuno-inflammatory response mediated by pathogenic oral bacteria results in the continuous release of reactive oxygen species and other radicals generated by the activation of immune cells. These reactive molecules promote the oxidation of nitrogenous bases, DNA strand breaks and errors during replication, contributing to genomic instability, a crucial event in the process of malignant transformation (Ionescu *et al.*, 2024).

Furthermore, bacteria such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* have been associated with the activation of anti-apoptotic and cell proliferation pathways. These bacteria may trigger intracellular signalling, for example via NF- κ B and other transduction cascades that promote cellular survival and expansion, hindering the elimination of cells with genetic damage through apoptosis. This effect was detailed in reviews that highlight how bacterial products modulate surface receptors and transcription factors involved in programmed cell death and inflammatory response, data integrated into analyses of tumour mechanisms (Karpinski, 2019).

In addition to inducing structural damage to DNA, oral dysbiosis is also associated with the epigenetic modification of critical regulatory genes. The function of the suppressor gene *TP53*, responsible for encoding the p53 protein, is particularly relevant in this context. Studies indicate that the prolonged presence of oral pathogens may interfere with the functioning of the repair and cellular control pathways in which p53 acts, reducing its efficacy in halting the cell cycle or inducing apoptosis in the face of genetic damage, as evidenced in recent literature on the microbiome and carcinogenesis. Although most reviews on p53 and the microbiome do not yet mechanistically map all the biochemical steps, there is consensus that the functional inhibition and regulatory alterations of this suppressor increase the probability of survival of mutated cells, facilitating tumour progression (Ionescu *et al.*, 2024).

Other studies also highlight that epigenetic modulation, such as the hypermethylation of promoters of critical genes, may be influenced by inflammatory mediators and bacterial metabolites, permanently altering the pattern of gene expression even after removal of the bacterial stimulus, suggesting a lasting reprogramming of the cellular phenotype towards carcinogenesis (Nikolic *et al.*, 2025).

In an integrated manner, it is observed that the production of carcinogenic metabolites, oxidative stress and epigenetic alterations establish a cycle of interconnected events that sustains the tumour microenvironment. The persistent presence of genotoxic compounds increases the number of mutations; chronic inflammation amplifies DNA damage and favours pro-survival pathways; and the loss of suppressor mechanisms, such as p53, prevents the elimination of genetically compromised cells. This combination of continuous biological processes provides a robust molecular basis for understanding how the oral microbiota may

be a relevant co-factor in oral and systemic carcinogenesis, broadening the perspectives of preventive approaches based on the modulation of the microbiota and the control of chronic inflammation (Nikolic *et al.*, 2025).

The oral microbiota is widely recognised as a relevant component in the modulation of systemic pathological processes, including carcinogenesis in organs distant from the oral cavity. In this sense, recent evidence points out that alterations in the oral microbial composition, specifically states of dysbiosis associated with periodontal disease, may influence the development of systemic neoplasms through inflammatory, immunological and metabolic mechanisms. This set of interactions has been described as the oral–intestinal–pulmonary axis (Gao *et al.*, 2022).

Bacterial translocation represents one of the main mechanisms involved in such an axis. In individuals with periodontitis, recurrent episodes of transient bacteraemia allow oral microorganisms or their structural components to be present in the systemic circulation. Species such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have been widely associated with systemic inflammatory processes and detected in tumour tissues beyond the oral axis, suggesting a potential role in the modulation of the tumour microenvironment (Bashir *et al.*, 2021).

In the context of pancreatic cancer, promising studies demonstrate a significant association between the composition of the oral microbiota and the risk of developing the disease. In a longitudinal analysis of a large cohort, the increased presence of periodontal pathogens, such as *Porphyromonas gingivalis* and *Parvimonas micra*, was associated with a greater risk of pancreatic adenocarcinoma, indicating that the oral microbiota may act as a predictive biomarker (Fan *et al.*, 2018). Systematic reviews reinforce that individuals with a history of periodontal disease present an increased risk of developing pancreatic cancer, suggesting a possible systemic inflammatory contribution mediated by oral microorganisms (Michaud *et al.*, 2017).

Beyond the gastrointestinal tract, the oral–pulmonary axis has also been investigated. The constant microaspiration of oral secretions may favour the colonisation of the lower respiratory tract by bacteria originating from the oral cavity. Studies of the total genetic material indicate that patients with lung cancer present significant alterations in the composition of the oral microbiota, including a reduction in bacterial diversity and enrichment of certain genera associated with chronic inflammation (Yang *et al.*, 2018). Recent meta-analyses suggest that lower diversity of the oral microbiota is associated with an increased risk of lung cancer (Liu *et al.*, 2023).

The processes involved include the persistent activation of pro-inflammatory pathways, such as NF- κ B, the production of inflammatory cytokines (IL-6, TNF- α) and the modulation of the antitumour immune response. *Fusobacterium nucleatum*, for example, may interfere with the T-cell-mediated immune response and favour an immunosuppressive environment in tumour tissues, contributing to neoplastic progression. Although a large part of the evidence is still of an associative nature, the accumulated data support the hypothesis that oral dysbiosis exerts a relevant systemic influence on the processes of carcinogenesis (Kostic *et al.*, 2013).

The abundant presence of certain microorganisms, such as bacteria of the genera *Fusobacterium*, *Porphyromonas*, *Parvimonas* or other organisms with pathogenic potential, such as fungi of the genus *Candida* spp. or the human papillomavirus in the oral cavity, may be treated as a clinical biomarker for the early onset of oral neoplasms. Although a deeper exploration is necessary to explain this intrinsic relationship between the oral microbiota and the onset of cancerous masses in the oral cavity, the processes of bacterial colonisation and translocation of the oral microbiota are pointed out as important for triggering tumour expansion in the tissues of the mouth or in other bodily structures (Sun *et al.*, 2020).

Comparing the oral microbiota between a healthy person and a carrier of SCC (Squamous Cell Carcinoma) in the oral tissues, it is possible to point out that the emergence of conditions favourable to tumour onset may be strongly driven by the interactions between different initial and subsequent colonising microbial species, such as the exchange of genetic material, communication through chemical signals, the production of carcinogenic metabolites, and the biochemical induction of chronic inflammation (Pignatelli *et al.*, 2022).

However, the oncogenic capacity of the microorganisms responsible for oral neoplasms is not limited only to the oral tissues, as there may be processes of transport of the oral microbial load to organs distant from the head and neck, such as the pancreas or the colon. The presence of certain periodontopathogenic bacteria is capable of being toxic to nearby cells belonging to the affected tissue, such as that of the pancreas or the lung, and is related to mutations in the p53 gene, responsible for oncogenic suppression and the induction of apoptosis in cells with signs of mutation. Furthermore, bacterial inspections of tumour tissue in patients with pancreatic cancer tend to point out the presence, at notable rates, of bacteria such as *Granulicatella adiacens*, which is part of the oral microbiome (Oliveira *et al.*, 2020).

Additionally, the abuse of alcoholic beverages, of tobacco use and of an unbalanced diet with low nutritional content have well-evidenced links with the triggering of various tumours, including oral neoplasms, being common habits among patients who present the

development of any degree of neoplasms in the space of the oral cavity. It is worth noting that, according to recent studies, it is possible to relate routine factors such as diet or the abuse of licit substances as more determinant in the onset of oral cancer than genetic factors, owing to the capacity for the manifestation of chronic inflammation in the tissues or the alteration of the genetic material responsible for the maintenance and control of the cell division process that ethanol, tobacco and other substances may cause (Pereira *et al.*, 2025).

From this presented context, the need arises to analyse therapeutic methods for the treatment of head and neck tumours. Initially, it is important to note that patients affected by oral neoplasms are generally men who have habits of alcoholism, smoking and high rates of potentially pathogenic microorganisms, such as bacteria of the genus *Streptococcus* spp., fungi of the genus *Candida* spp., among others (Peres *et al.*, 2022).

In addition, the most common post-oncogenic treatment for head and neck is radiotherapy, a method that may trigger harmful symptoms in the patient, such as compromise of the immune system, reduction of salivary flow and mucositis, which have the capacity to break the homeostatic balance of the oral environment, making it more susceptible to triggering inflammatory processes that may affect the antineoplastic treatment, whether through excessive proliferation of native organisms of the microbiota, or through the invasion and multiplication of external pathogens. Therefore, great clinical importance is attributed to the monitoring of the conditions of the immune system, the mucosa and salivary lubrication with the aim of preventing the onset of local or generalised bacterial infections (sepsis) (Peres *et al.*, 2022).

In view of this context, as the presence of dysregulations in the oral microbiota may trigger numerous conditions, such as caries, mucositis, periodontal diseases and the advent of oral neoplasms. It is worth noting that radiological treatments may present adverse conditions for the patient who undergoes them, breaking the homeostasis of the individual's oral microbiome. Owing to this, the use of therapeutic processes based on the modulation of the microorganism populations of the microbiome emerges as a safer possibility for antineoplastic treatment (Wang *et al.*, 2024).

Through recent studies, probiotics, periodontal control and other antimicrobial strategies promote benefits such as: the reduction of the rate of carcinogenic substances due to the stabilisation of bacterial proliferation, allowing a positive immunomodulatory effect from the cellular and bacterial relationships, inducing the cellular apoptosis of tumour cells through the action of bacteria of the genus *Lactobacillus* spp., preventing damage to the tissue genetic material owing to the antioxidant properties of certain substances emitted by the commensal bacteria of the mouth, etc. Consequently, interventions based on the modulation of the

unicellular organisms present in the oral environment become a target for studies aimed at their development in favour of increasing the options for combating oncogenesis and treating patients who already have squamous cell carcinoma in the oral region, allowing the reduction of conditions adverse to the health of carriers of head and neck cancer (Wang *et al.*, 2024).

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