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ENDEREÇO
Associação Médica do Paraná
Rua Cândido Xavier, 575 - Água verde 80240-280 Curitiba/PR - Brasil
Fone: (41) 3024-1415
E-mail: bioscience@bioscience.org.br

Faculdade Evangélica Mackenzie do Paraná (FEMPAR - supplement 2)

It is with enthusiasm that we present Supplement 2 of the Mackenzie Evangelical College of Paraná, a publication that translates the vigor, breadth and commitment of our academic community to scientific production, refined teaching and social intervention. This edition brings together, in a single editorial space, contributions that extend to the various levels of education—undergraduate, graduate, stricto sensu graduate (master's and doctorate), specializations, medical residencies—and are also distributed across different areas of activity, with special emphasis on health sciences and their interfaces.

The articles and reports presented here originate from experience, reviews and other works developed at the different levels of training of the institution. The editorial proposal is clear: to generate an institutional environment that fosters the visibility of FEMPAR's intellectual production, encourages the circulation of knowledge and favors the fruitful exchange of experiences. The multidisciplinary nature of this collection reflects the conviction that contemporary challenges in health, education, and the community require integrated, collaborative, and interprofessional perspectives.

More than a mere compilation of texts, this supplement represents an institutional commitment to academic excellence, methodological innovation, and social relevance. By exposing ideas, results and reflections, we enable our production to reach broad interlocutors — academics, professionals, managers and civil society — stimulating debates that transcend the walls of the institution. The dissemination of knowledge, understood as a transformative action, finds its stage here: FEMPAR reaffirms its role as an active agent in the training of critical, ethical professionals committed to collective health and well-being.

Finally, we would like to thank the authors, advisors, evaluation committees and editorial team who, with rigor and dedication, contributed to the realization of this work. We invite our readers to explore each contribution, to engage in the dialogues that are triggered here and to recognize, in this issue, the reflection of an institution that bets on the construction of knowledge as a vector of change.

Enjoy your reading!

Prof. Dr. Carmen Australia Paredes Ribas
General Director of the Mackenzie Evangelical College of Paraná – FEMPAR, Curitiba, PR, Brazil

SUMÁRIO

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Artigo de Revisão | Review Article

Relato de Caso | Case Report

BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.S2.e00001

Effects of climate change on cardiovascular health: a focus on temperature extremes

Efeitos das mudanças climáticas na saúde cardiovascular: um enfoque nos extremos de temperatura

Evelyn Kloster Mazur[1], Homero Grein Neto[1], Sofia Sant' Anna Pofahl Bíscaro[1], Bruno Henrique Strapasson Moraes[1], Isabela Bonk Palma[1], Luiz Eduardo Latorre Guimarães[1], Amanda Carvalho Garcia[1]

ABSTRACT

Introduction: Ambient temperature impacts cardiovascular health through multifaceted biological mechanisms, causing imbalances in thermal homeostasis, which impair the cardiovascular system. Temperature extremes lead to vascular changes, autonomic nervous system responses, arrhythmias, inflammation, and oxidative stress.

Objective: Analyze the existing scientific literature in order to synthesize the main information about the influence of climate change on cardiovascular events.

Method: Searches were conducted in the PubMed, ScienceDirect, Web of Science, and Scielo databases. The descriptors used were: "cardiovascular diseases, climate change, and body temperature regulation". The inclusion criteria comprised review articles published from 2005 onwards, in Portuguese and English. A total of 24 articles were selected.

Result: Cold causes vasoconstriction, tachycardia, and increased blood pressure, resulting in myocardial ischemia, especially in patients with coronary plaques. Cold exposure increases angiotensin-II, leading to vasoconstriction and hypertension. This mechanism overloads the myocardium and increases oxygen demand. Heat induces vasodilation and sweating, which increases cardiovascular demand due to elevated heart rate. Resulting dehydration alters hemoconcentration and electrolyte balance, triggering acute cardiovascular events.

Conclusion: Extreme cold and heat generate thermal stress, which induces systemic inflammation, contributing to the progression of cardiovascular diseases. Understanding the biological mechanisms that mediate the adverse effects of cold and heat on the cardiovascular system is essential for developing effective intervention strategies.

KEYWORDS: Cardiovascular diseases. Climate change. Body temperature regulation.

Central message

Climate change has significant impacts on cardiovascular health, especially during temperature extremes, especially impacting vulnerable populations such as the elderly and people with comorbidities. This study sheds light on how hot and cold flashes interfere with the proper functioning of the cardiovascular system and what the consequences of these changes are.

Perspective

Studies on climate change and cardiovascular disease indicate that exposure to temperature extremes is correlated with a significant increase in cardiovascular events such as stroke, heart failure, arrhythmias, and thrombus formation. Understanding these changes is of paramount necessity to predict and mitigate possible adverse effects triggered

RESUMO

Introdução: A temperatura ambiental impacta a saúde cardiovascular por mecanismos biológicos multifacetados, causando desequilíbrios na homeostase térmica, o que prejudica o sistema cardiovascular. Os extremos de temperatura geram alterações vasculares, respostas do sistema nervoso autônomo, arritmias, inflamação e estresse oxidativo.

Objetivo: Analisar as principais publicações sobre a influência das mudanças climáticas nos eventos cardiovasculares.

Método: Busca nas bases de dados PubMed, ScienceDirect, Web of Science e Scielo. Foram utilizados os descritores: "cardiovascular diseases, climate change e body temperature regulation". Os critérios de inclusão compreenderam artigos de revisão publicados a partir de 2005, em português e inglês. Foram selecionados 24 artigos.

Resultado: O frio provoca vasoconstrição, taquicardia e aumento da pressão arterial, resultando em isquemia miocárdica, especialmente em pacientes com placas coronárias. Exposição a ele aumenta angiotensina-II, levando à vasoconstrição e hipertensão arterial. Esse mecanismo sobrecarrega o miocárdio e aumenta a demanda de oxigênio. O calor induz vasodilatação e sudorese, o que aumenta a demanda cardiovascular pela elevação da frequência cardíaca. A desidratação decorrente altera a hemoconcentração e o balanço eletrolítico, desencadeando eventos cardiovasculares agudos.

Conclusão: Frio e calor extremos geram estresse térmico, que induzem inflamação sistêmica, contribuindo para progressão de doenças cardiovasculares. A compreensão dos mecanismos biológicos que mediam os efeitos adversos do frio e do calor sobre o sistema cardiovascular é essencial para o desenvolvimento de estratégias de intervenção eficazes.

PALAVRAS-CHAVE: Doenças cardiovasculares. Mudança climática. Regulação da temperatura corporal.

[1] *Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.*

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INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide1 and have become major evils of this century in Brazil and in most developed countries. In addition, coronary heart disease is the leading cause of mortality in the world, according to the World Health Organization (WHO)[1], being the second in Brazil (12.4%), followed by stroke (9.1%).[2] In addition, in Brazil, according to data from the Ministry of Health, the circulatory system was responsible for 31.46% of deaths, with the largest cause being higher than the sum of the following 2 (neoplasms and external causes).[3] In addition, evidence indicates that for every 1°C increase in ambient temperature, there is a 2.1% increase in cardiovascular mortality and a 0.5% increase in cardiovascular morbidity. These associations are especially worrisome in tropical regions, where the risks are higher.[4]

Cardiovascular diseases are usually silent, with a slow evolution, with a long asymptomatic period, but they can be identified, treated and controlled before any complication or the outbreak of a serious event.[5]

The relationship between climate change and cardiovascular health is complex and multifaceted, impacting the human body in several ways, and can occur through numerous biological mechanisms.[6] It is known that they are usually associated with thermoregulatory efforts caused by exposure to extreme cold and heat and involve vascular changes, autonomic nervous system responses, arrhythmias, inflammation, and oxidative stress.[7]

The objective of this review was to analyze the existing scientific evidence on the influence of climate change on cardiovascular events.

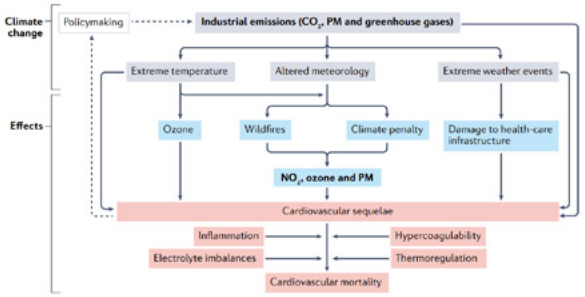
METHOD

This is a narrative review carried out in the PubMed, ScienceDirect, Web of Science and Scielo databases. The search used the following keywords: "cardiovascular diseases, climate change, body temperature regulation". The inclusion criteria included review articles from 2005 onwards, published in Portuguese and English, available in full text. Those who avoided the theme were excluded. In total, 24 articles were selected.

DISCUSSION

Mechanisms by which climate change affects the cardiovascular system include increased oxidative stress, inflammation, and hemodynamic changes (Figure). Exposure to extreme temperatures can disrupt thermal homeostasis, leading to dehydration and increased blood viscosity, which promotes thrombus formation.[8]

The fundamental mechanisms that contribute to the development of cardiovascular diseases in extreme temperature conditions are associated with several regulatory pathways. These include the sympathetic reaction to temperature, activation of the renin-angiotensin system (RAS) in response to cold, dehydration caused by both cold and heat, changes caused by extreme temperatures, and the systemic inflammatory response resulting from heat stroke.[10]



Source: Romanello et al.[9]

FIGURE — The effect of climate change on the development of cardiovascular diseases

In terms of direct impact, systemic inflammation caused by heat stress can increase the levels of several inflammatory markers, contributing to the progression of atherosclerosis. The most commonly elevated markers include C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1). C-reactive protein (CRP) is a marker of inflammation that is widely used in clinical practice. High levels of it are associated with a higher risk of cardiovascular events, such as myocardial infarction and stroke. IL-6 — a pro-inflammatory cytokine — is also often elevated in response to exposure to air pollutants and heat stress, promoting vascular inflammation and endothelial dysfunction. TNF-α is another key cytokine in systemic inflammation, contributing to endothelial cell apoptosis and atherosclerotic plaque formation. In addition, cell adhesion molecules such as ICAM-1 and VCAM-1 facilitate the adhesion of leukocytes to blood vessel walls, promoting inflammation and the progression of atherosclerosis.[11]

Exposure to cold causes vasoconstriction, tachycardia and increased blood pressure. These effects can lead to myocardial ischemia, especially in patients with coronary plaques, which can thicken and rupture. Changes in hemoconcentration (blood concentration of coagulation factors, platelets, cholesterol, fibrinogen, and erythrocytes) due to polyuria contribute to this process. In addition, during the colder seasons, the level of cholesterol in the blood is usually higher. These mechanisms can lead to increased vascular resistance and blood pressure, coronary spasms, the formation and rupture of plaques, and even thrombosis, which can cause cardiovascular events.[12]

Other mechanisms related to activations of the sympathetic system and the renin-angiostesine system have been associated with increased blood pressure and cardiovascular events, such as myocardial infarction. Research has shown increased sympathetic activation and angiotensin-II levels after exposure to cold. Mechanisms related to the growth of atherosclerotic plaque, in addition to increased instability and the possibility of plaque rupture during

cold, have been pointed out.[13]

The body, aiming to generate heat in the coldest periods, intensifies muscle activity, thus causing overload on the heart.[14] In addition to the vasoconstriction caused by lower air temperatures, there are also physiological factors that change with low temperatures. The second would be the greater activation of clot-forming factors, causing a greater occurrence of ischemic diseases, such as infarction.[15]

Studies indicate that exposure to cold air can significantly increase plasma angiotensin-II levels.[16,17] At low temperatures, the release of norepinephrine and the activation of the renin-angiotensin system can cause systemic vasoconstriction and arterial hypertension. This increases myocardial work and oxygen demand, increasing the risk of cardiovascular and cerebrovascular events. Interestingly, epinephrine levels do not appear to be affected by lower temperatures, suggesting that the increase in norepinephrine may be due to the release of sympathetic nerve endings rather than secretion from the adrenal medulla.[18]

Exposure to heat, on the other hand, causes vasodilation and sweating. These mechanisms aim to reduce the increase in core temperature, but imposing acute demands on the cardiovascular system. In this chain of events, blood accumulates in the cutaneous region, reducing the central blood volume, in the chest and abdomen region. Due to this reduction, cardiac output is improved through increased heart rate. This may be one of the reasons why heart failure patients respond poorly to heat stress. Heat induces sweating and increased blood volume in the skin regions, which cause dehydration, increased blood viscosity, hypotension, and increase cardiac overload, which are also related to cardiovascular problems. Exposure to heat also causes changes in hemoconcentration, related to dehydration caused by sweating. Also in relation to hydration, changes in electrolyte and acid-base balance can be considered as a trigger for acute cardiovascular events.[19]

In addition, exposure to extreme heat can lead to dehydration and increased blood viscosity, promoting the formation of thrombi and, consequently, acute cardiovascular events. On the other hand, intense cold waves also contribute to cardiovascular mortality, as they can cause constriction of blood vessels and increased blood pressure, exacerbating the risk of heart attacks and strokes.[20] Therefore, dehydration contributes to cardiovascular risk not only through volume depletion, but also through hemoconcentration and increased blood viscosity. Hyperthermia can cause electrolyte abnormalities, increasing the risk of cardiac arrhythmias.[21,22] Hypothermia, on the other hand, can induce bradycardia and trigger potentially fatal arrhythmias. Changes in the electrocardiogram are seen in individuals with low body temperatures.[23] Heat can cause changes in heat-sensitive proteins, activating an inflammatory cascade that contributes to multi-organ failure.[23,24] Heat stroke is a severe heat-related condition that leads to multiple organ dysfunction and encephalopathy, mainly affecting the elderly, chronically ill patients, or patients with cardiovascular disease.[23,25]

CONCLUSION

Temperature variations have a significant impact on cardiovascular health, especially among vulnerable populations, such as the elderly and people with preexisting comorbidities. After observing the pathophysiological mechanisms of cold and heat on metabolism, it was defined that extreme cold is associated with an increase in the incidence of myocardial infarction, arrhythmias and stroke, and on the other hand, extreme heat can cause electrolyte disturbances and thermal overload, leading to a higher incidence of heart failure, arrhythmias and also stroke. In this sense, it is essential to understand these biological mechanisms for the development of effective intervention strategies, and it is crucial to implement preventive measures, such as monitoring cardiovascular health during hot and cold waves, especially in risk groups. By prioritizing these actions, it will be possible to mitigate the adverse effects of climate change on the cardiovascular health of the population.

Authors' contributions

Evelyn Kloster Mazur: Conceptualization
Homero Grein Neto: Formal analysis
Sofia Sant' Anna Pofahl Biscaro: Research
Methodology: Bruno Henrique Strapasson Moraes
Isabela Bonk Palma: Project Administration
Luiz Eduardo Latorre Guimarães: Writing (original draft)
All authors: Writing (proofreading and editing)

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Genetic counseling and autism: new perspectives for diagnosis and intervention

Aconselhamento genético e autismo: novas perspectivas para diagnóstico e intervenção

João Marcos Valentim dos Santos[1], Isabela Garrett Portugal[1], Marcela Sarú Campos[1], Mariana Müller Angulski[1], Bruno Henrique Moraes Strapasson[1], Tailla Cristina de Oliveira[1], Liya Regina Mikami[1]

ABSTRACT

Introduction: Autism Spectrum Disorder is a neurodevelopmental disorder of multifactorial origin, affecting social, behavioral, and communication skills from early childhood. With a global prevalence of 1.25%, genetic counseling is crucial to understand the genetic factors involved and estimate the risk of new cases within the family.

Objective: To analyze the importance of genetic counseling in the context of autism, focusing on genetic factors and the recurrence risk of the disorder.

Method: A systematic literature review was conducted in PubMed, SciELO, BVS, Lilacs, and Google Scholar databases, in Portuguese, English, and Spanish. The search included descriptors as "autism", "genetic counseling", "genetics", and "recurrence risk", resulting in the selection of 26 relevant articles.

Result: Most cases of Autism Spectrum Disorder are genetically determined, making genetic counseling essential for assessing recurrence risk and the genetic and environmental factors involved. The recurrence risk varies according to the degree of kinship, being higher among close relatives. Heritability of the disorder is more pronounced in monozygotic twins, and an increased risk is also observed among siblings and in families with other cases of Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder. The former is more prevalent in boys. Maternal effects during the prenatal period do not show significant influence.

Conclusion: Genetic counseling is essential for clarifying the disorder and is important in both public and private sectors to inform families about recurrence risks and the genetic factors involved, given its high prevalence in the general population.

KEYWORDS: Autism spectrum disorder. Genetic counseling. Genetics.

Central Message

Autism Spectrum Disorder (ASD) is one of the neurodevelopmental disorders with the fastest growing incidence in the world. An estimated 1 in 36 American children have ASD. This incidence increases when there is more than one case in the family. This issue generates intense suffering, especially for parents, who have increasingly sought genetic counseling services to clarify their doubts and know the probability of family recurrence. This review addresses the prevalence, risk of recurrence, and the importance of genetic testing for patients and their families, as well as showing the genetic factors that have already been associated with increased susceptibility to the development of ASD.

Perspective

Through genetic counseling, a form of preventive medicine and improvement of health care is obtained, offering a logical explanation for the condition, especially those of genetic etiology, establishing the risks of familial recurrence, and expanding the knowledge of the disorder in order to influence its treatment and prognosis.

RESUMO

Introdução: O Transtorno do Espectro do Autismo é neurodesenvolvimental de origem multifatorial, que compromete habilidades sociais, comportamentais e de comunicação desde a infância. Com prevalência global relativamente elevada, o aconselhamento genético é essencial para compreender os fatores genéticos envolvidos e estimar o risco de novos casos na família.

Objetivo: Analisar a relevância do aconselhamento genético no contexto do autismo, focando nos fatores genéticos e no risco de recorrência do transtorno.

Método: Foi realizada revisão sistemática da literatura nas bases de dados PubMed, SciELO, BVS, Lilacs e Google Scholar, em português, inglês e espanhol. A busca incluiu os descritores "autismo", "aconselhamento genético", "genética", e "risco de recorrência", resultando na seleção de 26 artigos relevantes.

Resultado: A maioria dos casos tem origem genética, o que torna o aconselhamento genético essencial para avaliar o risco de recorrência e os fatores genéticos e ambientais envolvidos. O risco de recorrência varia de acordo com o grau de parentesco, sendo mais elevado entre parentes próximos. A hereditariedade do transtorno é mais pronunciada em gêmeos monozigóticos, e também se observa risco aumentado entre irmãos e em famílias com outros casos desse transtorno ou Transtorno de Déficit de Atenção e Hiperatividade. O Transtorno do Espectro do Autismo é mais prevalente em meninos, e o efeito materno no período pré-natal não mostra influência significativa.

Conclusão: O aconselhamento genético é crucial para esclarecer o transtorno, sendo importante tanto no setor público quanto privado, para informar as famílias sobre os riscos de recorrência e os fatores genéticos envolvidos, dado seu alto impacto na população geral

PALAVRAS-CHAVE: Transtorno do espectro autista. Aconselhamento genético. Genética.

[1] Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts social, behavioral, and communication skills, and is characterized by stereotypies, rigidity in routine, and impact on the understanding of sensory stimuli.[1] It begins in childhood and has as its etiology genetic and environmental factors that can modulate the degree of impairment of the disorder[2], which can be both idiopathic and syndromic.

These causes can be multifactorial caused by the presence of genetic variants in genes already associated with the disorder, maternal immunological and environmental factors during pregnancy, bringing autistic people impairments in social relationships, poor eye contact, lack of attention, global developmental delay and even impaired intellectual development.[3] Among the genes already associated with ASD with a high level of confidence are: ADNP, ANK2, ARID1B, ASH1L, ASXL3, CHD2, CHD8, CUL3, DSCAM, DYRK1A, GRIN2B, KATNAL2, KMT2A, KMT5B, MYT1L, NAA15, POGZ, PTEN, RELN, SCN2A, SETD5, SHANK3, SYNGAP1, TBR1, TRIP12 and UBE3A.

Palmer et al.[4] in 2017 estimated that the general population incidence of ASD is 1.25%. In Brazil, in 2023 alone, it was estimated that there are about 2 million Brazilians with autism, which represents that 1% of the population has the disorder, according to a survey carried out by the Brazilian Institute of Geography and Statistics (IBGE). In addition, it currently affects 1 in 59 children under the age of 8 according to the Developmental Disabilities Monitoring Network.[5] Based on these data, the high prevalence of the disorder is remarkable; therefore, the demand for genetic counseling services has increased, both at the request of neuropediatricians and pediatricians, and at the initiative of the family itself to obtain information and whether there is a risk of having others affected in the family nucleus.

Genetic counseling is also useful for the early diagnosis and treatment of some conditions and, as a consequence, avoid damage caused by it. Thus, this medical practice is performed by physicians with specialization in medical genetics and is applied to various diseases, and in the present study the emphasis is on genetic counseling for family members of patients with ASD.

Autism is not always easily diagnosed since it is a comorbidity of another condition. The diagnosis of idiopathic ASD is predominantly clinical; however, technological advances in genetics are providing specific genetic tests to confirm the diagnosis and, based on this, genetic counseling to understand the result is considered.

The etiology of ASD involves an important genetic factor, influenced by the segregation of variants in the family and the variation in risk, according to the degree of kinship. Family segregation is usually measured by the risk of family recurrence, which serves as an indication of a genetic factor in ASD and is variable according to the degree of kinship. Thus, it can be placed as another important factor for the realization of counseling to inform families with an autistic child about the possibility of having other children with the same disorder or another neurodivergence.[6] To provide a safe estimate of the risk of recurrence (RR) for ASD, it is necessary to perform a detailed genetic diagnosis in the child, including defining appropriate testing strategies.

A common way to estimate RRa is sibling study. The overall risk of ASD recurrence for a child with 1 or more siblings with autism has been estimated to be between 6.1% and 24.7%[4], and this prevalence is also influenced by sex. Boys are 4 times more likely to develop autism than girls. This lower incidence among girls may also be due to greater difficulty in giving the diagnosis since they better mask the symptoms of ASD.

Carter and Scherer[7] point that the RR does not influence the levels of ASD support (I, II, III); however, the sex of the autistic child has an impact on the RR, since, if the couple has an older child with autism, there is a risk of having another male child with ASD. However, if the eldest child with autism is a girl, the risk of having a second male child with autism can be as high as 21%.

Understanding the proportion in which ASD diagnoses are shared among siblings in a family contributes to the interpretation of the genetic and environmental factors that contribute to the RR of ASD, providing more effective screening and counseling and fostering closer monitoring for subsequent siblings.

In view of this, the present study aimed to show the importance of genetic counseling in autism and to analyze the risks of recurrence for family members and patients, which is a great source of concern in having more family members with the disorder, which can even manifest itself in varying degrees and associated with other neurodevelopmental comorbidities.

METHOD

The literature review was carried out with data collected from the PubMed, SciELO, VHL (Virtual Health Library), Lilacs and Google Scholar databases. The descriptors used for the research were: autism; genetic counseling; risk of recurrence, and its equivalents in English and Spanish, with AND or OR search between the years 2013 and 2024. Through this search, 5,480 articles were found, which had the title and/or abstract read, and later, 26 articles were read in full and selected for this study (Table).

DISCUSSION

ASD: Associated genes and diagnostic tests

Autism is recognized as the neurodevelopmental disorder with an inherited rate of approximately 85%.[8] In addition, approximately 10%1 of individuals with it are from families with no positive family history

TABLE — Articles selected for literature review[1-26]

Title	Authors	Year	Country	Study Type
Autism spectrum disorder in the genetics clinic: a review	Carter and Scherer[7]	2013	Canada	Literature review
Heritability of autism spectrum disorders: a meta-analysis of twin studies	Tick et al.[6]	2015	United Kingdom	Meta-analysis
Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders	Jokiranta-Olkoniemi et al.[25]	2016	Finland	Cohort
association of sex with recurrence of autism spectrum disorder among siblings.	Palmer et al.[4]	2017	USA	X
Information needs in genetic testing: A needs assessment survey among Taiwanese parents of children with autism spectrum disorders	Chen et al.[18]	2018	USA	Cross-sectional study
Etiological investigation of autism spectrum disorders: State of the Art	Gonçalves, Guardino and Leão[14]	2018	Portugal	Meta-analysis
Autism. Genetic and biological aspects	Arberas and Ruggieri[3]	2019	Argentina	Meta-analysis
Recessive gene disruptions in autism spectrum disorder	Doan et al.[26]	2019	USA	X
Sibling recurrence risk and cross-aggregation of attention-deficit/hyperactivity disorder and autism spectrum disorder	Miller et al.[9]	2019	USA	X
Association of genetic and environmental factors with autism in a 5-country cohort	Bai et al.[24]	2019	Sweden	Cohort
Recurrence risk of autism in siblings and cousins: a multinational, population-based study	Hansen et al.[23]	2019	Denmark	Cohort
Genetic couseling in neurodevelopmental disorders	Blesson and Cohen[2]	2020	USA	Meta-analysis
Adaptation and validation of the Genetic Counseling Outcome Scale for autism spectrum disorders and related conditions	Yusuf et al.[17]	2020	Canada	Validation study
Factors affecting family compliance and genetic testing of children diagnosed with autism spectrum disorder	Hendel et al.[16]	2020	Israel	Cross-sectional observational study
Genetic studies and neurodevelopment of the utility of the genetic model	Calleja-Pérez et al.[10]	2020	Spain	Literature review
Genetic counseling: access for families of patients with congenital diseases	Silva[22]	2020	Brazil	Cross-sectional study
Genetic couseling as preventive intervention: toward individual specification of transgerational autism risk	Marrus et al.[8]	2021	USA	Historical cohort
Access, utilization and awareness for clinical genetic testing in autism spectrum disorder in sweden: a survey study	Hellquist and Tammimies[5]	2021	Sweden	Cross-sectional study
Parental perceptions of genetic testing for children with autism spectrum disorders	Lucas et al.[11]	2021	USA	Classical cohort
Predictors of empowerment in parents of children with autism and related neurodevelopmental disorders who are undergoing genetic testing	Peltekova et al.[15]	2021	Canada	Classical cohort
Neuroanatomy and neurophysiology in the study of autism spectrum disorders	Rodríguez et al.[19]	2021	Cuba	Meta-analysis
The pathogenesis of autism spectrum disorder	Sanabria-Barradas et al.[13]	2022	Mexico	Meta-analysis
Shared decision-making in genetic counseling: a scoping review	Chenyang et al.[20]	2022	China	Meta-analysis
Historical perspective of autism spectrum disorder	Jaramillo-Arias et al.[21]	2022	Colombia	Meta-analysis
The autism spectrum: behavioral, psychiatric and genetic associations	Genovese and Butler[1]	2023	USA	Literature review
Autism and duplication of the 17q12q21.2 region with array-CGH: a case report	Weingartner et al.[12]	2023	Brazil	Case report

for the disorder, referred to as simplex families, and are usually caused by de novo microdeletions or microduplications. On the other hand, individuals with a positive family history for the disease are called multiplex families. Research reveals that despite the significant heredity of ASD, most children with autism are children of unaffected parents.[2,8] In addition, the risk of developing ASD among children whose parents have siblings affected by the disease is 2 to 3 times higher and the occurrence among siblings is 20 times higher than in the general population, highlighting the need to recognize the genetic factors present in these families.[3]

Genetic counseling in autism

The follow-up of a geneticist for patients with autism and their families can help in several aspects, such as having an early diagnosis, assessing the risk of recurrence and understanding the genetic diagnosis of the disorder.[9] There is great concern among families about having a child with ASD when there is a family history, in which case genetic counseling is very useful to analyze this possible risk of recurrence. Thus, genetic counseling for autistic people and their families can help in understanding the diagnosis and influence the reproductive decision-making of these individuals.[9]

In autism, as in other neurodevelopmental disorders, genetic counseling can be difficult for parents and guardians of individuals with autism to accept.[10] Therefore, it is of great importance to use strategies to break stigmas that are responsible for the denial of having a child with a genetic disease, such as autism. These strategies should make them not feel guilty about the child's disorder or blame their spouses, or even be stigmatized and need help to deal with their child's condition in the best way.[11]

ASD is a condition that directly affects the social, emotional and behavioral life of the individual, compromising the construction of solid relationships and limiting the ability to interact and express themselves, with the focus often on restricted interests and repetitive acts, manifesting itself mainly in early childhood.[11,17,18] In order to minimize damage and delays in the child's integral development, an early therapeutic approach is of great importance, which should provide explanations and guidelines for an assertive multidisciplinary treatment. Most of the time, the geneticist who plays this role is the geneticist through genetic counseling.

Genetic diagnosis helps in setting realistic expectations for treatment and guiding family planning decisions, as well as allowing the person with autism to enhance their view of their own state.[11] Although, in some cases, counseling is not very enlightening for some parents or does not provide a direct benefit,[11,15] the experience of doing it still presents many gains, since it helps to empower and inform family members, who no longer acquire a passive position and start to have knowledge about the resources that enable them to gain control over the situation, collaborating in the progress of the health condition of the ASD

patient with the acquisition of quality therapies and improvement of training as caregivers.[11,15,17,18]

Risks of recurrence in ASD

The heritability of autism is described in approximately 80% of cases,[21] that is, genetics has a great influence on the development of the disorder. Jaramillo-Arias et al.[21] showed that 18% to 20% have a somatic genetic cause, that is, not hereditary, further contributing to the attention to the role of genetics in the process of understanding the disorder and its etiology.

According to a study carried out in 5 countries, in which 3 were Nordic (Denmark, Sweden and Finland) it was concluded that genetic factors explained 73.9% of the risk for developing ASD, and in 26.5% of cases they were related to gene-environment interaction.[24]

Considering that ASD is a disorder mainly of genetic cause, there are relevant data in the literature regarding the risk of recurrence of the disorder in families, with several studies that show its prevalence in siblings, twins, cousins, presenting, however, variation in family risk by the degree of kinship.[19] Thus, the determination of the empirical risk of recurrence becomes an important resource to inform families about the risks involved in presenting a relative with ASD. Therefore, estimating the risk of ASD recurrence helps for a better clinical and etiological understanding.[26]

The risk of recurrence between siblings is a possible way to assess shared genetic contributions. One way to ascertain this family risk is by analyzing siblings born after at least one child diagnosed with ASD. This type of investigation also estimates the recurrence of other neurodevelopmental diseases, such as attention deficit hyperactivity disorder (ADHD), such as if a couple has a child with ASD or ADHD and decides to have another child, they have a high chance of that second child developing any of these disorders. This estimate mentioned above reveals that the risk of ADHD is 51.92% and the risk of ASD is 48.10%, in the case of a family that already has at least one child with ASD or ADHD.[26]

Some research considers that the overall risk of ASD recurrence among siblings is between 6.1% and 24.7%.[4] However, there is an estimate regarding the risk of sex-specific recurrence. Palmer et al.[4] showed that people with autism have a RR of autism of 4.2% in female siblings and about 12.6% in males. If a woman has this disorder, the authors demonstrated that ASD was present in 7.6% of female siblings and 16.7% in males.[4]

There is a higher prevalence of ASD in males, with men being 4 times more affected than women.[11] This occurs due to the presence of a marked male bias, since in females ASD carriers have an excess of biallelic loss-of-function mutations.

Tick et al.[6] studies involving monozygotic and dizygotic twins also point to information on the heritability of ASD in these individuals; results of 74% and 93% of heritability of ASD in twins were found in the meta-analyses, and a 98% agreement in monozygotic twins against 44-60% in dizygotic twins.[3]

According to Hansen et al.[23], the concordance rate among monozygotic twins was 2 times higher than that of dizygotic twins, and the concordance rate among full siblings was up to 3 times higher than in half-siblings. The authors also point to the risk of ASD recurrence in maternal half-siblings at 5.8%, while paternal half-siblings have 3.9%, and RR in cousins at 1.9%.

The maternal effect[21] is characterized by the influence that the mother, during pregnancy, can have on the development of traits related to ASD in the child, such as characteristics or conditions that impact the child's health. This phenomenon does not have such a significant contribution to the development of the disorder, constituting a minimal association, estimated at between 0.4 and 1.6%.[21]

Regarding the influence of the shared environment, that is, particularities of the family or domestic environment that can contribute to the similarity between family members, in addition to the genetic,[21] it is not relevant to the risk of ASD.[21] However, there are several limitations that may interfere in the elaboration of this finding, given the varied genetic structure of different populations studied and analytical models sensitive to small samples.[21]

ASD, in many cases, is established simultaneously with several other disorders, such as intellectual disability, attention-deficit/hyperactivity disorder, behavioral disorders, and anxiety.[22] It is believed that the probability of acquiring psychiatric and neurodevelopmental disorders is 2 times higher[22] among siblings of autistic people, due to associated environmental or genetic factors.[22] This assumption was reinforced by a twin study, in which a dizygotic twin was diagnosed with ASD, increasing the likelihood that his brother would develop attention deficit hyperactivity disorder (ADHD), developmental coordination disorder (DCD), tics, and learning disability.[22]

Also in this study, about 36.9% of individuals with ASD had a sibling diagnosed with any psychiatric or neurodevelopment,[22] with the most prevalent risks being ASD, OCD, ADHD, learning and motor coordination deficits, as well as intellectual disability.[22] Childhood-onset disorders obtained strong associations, which were found without considering whether the child with autism had intellectual disability or not.[22] However, it is necessary to consider the divergences in studies that deal with the subject, since some of them mention a low level of cognition in the proband, others have evidenced a high level of verbal IQ, as well as there are studies reporting indifference, which reflects the wide spectrum of variation in autism.[22]

It is also assumed that childhood-onset disorders have etiological similarity and may share risk factors, with the heritability of these conditions estimated as high, in addition to environmental factors contributing to the process, as they were associated with these

disorders, in cases of prenatal infection/inflammation, obstetric or perinatal complications, and parental age.[22]

Therefore, this study highlights the importance of research regarding psychiatric and neurodevelopmental disorders among siblings of children with ASD, essential to obtain detailed and specific information about clinical, treatment, etiology, prevention and prognosis. Thus, it is of great importance that the siblings of the individual with ASD be carefully monitored by the health professional in charge. Through genetic counseling, parents should be informed about the disorder, which should have its aspects addressed in a broad way, which will contribute to the search for help, not only for the diagnosed subject, but also for their family members, who must undergo an evaluation.[4,19,22,26]

CONCLUSION

Due to the high heritability of ASD, it is coherent to use genetic counseling for this condition to bring significant information, especially in the analysis of the risks of recurrence. The overall risk of ASD recurrence among siblings is 6.1% and 24.7%, with 74% and 93% of ASD heritability in twins and 2 times higher among monozygotic twins than in dizygotic twins. In addition, there is a 4-fold higher prevalence of ASD in males and a risk of 48.10% in the case of a family that already has at least one child with ASD or ADHD. Therefore, genetic counseling to determine the empirical risk of recurrence is an important resource, if not essential, to inform families about the risks involved in presenting a family member with ASD.

Authors' contributions

João Marcos Valentim dos Santos: Preparation and initial writing
Isabela Garrett Portugal: Methodology
Marcela Sarú Campos: Methodology
Maria Müller Angulski: Study data statistics
Bruno Henrique Moraes Strapasson: Creation of models
Tailla Cristina de Oliveira: Critical review
Liya Regina Mikami: Critical review and final writing

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Concordance of glandular extension between cytology and histopathology in the analysis of high-grade lesions of the uterine cervix

Concordância da extensão glandular entre citologia e histopatologia na análise das lesões de alto grau da cérvice uterina

Bruno Granja Marcos[1], Gabriela Helena Mota Gonçalves[2], Samya Hamad Mehanna[2], Luiz Martins Collaço[2], Julia Wansaucheki[2]

ABSTRACT

Introduction: High-grade cervical lesions with glandular extension pose diagnostic challenges that affect clinical management. Glandular occupancy can mimic other lesions, impacting therapeutic decisions. In this context, analyzing the concordance between cytology and histopathology is crucial to optimize diagnostic protocols and individualized treatment.

Objective: To evaluate the efficacy of cytology (cervicovaginal examination) in detecting high-grade intraepithelial lesions with glandular occupancy, comparing its results with histopathology of samples obtained by conization (LEEP) to determine diagnostic accuracy.

Method: This is a cross-sectional, retrospective study based on the analysis of medical records of patients with high-grade lesions of the cervix. Data were collected from cytological and histopathological reports, including information on the presence of glandular occupancy.

Result: Of the 266 patients with these lesions who underwent LEEP, 42 were included due to follow-up. Ages ranged from 20 to 68 years (mean, 40). Glandular occupation was observed in 15 (35%). Cytological criteria for glandular occupation were met in 3, with histological confirmation in only 1. The agreement between cytological and histopathological findings revealed a sensitivity of 33.3%, a specificity of 80%, a positive predictive value of 33.3%, a negative predictive value of 80%, and an efficacy of 69.3%. Post-LEEP recurrence occurred in 30.9% of cases with histological glandular occupation.

Conclusion: The efficacy of cytology in detecting glandular occupation was less than 70%, suggesting the need for additional diagnostic methods, such as colposcopy or imaging, to ensure a more accurate diagnosis and improve prognosis.

KEYWORDS: Cytology. Glandular occupation. High-grade lesion. Gynecology. HSIL. Uterine cervix.

RESUMO

Introdução: Lesões cervicais de alto grau com extensão glandular representam desafios diagnósticos que afetam o manejo clínico. A ocupação glandular pode mimetizar outras lesões, impactando as decisões terapêuticas. Nesse contexto, a análise da concordância entre citologia e histopatologia é crucial para otimizar protocolos diagnósticos e o tratamento individualizado.

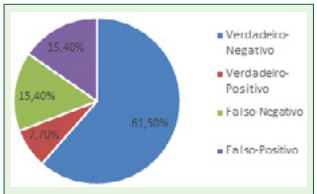
Objetivo: Avaliar a eficácia da citologia (exame cérvico-vaginal) na detecção de lesões intraepiteliais de alto grau com ocupação glandular, comparando seus resultados com a histopatologia de amostras obtidas por conização (CAF), a fim de identificar a precisão diagnóstica.

Método: Trata-se de estudo transversal e retrospectivo, realizado a partir da análise de prontuários de pacientes com lesões de alto grau da cérvix uterina. Foram coletados dados de laudos citológicos e histopatológicos, incluindo informações sobre a presença de ocupação glandular.

Resultado: Das 266 pacientes com essas lesões submetidas à CAF, 42 foram incluídas devido ao seguimento. A idade variou de 20 a 68 anos (média de 40). Ocupação glandular foi observada em 15 (35%). Critérios citológicos para ocupação glandular foram encontrados em 3, com confirmação histológica em 1 apenas. A concordância entre os achados citológicos e histopatológicos revelou sensibilidade de 33,3%, especificidade de 80%, valor preditivo positivo de 33,3%, valor preditivo negativo de 80% e eficácia de 69,3%. Recidiva pós-CAF ocorreu em 30,9% com ocupação glandular histológica.

Conclusão: A eficácia da citologia na detecção de ocupação glandular foi inferior a 70%, sugerindo a necessidade de métodos diagnósticos adicionais, como colposcopia ou exames de imagem, para garantir diagnóstico mais preciso e melhorar o prognóstico.

PALAVRAS-CHAVE: Citologia. Ocupação glandular. Lesão de alto grau. Ginecologia. HSIL. Cérvice uterino.



Confirmed cytological diagnoses of glandular occupation by histopathology (n = 42)

Central Message

The evaluation of the agreement between cytology and histopathology in the detection of glandular extension in high-grade lesions of the uterine cervix is crucial since glandular occupation can impact clinical management and increase the risk of recurrence. Accurate identification of these lesions is essential to optimize therapeutic decisions and improve patients' prognosis.

Perspective

The limited efficacy of cytology in detecting glandular occupancy in high-grade lesions suggests the need for complementary diagnostic methods, such as colposcopy and imaging, to refine diagnostic accuracy. Incorporating new approaches can lead to more individualized treatment and reduction in recurrence rates, thereby improving clinical outcomes for patients with high-grade cervical injuries.

[1] Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil;
[2] Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

Squamous cell carcinoma of the uterine cervix, in addition to being the third most prevalent neoplasm in the female population in Brazil, is also the fourth leading cause of deaths of women from cancer in the country and in the world.[1,2] In most cases, the disease is caused by persistent infection by oncogenic strains of the Human Papilloma Virus (HPV), evolving slowly and gradually.[3]

Precursor lesions can be cytologically classified as low-grade intraepithelial lesions (LSIL), corresponding to cervical intraepithelial neoplasia (CIN) grade I, or high-grade intraepithelial lesions (HSIL), corresponding to CIN grades II and III.[3]

Cervical cancer screening can be done quickly and inexpensively by Pap smear testing and, once diagnosed, these precursor lesions are curable in almost all cases.[4] In the planning of treatment for those diagnosed with HSIL, it is essential to consider the presence of glandular occupation because it is associated with a higher rate of postoperative recurrence, often requiring deeper resections.[5]

There are cytological criteria that can be used to detect glandular occupation; however, there are not many studies that evaluate its sensitivity and specificity.[5] The objective of this study is to evaluate the efficacy of the criteria listed for the detection of glandular occupation in cytology by means of the Pap smear, relating it to the histopathological results of the follow-up of patients undergoing treatment by high-frequency surgery (LEEP).

METHOD

This research is in compliance with ethical aspects and was approved by the Institutional Ethics Committee, with the Certificate of Presentation of Ethical Appreciation (CAAE) 99859718.9.0000.0103 and the approval opinion number 2.952.834. This is a retrospective observational study between January 2014 and December 2018, involving patients who underwent high-frequency surgery (LEEP) with a diagnosis of HSIL at the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil.

Data were obtained from the electronic medical records, and the age of the leveraged patients, the cytological diagnosis (Pap smear) and the anatomopathological reports related to LEEP were analyzed. The cytological slides were reviewed to identify glandular occupation criteria defined by the literature, such as atypical epithelial cells with HSIL characteristics, three-dimensional clusters of atypical squamous epithelial cells with adhered benign endocervical epithelium, digitiform three-dimensional clusters of atypical squamous epithelial cells from borders covered by intact epithelium, and absence of cytological findings of adenocarcinoma in situ of the uterine endocervix. Subsequently, follow-up cytology was also reviewed to determine, whether or not, the lesions regressed.

In the histopathological reports, the presence or absence of glandular occupation was verified. Patients whose CAFs were negative for HSIL and patients who did not have previous cytology at the service were excluded from the study.

After reviewing the slides, the cytology results were compared to the histopathological results to determine epidemiological indices such as efficacy, positive predictive value, negative predictive value, sensitivity, and specificity. The following were considered: 1) true positives (PV), when they had glandular occupation both in cytology and anatomopathology; 2) true negative (VN) regarding glandular occupation in cytology and also in anatomopathological analysis; 3) false positives (PF) when there was glandular occupation in the cytology and negative in the anatomopathological examination; 4) false negatives (FN) when negative for glandular occupation in cytology and positive in anatomopathological analysis.

Sensitivity was defined as PV/VP + FN; specificity by VN/VN + FP; and diagnostic accuracy by PV+VN/(PV +FP + VN +FN).

RESULT

Initially, 266 patients who underwent conization using the LEEP technique were analyzed, but only 42 were included in the sample, as they had follow-up cytology. In this group, the women's ages ranged from 20 to 68 with a mean of 40 years (Figure 1). All cases were diagnosed with HSIL and there was a total of 15 occurrences of glandular occupation diagnosed on histopathology, corresponding to approximately 35% of the sample.

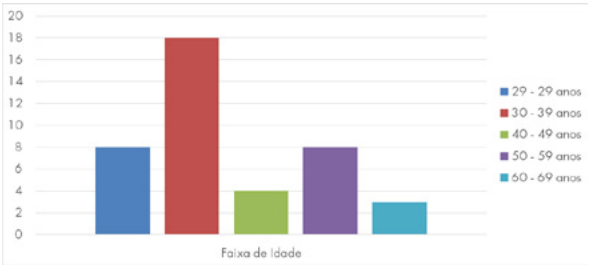

FIGURE 1 — Age group of the patients (n = 42)

Only 13 patients submitted to LEEP had previous cytology. Of these, 3 had cytological criteria for glandular occupation, but only 1 had histological confirmation in LEEP.

Among the 10 patients who did not meet the criteria for glandular occupation in cytology, 8 had their negativity confirmed by LEEP. Thus, in the cytohistological comparison, true-negative cases predominated (61.5%, Figure 2).

A total of 13 recurrences were recorded in the follow-up cytopathology, representing 31% of the sample. Among these recurrences, only 4 occurred in patients with diagnosed glandular occupation.

Statistical analysis

After statistical calculations of the data obtained, it was found that the criteria used for cytological evaluation of occupation in this study had a sensitivity

of 33.3%, specificity of 80%, positive predictive value of 33.3%, negative predictive value of 80% and efficacy of 69.3%.

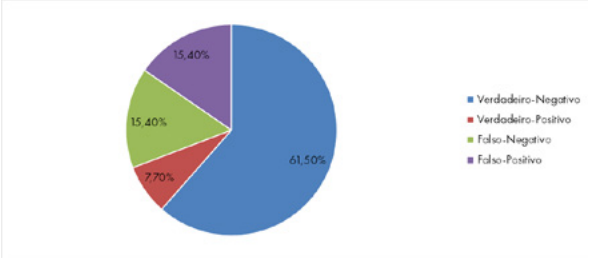

FIGURE 2 — Comparative results of cytological diagnoses of glandular occupation confirmed by histopathology (n = 42)

DISCUSSION

In the current literature, it is stated that glandular occupation is the most important risk factor for recurrence after LEEP, being present in 35% of cases of HSIL recurrence.[6] The data of this study corroborate the literature, since the extension of the lesions to the endocervical glands was present in 30.7% of the cases with proven recurrence.

Among the patients evaluated, only 15 of the 42 (35.7%) had glandular occupation. This is in slight disparity with published data since the average reported is 68.9% of those with HSIL.[7]

Regarding age, there is a peak of CAFs between 30 and 39 years of age, justified by the fact that the incidence of intraepithelial lesions of the uterine cervix reaches its maximum point around 30 years of age.[3] There was a 30.9% recurrence rate among the patients after the initial LEEP, indicating a rate higher than that observed in other studies, which indicate recurrences ranging from 5 to 13% of the cases.[8,9] This, however, may be due to the restricted sample size of this study, in addition to the fact that other characteristics associated with recurrences were not included, such as neoplasm-free margins in the CAFs, relationship with HPV subtype, risk factors such as smoking, and immunodeficiency.[10]

As can be inferred from Figure 2, the cytological criteria for glandular occupation showed a high rate of negative results when compared to the false-negative rate, thus indicating good specificity and low sensitivity for the sample studied, in which the slides were reviewed by a cytopathologist experienced in cervical-vaginal smears.

Regarding the difficulties of the research, it should be noted that those treated in 2012 and 2013 at the hospital could not be included in this study because their records were incomplete. Also, from the initial estimate, 197 were excluded from the study because their CAFs were reported negative for HSIL. In addition, 27 patients were excluded because they had been referred from another service and did not have cervicovaginal cytology at the institution.

The criteria listed have been shown to be effective for the detection of glandular occupation in cytology. Although their positive predictive value and sensitivity are low, they have shown promise in the exclusion of glandular occupation due to their high specificity and negative predictive value. At follow-up, a high rate of recurrence was observed, indicating the need for further investigations regarding the group evaluated. The conclusions drawn from this study are subject to the bias generated by the small sample. This, together with the lack of established parameters regarding cytological criteria for diagnosing glandular occupation, makes it necessary to conduct research with larger populations in the future.

CONCLUSION

In the present study, the efficacy of cytology in detecting glandular occupation in high-grade squamous lesions of the uterine cervix was 69.3%, which is relevant data to be described in the cervical-vaginal examination reports, because among the patients with glandular occupation proven in histopathology followed after LEEP, 30.9% had recurrence.

Authors' contributions
Samya Hamad Mehanna: Formal analysis, supervision, writing.
Gabriela Helena Mota Golçalves: Project administration, supervision
Bruno Granja Marcos: Methodology, formal analysis.
Luiz Martins Collaço: Conceptualization, writing, revision and editing.
Julia Wansaucheki: Writing, proofreading and editing.

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Clinical and epidemiological profile of elderly patients evaluated at a tertiary hospital after same-level falls

Perfil clínico e epidemiológico de idosos avaliados em hospital terciário após quedas do mesmo nível

Felippe Bohnen de Jesus[1], Gabriel De Cecco Medeiros[1], Mariane Martins Balduino Piotto[1], Ariadna Lorrane Romualdo[1], Paulo Ricardo Bittencourt Guimarães[2], Victoria Zehgbi Cochenski Borba[2], Maria Augusta Karas Zella[1]

ABSTRACT

Introduction: Aging leads to various biochemical, morphological, and functional changes, including gait alterations, visual impairment, and reduced muscle strength. These factors increase the risk of unintentional falls, which may result in contusions, fractures, psychological trauma, and even death. In 2018, falls accounted for 12,000 deaths among older adults in Brazil.

Objective: To analyze the clinical and epidemiological profile of older adults who sustained fractures due to same-level falls and to assess risk factors for osteoporosis and fractures.

Methods: Cross-sectional observational study including patients aged ≥60 years admitted to a tertiary hospital following a fall. Cases involving high-energy trauma mechanisms were excluded. Patients were equally divided into a fractured group (FG) and a non-fractured control group (CG). Risk factors were assessed, and the risk of osteoporosis and fractures was estimated using validated calculators.

Results: The sample included 100 patients (mean age ± 71.78 years; mean BMI ± 25.89 kg/m²), predominantly female. A significant difference was observed in sarcopenia assessment: fractured individuals had lower calf circumference, waist circumference, and handgrip strength values. No significant differences were found regarding fall questionnaire responses or the use of medications associated with osteoporosis and falls. Significant differences were observed between FG and CG concerning the risk of hip fractures and major fractures, as evaluated by the FRAX tool. The IOF One-Minute Osteoporosis Risk Test was not effective in distinguishing between groups.

Conclusion: Contrary to expectations, variables such as BMI, smoking, physical inactivity, comorbidities, oral glucocorticoid use, and previous falls did not differentiate the groups. However, in addition to age and fracture history, sarcopenia and hyperthyroidism emerged as important predictors of fractures following these events.

KEYWORDS: Bone fracture. Aged. Osteoporosis. Sarcopenia. Accidental falls.

RESUMO

Introdução: O envelhecimento acarreta diversas alterações bioquímicas, morfológicas e funcionais. Destacam-se alteração de marcha, dificuldades visuais e redução da força muscular. Esses fatores aumentam o risco de quedas não intencionais, que podem resultar em contusões, fraturas, trauma psicológico e até óbito. Em 2018, quedas ocasionaram 12.000 mortes entre idosos no Brasil.

Objetivo: Análise do perfil clínico e epidemiológico de idosos que sofreram fraturas por quedas do mesmo nível e avaliação dos fatores de risco para osteoporose e fraturas.

Método: Estudo observacional de corte transversal, com pacientes ≥ 60 anos atendidos em hospital terciário após queda. Foram excluídos mecanismos de trauma de alta energia. Os pacientes foram divididos equitativamente em grupo fraturado (GF) e grupo controle não fraturado (GC). Avaliou-se fatores de risco e calculou-se risco de osteoporose e fratura com calculadoras validadas.

Resultados: A amostra incluiu 100 pacientes (idade ± 71,78 anos e IMC médio ± 25,89 kg/m2), sendo a maioria mulheres. Observou-se diferença significativa na avaliação de sarcopenia: indivíduos fraturados apresentaram menores valores de circunferência da panturrilha, circunferência da cintura e medida de preensão palmar. Não foram encontradas diferenças significativas nas respostas ao questionário de quedas e no uso de medicamentos associados à osteoporose e quedas. Houve diferenças significativas entre os GF e GC em relação ao risco de fraturas de quadril e fraturas maiores, avaliados pela ferramenta FRAX. O Teste de Risco de Osteoporose de Um Minuto da IOF não foi útil para distinguir os pacientes dos grupos.

Conclusão: Ao contrário do suposto esperado, variáveis como IMC, tabagismo, sedentarismo, presença de comorbidades, uso de glicocorticoides orais e o número de quedas prévias não foram capazes de distinguir os grupos. No entanto, além da faixa etária e histórico de fraturas, sarcopenia e hipertireoidismo emergiram como importantes preditores de fraturas após esses eventos.

PALAVRAS-CHAVE: Fraturas ósseas. Idoso. Osteoporose. Sarcopenia. Acidentes por quedas.

Central Message

The study shows that variables traditionally considered as risk factors for fractures in the elderly, such as body mass index (BMI), smoking, sedentary lifestyle, and some comorbidities, were not able to distinguish fractured patients from those who did not suffer fractures after falls of the same level. However, factors such as sarcopenia and hyperthyroidism emerged as relevant predictors for osteoporotic fractures, highlighting the need for prevention strategies that include the assessment of muscle strength and the control of hormonal disorders.

Perspective

The findings challenge the traditional view on risk factors for fractures in the elderly, suggesting that fall prevention should go beyond the conventional approach focused only on bone density and the presence of comorbidities. The identification of sarcopenia as a relevant factor reinforces the importance of muscle rehabilitation programs and adequate endocrine follow-up in the prevention of fractures. These results may contribute to the formulation of more effective clinical guidelines for the management of fracture risk in the elderly population.

[1] Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil;
[2] Federal University of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

Elderly people are more prone to falls due to the higher incidence of risk factors, such as visual difficulties, decreased muscle mass, weakness and increased use of medications. In addition, falls in this age group substantially increase the risk of fractures, since they occur in a group of people with a higher incidence of comorbidities, such as osteoporosis.[1]

It is estimated that about a third of individuals aged 60 and over fall at least once a year.[2] The risk is more significant when in octogenarians and nonagenarians, where the annual incidence of falls can reach 50%.[3] In addition, the data still point to falls as the main cause of fractures in the elderly, especially in those with osteoporosis. In Brazil, in 2018, there were about 12,000 deaths from falls in people over 60 years of age, 84% of whom were over 70 years of age.[4]

Based on these reflections, the following question arose in this study: Why do some patients fracture as a result of falls from the same level while others do not? What factors contribute to both the risk of falling and the risk of fracture? What are the clinical findings that can result in fracture?

Fractures resulting from falls from the same level are caused by specific clinical factors, among the risk factors include previous fracture due to frailty, hip fracture due to frailty in a first-degree relative (mother or father), tobacco use, use of glucocorticoids, diagnosis of rheumatoid arthritis, secondary osteoporosis (caused by different diseases) and use of 3 or more units of alcoholic beverage per day.[5]

Unintentional falls occur due to the sum of risk factors, and it is difficult to restrict the fall event to a single factor or a causal agent. The reasons for falls may be related to age, gender, prolonged hospitalization, debilitating diseases, generalized muscle weakness, unsteady gait, confusion or disorientation, incontinence, history of previous falls, visual deficit or linked to the use of medications with hypnotic action, sedative, vasodilators, diuretics and antidepressants, among others.[6]

Because most fractures result from falls, the etiology of fractures and fractures is partially overlapped. The factors associated with falls (recurrent and with injuries), determined by retrospective studies, the circumstances and consequences of these events, indicated in prospective designs, have been widely studied and reported in the literature. It is considered essential to increase knowledge about the problem, its characteristics and consequences.

The objective of this study was to analyze the clinical and epidemiological profile of patients aged 60 years or older who suffered fractures after falls at the same level, treated at a reference teaching hospital. Part of the detailed approach to the profile, integrating proven risk factors for the development of osteoporosis and fractures, we sought to identify which of these factors are most relevant in the context. Thus, it is intended to contribute to the improvement of strategies for the prevention and management of these fractures, providing evidence that can guide health policies and more effective clinical practices for the elderly population.

METHOD

This was a cross-sectional observational study conducted from March 2022 to March 2023, approved by the Research Ethics Committee of the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil, under protocol 5,307,196 in accordance with the guidelines established in Resolution No. 466/2012 and Resolution No. 510/2016 for research involving human beings. The research was conducted at the Mackenzie Evangelical University Hospital mentioned above, covering both patients hospitalized due to fractures after low-energy trauma and those hospitalized for other causes, but with a history of falls at the same level.

Men and women aged 60 years or older, who had a history of falls from the same level, with mental fitness to perform the tests and questionnaires were included. The exclusion criteria were the presence of communication difficulties, clinical conditions that prevented participation, not accepting to participate in the evaluation or not filling out the Informed Consent Form. The researchers were previously trained by the study coordinator, in order to standardize data collection.

Eligible patients underwent a comprehensive evaluation, which included the collection of demographic data, such as gender and age, and the application of a questionnaire from the Brazilian Osteoporosis Manual. This questionnaire assessed the risk of falls, addressing the occurrence, frequency and consequences of falls in the last 12 months, in addition to investigating the feeling of insecurity and imbalance when walking.[7] In addition, they were asked about the possible causes of falls, such as slips, trips, loss of balance, muscle weakness, dizziness, convulsions, hypotension, among others. Regarding the risk factors for osteoporosis and the characterization of the population studied, the patients' continuous use medications were recorded and the International Osteoporosis Foundation (IOF) One-Minute Osteoporosis Risk Test was applied.[8] This test considers several factors, including a family history of osteoporosis, fractures and dorsal kyphosis, BMI less than 19 kg/m^2, history of falls, use of corticosteroids, loss of height, previous diagnosis of rheumatoid arthritis, history of early menopause or cessation of menstruation, oophorectomy, sexual impotence, and lifestyle habits (intake of milk and dairy products, physical activity, smoking and time of exposure to the sun). The risk of fracture at 10 years was assessed using the online tool FRAX9, without bone densitometry.

Anthropometric data such as weight, height measurement, BMI calculation (weight/height^2), waist and calf waist were evaluated. In the clinical evaluation, the handgrip test/strength (HGS) was evaluated by measuring the maximum isometric force exerted on a

hydraulic hand dynamometer in kilogram/force (Kgf), following the recommendation of the American Society of Hand Therapists (ASHT). For this, the Jamar® analog hydraulic dynamometer (Lafayette Instrument, USA) was used.

Statistical analysis

The collected data were tabulated and analyzed in statistical software. To describe the categorical variables, contingency tables were constructed. To describe the quantitative variables, descriptive measures were calculated as mean, minimum, maximum and standard deviation. To compare the groups, the Chi-square test (or Fisher's exact test, for lower frequencies) was applied, considering $p < 0.05$ as significant. The entire dataset that supports the results of this study is available upon request to the corresponding author Felippe Bohnen de Jesus.

RESULTS

The study sample consisted of 50 fractured patients (FG) and 50 unpaired control patients (CG). The mean age of the FG was 75.38 ± 9.46 years and of the CG 68.18 ± 6.57 years (p = 0.0001). The clinical characteristics of the groups evaluated are described in Table 1.

TABLE 1 — Demographic and clinical data of the fractured and control groups

Variables	Control group (n,%)	Fractured group (n,%)	p-value*
Gender Male Female	29 (58%) 21 (42%)	36 (72%) 14 (28%)	0,14
Has already undergone bone densitometry	9 (18%)	22 (44%)	0,005
Hyperthyroidism	0 (0%)	7 (14%)	0,006
Diabetes mellitus	6 (32%)	23 (46%)	0,15
Chronic kidney disease	2 (4%)	1 (2%)	0,56
Prostate or breast cancer	2 (4%)	1 (2%)	0,56
COPD	3 (6%)	2 (4%)	0,65
Celiac disease or inflammatory bowel disease	2 (4%)	0 (0%)	0,15

*Pearson's Chi-square test

When using the questionnaire to assess the risk of falls from the Brazilian Osteoporosis Manual, no statistical difference was observed between the groups (p = 0.98). Both groups had a similar number of decreases, and have similar perceptions of imbalance and insecurity

TABLE 2 — Assessment of the Risk of Falls in the CG and FG

Variables		Control group	Fractured group	p-value*
Number of falls in the last year	1 time 2 times 3 times > 3 times	27 (54%) 13 (26%) 6 (12%) 4 (2%)	26 (52%) 12 (24%) 6 (12%) 6 (4%)	0,98
Do you lack the balance or instability to stand and sit?	yes	25 (50%)	31 (62%)	0,23
Are you unsure or worried about falling?	yes	23 (46%)	27 (54%)	0,42

*Pearson's Chi-square test

The One-Minute Osteoporosis Risk Test (IOF) indicated that the majority of the CG (60%) obtained a score lower than 5, presenting a low risk of osteoporosis. On the other hand, in the FG, the majority (54%) obtained 5 points or more, i.e., revealing a high risk of osteoporosis, in agreement with the history of atraumatic fractures in adulthood. In addition, in the FG, the hyperthyroidism comorbidity was more prevalent (p <0.00001).

In the analysis of the correlation between osteoporosis medications and the occurrence of falls in the groups studied, no statistically significant difference was identified in the use of these medications in relation to fractures (p = 0.81). For example, 52% of participants in both groups did not use chronic medications. Although the use of glucocorticoids for more than 3 months was more prevalent in the FG, this difference was not statistically significant (p = 0.749). In addition, the use of medications such as proton pump inhibitors (PPIs), selective serotonin reuptake antidepressants (SSRIs), and anticonvulsants was more frequent in the CG.

As shown in Table 3, among the clinical risk factors evaluated in the FRAX-Brazil calculator, the items age and history of previous fracture were the only different and higher items in the FG when compared to the CG (p = 0.0001 and p = 0.00001, respectively).

TABLE 3 — Evaluation of clinical risk factors from the 10-year fracture risk calculator (FRAX-Brazil) in CG and FG

Variables	Control Group	Fractured Group	p-value*
Average age (years)	68,18	75,38	0,0001
BMI (kg/m²)	26,78	25	0,39
Previous fracture	0 (0%)	25 (50%)	0,00001
Parents with hip fracture	5 (10%)	5 (10%)	1
Smoking Chain	15 (30%)	9 (18%)	0,16
Glucocorticoids	5 (10%)	6 (12%)	0,75
Rheumatoid arthritis	8 (16%)	4 (8%)	0,22
Secondary osteoporosis**	8 (16%)	12 (24%)	0,32
Alcohol 3 doses or more units daily	9 (18%)	3 (6%)	0,065
Have you ever had bone densitometry?	9 (18)	22 (44%)	0,005

*Pearson's Chi-square test

As a result of the FRAX calculator, the high risk for major and hip fractures was higher in the FG, present in 48% (p = 0.00001) and 60% (p = 0.00001) of the patients, respectively (Table 4).

TABLE 4 — Evaluation of clinical risk factors from the fracture risk calculator in 10 years (FRAX-Brazil) in the CG and FG

Major fractures	Control group	Fractured group	p-value*
High risk	50 (10%)	24 (48%)	0,00001
Medium risk	27 (54%)	26 (52%)	
Low risk	18 (36%)	0 (0%)	
Hip fracture			
High risk	10 (20%)	30 (60%)	0,00001
Medium risk	22 (44%)	19 (38%)	
Low risk	18 (36%)	1 (2%)	

*Pearson's Chi-square test; **Secondary osteoporosis: type 1 diabetes, osteogenesis imperfecta, untreated hyperthyroidism, hypogonadism or early ovarian failure (<45 years), chronic malnutrition or malabsorption, and liver disease

Compared to the CG, the FG group had lower values for calf circumference (p = 0.012), handgrip (p = 0.015), and waist circumference (p = 0.034), as shown in Table 5.

TABLE 5 — Evaluation of sarcopenia in CG and FG

Variable	Group	Average	n	DP*	Minimum	Maximum
Palmar grip	Control	23.68	50	10.09	3	48
	Fracture	18.90	50	10.67	0	55
Calf circumference	Control	33.01	50	4.73	19	43
	Fracture	31.08	50	4.11	22	40
Waist circumference	Control	98.68	50	12.00	70	127
	Fracture	93.43	50	13.21	70	132

* SD=standard deviation

DISCUSSION

When analyzing the demographic data collected, it was observed that the mean age of the FG (75.38 years) is significantly higher compared to the mean age of the CG, of 68.18 years. (p = 0.0001). This data collaborates with studies that indicate that the risk of fracture in most skeletal sites accelerates with aging regardless of BMD.[10,11] It was found that the risk of fracture was not preceded by a greater number of falls, as the groups have similar incidences.

Applying the IOF One-Minute Osteoporosis Risk Test, it was found that most patients without fractures (60%) scored less than 5 points on the questionnaire, presenting a low risk of osteoporosis. In the FG, it is observed that most individuals (54%) scored 5 points or more, revealing a high risk of osteoporosis. However, when comparing the groups, this data was not statistically significant.

This data becomes critical when related to another demographic data: most fractured patients (56%) had never undergone bone densitometry, i.e., despite being considered at high risk for osteoporosis, they had never undergone a diagnostic examination before the occurrence of fractures. Despite this, the FG still performed more bone densitometry than the CG (p = 0.005).

In view of the exploratory and descriptive nature of this study, which sought not only to understand issues related to the predisposing factors for fractures in the elderly, but also to describe the clinical profile of the sample to be studied, some risk factors for osteoporosis stood out. Among them, the presence of previous hyperthyroidism in the FG stands out, affecting 14% of the patients, in collaboration with the study published by Blum et al.[12] in 2015, which investigated the association of subclinical hyperthyroidism has been associated with a 36% increase in the risk of hip fracture, a 28% increase in the risk of any fracture, and a 16% increase in the risk of fracture outside the spine, compared to normal thyroid condition, and is associated with low bone density in both men and women.[12]

Regarding the non-modifiable risk factors of the IOF test, the most frequently found were the occurrence of a previous fracture (50%), more than one fall in the last year (48%) and the loss of more than 3 cm in height after the age of 40 (48%). In addition, 30% of the women interviewed claimed to have had menopause before the age of 45 and about 69% of the men experienced symptoms related to low testosterone, such as impotence and lack of libido.

Regarding risk factors related to lifestyle habits, in the FG the main risk factors included lack of intake of dairy products or calcium tablets (28%), exercise quota of less than 30 minutes per day (22%) and sun exposure of less than 10 min per day or not using vitamin D supplements (24%). These results corroborate those found by Lin et al.[13,] and published in 2020, in which after using the IOF One-Minute Osteoporosis Risk Test for 455 institutional caregivers, with a mean age of 43.5 ± 11.5 years (range = 20-76 years), the same risk factors were demonstrated as the most frequently reported.[13]

Through the fracture risk assessment instrument (FRAX), it can be observed that FG has a higher risk of developing major and hip fractures in the next 10 years. Individuals classified as high risk for major fractures are approximately 48% in the FG and only 10% in the CG. In relation to hip fractures, the difference is even more pronounced, with 60% against 20%.

In the evaluation of handgrip strength with the use of a dynamometer - a validated method for the evaluation of sarcopenia - the FG presented significantly lower values (mean of 18.9kgf). According to the consensus of the Asian Sarcopenia Working Group (AWGS) 2019, low muscle strength is defined as handgrip strength <28 kgf for men and <18 kgf for women.[14]

In the absence of other available methods for assessing sarcopenia, calf circumference measurement may be used. The AWGS 2019 update proposes screening of calf circumference (<34 cm in men and <33 cm in women) to facilitate early identification of people at risk of sarcopenia.[15] In the study, the FG had significantly lower values than the CG (p = 0.012), with a mean of 31.08 cm, at risk for sarcopenia.

In a 2-year longitudinal study, and published in 2022, Yoo et al.[16] selected 926 non-sarcopenic elderly people and divided them according to the presence of obesity (based on BMI, waist circumference (WC) and body fat percentage). The groups of obese and non-obese individuals were compared according to the parameters of sarcopenia. It was observed that the reduction in appendicular skeletal muscle mass was significantly lower in the obese group with high WC in men and women (p < 0.[01).] However, elevated WC was associated with a low incidence of sarcopenia only in women.[16]

In parallel with this study, the data obtained showed that the CG had higher WC values when compared to the FG (p = 0.034). Considering that the mean waist circumference (WC) in the CG was 98.68 cm, it is important to relate it to the cutoff points established by the Nutrition Screening Initiative/NSI to identify central obesity: 88.[7] cm for women and 96 cm for men.[17] Based on these data, it is possible to explore the possibility of a protective effect exerted by obesity against sarcopenia, which may, consequently, have decreased the risk of fractures in this group.

The specific clinical factors described in the literature[17-19] that favor fractures resulting from falls at the same level, such as previous fracture due

to frailty, hip fracture due to frailty in a first-degree relative (mother or father), tobacco use, use of glucocorticoids, diagnosis of rheumatoid arthritis, secondary osteoporosis (caused by different diseases) and use of 3 or more units of alcoholic beverage per day, in the population studied, no risk factors were shown to clinically differentiate FG from control. An observational, cohort study carried out with 143 individuals showed results that are in line with these: there were no statistically significant differences in age, weight, height, number of coexisting diseases, types of diseases (diabetes mellitus, hypertension) and number of medications between the groups with and without falls. The authors do not deny that the low relevance of the parameters may be a reflection of a limited sample.[20]

One of the limitations of this study, which can affect the representativeness of the sample, lies in the unpredictable nature of the profile of patients available for study in the established period, which made it impossible to match the CG and FG according to the patients' gender. Thus, it was decided to prioritize a larger sample group to the detriment of matching according to the gender of the members. In addition, the limited demand for fractured patients that the teaching hospital received in the period was also a limiting factor. It is believed that, despite the considerable sample size presented in this study, an even larger sample group would possibly be able to point out other risk factors that were shown to be statistically irrelevant here.

CONCLUSION

The analysis of the profile of patients aged 60 years or older treated at a tertiary referral hospital after falls from the same level showed that, contrary to what is expected and plausible, variables such as BMI, smoking, sedentary lifestyle, presence of comorbidities (rheumatoid arthritis, diabetes mellitus, chronic renal failure, COPD), use of oral corticosteroids, and the number of previous falls were not able to distinguish FG from CG. However, in addition to the well-documented influence of age group and history of previous fractures, factors such as sarcopenia and hyperthyroidism have emerged as important predictors of fractures after low-energy trauma.

Authors' contributions

Felippe Bohnen de Jesus – Conceptualization, Research, Writing (original draft), Writing (review and editing)

Gabriel De Cecco Medeiros – Conceptualization, Research, Writing (original draft), Writing (proofreading and editing)

Mariane Martins Balduino Piotto – Conceptualization, Writing (original draft), Writing (proofreading and editing)

Ariadna Lorrane Romualdo – Conceptualization, Writing (original draft), Writing (proofreading and editing)

Paulo Ricardo Bittencourt Guimarães – Methodology, Writing (original draft), Writing (proofreading and editing)

Victoria Zehgbi Cochenski Borba - Writing (original draft), Writing (proofreading and editing)

Maria Augusta Karas Zella – Methodology, Project Administration, Writing (original draft), Writing (proofreading and editing)

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Is beige adipose tissue induced by physical exercise?

O tecido adiposo bege é induzido pelo exercício físico?

Aglatha Maalli Santana[1], Alana Caroline Carvalho Chagas[1], Laura de Andrade Mazia[1], Rebeca Medeiros da Silva[1], Luana de Almeida Chagas da Silva[1], Irlena Monica Wisniewska de Moura[1]

ABSTRACT

Introduction: Adipose tissue is divided into yellow, brown and beige. Beige has a thermogenic function in newborns and recent research has shown its potential for improving metabolic health in adults; its synthesis is associated with practice of physical exercise and related to the potential treatment of obesity.

Objective: To present the histology of adipose tissue, its general characteristics, formation, biochemical and physiological mechanisms, as well as the relationship between beige adipose tissue, physical exercise, and obesity.

Method: Narrative review, comprising 27 articles, available in PubMed and Scielo databases and technical scientific books. The descriptors used were "beige adipose tissue", "exercise", "adipose tissue".

Result: Yellow adipose tissue is related to the storage of triglycerides and energy maintenance. Brown is primarily thermogenic, its adipocytes using the energy contained in triacylglycerols to release heat. Beige consists of a combination of unilocular and multilocular adipocytes and can imitate the metabolic function of brown adipose tissue when stimulated. The hormone irisin, stimulated by physical exercise, induces the mRNA of uncoupling protein 1 which promotes the darkening of yellow adipose tissue, forming beige adipose tissue. Regular physical activity increases mitochondrial biosynthesis, increasing the oxidative and thermogenic capacity of beige adipose tissue. This effect may be beneficial against obesity.

Conclusion: Regular physical exercise has a great impact on the modulation of beige adipose tissue, promoting the conversion of yellow adipose tissue into beige, favoring energy expenditure and the secretion of metabolic regulation molecules. Thus, physical exercise is powerful ally in the treatment of obesity, as it stimulates the formation of beige adipose tissue.

KEYWORDS: Beige adipose tissue, exercise, adipose tissue

RESUMO

Introdução: O tecido adiposo é dividido em amarelo, marrom e bege. O bege tem função termogênica em recém-nascidos e pesquisas recentes mostram seu potencial na melhoria da saúde metabólica em adultos, sendo sua síntese associada à prática de exercícios físicos e relacionada ao potencial tratamento da obesidade.

Objetivo: Apresentar a histologia do tecido adiposo, suas características gerais, formação, mecanismos bioquímicos e fisiológicos, bem como, a relação entre tecido adiposo bege, exercícios físicos e o tratamento da obesidade.

Método: Revisão bibliográfica narrativa composta por 27 artigos, disponíveis nas bases de dados PubMed e Scielo e livros técnicos científicos. Os descritores utilizados foram "beige adipose tissue", "exercise", e "adipose tissue".

Resultado: O tecido adiposo amarelo está relacionado com o armazenamento de triglicerídeos e manutenção energética; o marrom é primordialmente termogênico, seus adipócitos utilizam a energia contida nos triacilgliceróis para liberar calor; o bege é constituído pela junção dos adipócitos uniloculares e multiloculares, podendo imitar a função metabólica do tecido adiposo marrom quando estimulado. O hormônio irisina, estimulado pelo exercício físico, induz o mRNA da proteína desacopladora 1 que promove o escurecimento do tecido adiposo amarelo formando o bege. A atividade física regular aumenta a biossíntese mitocondrial elevando a capacidade oxidativa e termogênica do tecido adiposo bege; esse efeito pode ser benéfico contra a obesidade.

Conclusão: Exercícios regulares têm grande impacto na modulação do tecido adiposo bege, promovendo a conversão do amarelo em bege; também favorece o gasto energético e a secreção de moléculas de regulação metabólica. Assim, o exercício físico é grande aliado para tratar a obesidade, uma vez que estimula a formação do tecido adiposo bege.

PALAVRAS-CHAVE: Tecido adiposo bege, exercício, tecido adiposo

Mensagem Central

Beige adipose tissue plays a relevant thermogenic and metabolic role and can be induced from white adipose tissue through physical exercise. The activation of hormonal pathways, particularly mediated by irisin and uncoupling protein 1, is associated with increased energy expenditure and improved metabolic profile, representing a potential adjuvant strategy in the treatment of obesity.

Perspectiva

Evidence that physical exercise positively modulates beige adipose tissue reinforces its indication as a non-pharmacological intervention in obesity management. The clinical application of this knowledge may contribute to more effective, safe, and sustainable therapeutic approaches for the control of metabolic diseases.

[1]*Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brasil.*

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INTRODUCTION

Adipose tissue (AT) participates in the formation of body mass in individuals and represents 20% to 28% of the body mass of healthy individuals, and can reach up to 80% in obese people.[1,2] Primarily, AT is formed by adipocytes, which are specialized and responsible for accumulating triglycerides in order to store energy that will later be metabolized to other cells in the body.[1] The storage of energy in the form of triglycerides is exerted by yellow adipose tissue (AAT) and its main deposits are in the dermis and subcutaneous tissue, that is, in the adipose panniculus.[1] Brown adipose tissue (TAM) is responsible for dissipating energy in the form of heat.[1] AT has several functions, such as thermogenic, physiological and endocrine.[1]

Recently, beige adipose tissue (BAD) was discovered, which is made up of unilocular and multilocular adipocytes, it is commonly located in the subcutaneous tissue and its origin may be associated with the practice of physical exercise.[2]

Thus, the objective of this review was to present, in addition to the histology of adipose tissue, its general characteristics, formation, biochemical and physiological mechanisms, as well as the relationship between beige adipose tissue, physical exercise, and the treatment of obesity.

METHOD

Narrative review of the literature composed of articles available in the PubMed and Google Scholar databases carried out in April 2024. The keywords used were "beige adipose tissue", "exercise", and "adipose tissue". The final sample consisted of 23 articles.

DISCUSSION

Adipose tissue is formed by adipocytes, which are responsible for the accumulation of triacylglycerols (TAGs) in droplets, which are lodged in their cytoplasm. GADs originate from ingested lipids that are absorbed by the epithelial cells of the small intestine, from lipids originating from the liver and transported by the bloodstream, from lipids synthesized in fat cells, liver cells, muscle cells, and other cells from glucose.[3] They are deposited in the lipid vacuola (lipid storage vacuole), which contains enough energy to meet the energy needs of a healthy adult for at least 2 months.[1,2]

In addition, it is vascularized tissue whose function is to provide support for organs, energy regulation and physiological processes, such as maintaining body temperature, angiogenesis, adipogenesis and restructuring of the extracellular matrix.[1,2] Cells constitute 30% of the volume of tissue, due to their size, and the other 70% are represented by endothelial cells of blood capillaries, fibroblasts, among other cells.[1] There are 3 types of adipose tissue: yellow, brown, and beige.[2]

Yellow adipose tissue

Yellow adipose tissue (AAT) or unilocular adipose tissue is composed of unilocular adipocytes, which are responsible for accumulating TAGs in the form of lipid droplets and have little mitochondrial content.[4] Histologically, the single lipid drop fills almost the entire cytoplasm, as they are large and lack of membrane, displacing the flattened nucleus to the periphery of the cell.[2] When organic solvents are used during the preparation of the slides of the histological sections, they remove the contents of the droplet; for this reason, the adipocyte alone shows under the optical microscope only a thin layer of cytoplasm in the periphery of the cell around the space left by the removed lipid droplet.[2]

TAA corresponds to most adipose tissue in adult humans and its name corresponds to its color, which can vary between white and dark yellow depending on the diet ingested, and the yellowish color comes mainly from carotenes dissolved in the fat droplet that is vascularized in smaller quantities compared to brown adipose tissue (TAM).[1,2]

Its performance is related to energy storage and maintenance, it also promotes thermal insulation in the skin and subcutaneous tissue, as fat is not a good conductor of heat.[2] In addition, the TAA is responsible for absorbing mechanical shocks, keeping some organs in their proper positions, and filling spaces between tissues.[2] TAA is also an endocrine gland, in which it releases its contents directly into the bloodstream, which synthesizes molecules such as adiponectin, resistin and leptin, a protein hormone that acts mainly in the hypothalamus, reducing food intake and increasing energy expenditure.[2]

Brown adipose tissue

Brown adipose tissue (TAM) or multilocular tissue is composed of several lipid droplets in smaller size in its cytoplasm, which is why it is also called TAM.[4] Its characteristic color is the result of the large amount of cytochromes present in the mitochondria of its cells and its abundant vascularization by blood capillaries.[2] It exists in small quantities and with limited location in the body, being in the human species more abundant in newborns than in adults, due to the deficient thermoregulation of newborns, it collaborates to maintain body temperature.[2]

TAM is primarily thermogenic, playing an important role in thermoregulation, in which its adipocytes use energy contained in TAGs to release heat.[2] They do this through a protein called thermogenin or UCP1 (uncoupling protein 1), which uncouples oxidative phosphorylation and ATP synthesis, so that the energy generated by the flow of protons in the mitochondria is dissipated as heat.[2] This heat emitted warms the blood that is distributed throughout the body, warming it.[2]

Beige adipose tissue

Beige adipose tissue (BAD) is made up of unilocular adipocytes of yellow adipose tissue (TAM) and multilocular adipose adipocytes of brown adipose

tissue (TAM); however, it is still doubtful whether it is a third type of adipose tissue. It is commonly located in the subcutaneous tissue, but its adipocytes seem to originate from different precursors of the other 2 types of tissue.[2] Its multilocular adipocytes are thermogenic, featuring uncoupling protein 1 (UCP 1), just as TAM in your mitochondria results in the release of heat to your blood capillaries.[2]

The origin of its cells are from mesenchymal cells.[2] However, there are disagreements about the precursors of BAD, and some authors suggest that it is likely that transformation of yellow adipocytes into beige adipocytes is likely.[2] Beige have several lipid droplets and are thermogenic and, like TAM, have UCP1, better known as thermogenic, effectively functioning as heat generators.[5]

Its adipogenesis

Boychenko et al.[6] point out that beige adipose tissue is influenced in transcription by industrial chemicals (pollutants), environmental disruptors and other substances from the external environment, as well as the activity of phytochemical dietary molecules, impact the transdifferentiation process connected in transcription elements. In addition, "small molecule compounds" such as fibroblasts, endothelial cells, and myoblasts function as inducers of TAA adipocytes in beige adipocytes, as well as endocrine regulation that influences the adipogenesis process, but which is more sensitive to xenobiotics.[6]

Its therapeutic potential in obesity and metabolic diseases

Activating or increasing the amount of beige adipose tissue in an individual can improve glucose, cholesterol, triglyceride levels, inflammation, weight gain and loss, insulin sensitivity, and glucose tolerance.[7] This theory was justified by Gonzalez et al.[7] which showed that microvascular fragments from humans have potential use to generate adipose microtissues that resemble the genetic and functional characteristics of BAD; as a result, the transplantation of this tissue showed improvements in glucose metabolism and insulin sensitivity, as well as reductions in body mass and decreased adiposity. It was noted that the metabolic function of beige adipose tissues was essential to obtain potential therapeutic results in the treatment of diabetes and obesity. Therefore, this physiological impact indicates that beige adipose tissues are a therapeutic option with potential application on the treatment of obesity and metabolic diseases, although the understanding of the development of beige adipose tissue in humans is still limited.[7]

Hormone production

Adipose tissue is considered the largest endocrine gland in the body because it maintains metabolic balance, through the hormonal secretions of adipocytokines (interleukin 6, angiotensinogen, adipokines, leptin, adiponectin), peptides and bioactive proteins.[2]

Leptin and adiponectin are the main hormones secreted by this tissue.[8] The first is secreted according to the size of adipocytes and the amount of adipose tissue.[8] It acts on the central nervous system by reducing food intake, increasing energy expenditure, in addition to interfering with other tissues such as skeletal muscle, liver and pancreas.[8,9] There is also the hormone ghrelin, secreted by the stomach and stimulated during fasting, which, together with leptin, is associated with body weight, sympathetic nervous system tone, and neuroendocrine responses to coordinate homeostasis.[10]

Adipocytokine influences metabolism by promoting fatty acid oxidation and reducing lipogenesis, in addition to decreasing abnormal fat deposition in the liver and muscle.[8] It also stimulates glucose uptake by the muscle and increases fatty acid oxidation in both the muscle and liver, which causes greater insulin sensitivity.[8] The practice of physical exercise increases the production of this hormone, promoting the regulation of its receptors in skeletal muscle.[8]

This endocrine function of the tissue varies according to its location, since subcutaneous adipocytes have little capacity to produce adipokines; adipocytes that are located around the viscera secrete adipokines in large quantities.[2]

Histogenesis

Fat cells are derived from undifferentiated mesenchymal cells. For the formation of adipose tissue-forming adipocytes, mesenchymal cells undergo a reduction in their cytoplasmic prolongations, thus beginning to store lipid drops within the cytoplasm, forming lipoblasts or pre-adipocytes, young cells, which when they mature form adipocytes.[11] During the formation of TAA adipocytes, lipid droplets are initially small and isolated.[11] Subsequently, they come together to form a single droplet – characterizing the unilocular fat cell.[1,12] In the multilocular adipocytes of the TAM, their lipid droplets remain separate and, in addition to the different morphology, they are differentiated by receiving stimuli that also differentiate their functions.[11]

Much is discussed about the precursors of beige adipose tissue (BAD) and research shows that it is possible to transform white adipocytes into beige, which is made up of the combination of unilocular adipocytes from TAA and multilocular adipocytes from TAM – hence the name TAB.[1] It is noteworthy that this tissue is located mainly in the subcutaneous tissue and it is presumed that its multilocular cells originate from precursors distinct from TAA and TAM.[1]

Research shows that the beige cell is a type of cold-inducible adipocyte, rich in mitochondria and appears in TAA. TAM activity is significantly related to cold defiance, body mass index, and age, which are actually beige adipocytes.[3] During the beige to yellow transition, mitochondria are degraded in adipose tissue by the activation of autophagy.[3]

Relationship of beige adipose tissue with physical exercise

Physical activity has many beneficial effects on people's health, such as preventing or delaying the onset

of type 2 diabetes, obesity and metabolic diseases.[13,14] Several studies suggest that both physical exercise and exposure to specific environments can stimulate beige tissue in yellow adipose tissue (BAT), due to the ability of beige cells to discard excess caloric intake in heat, this effect can be beneficial against obesity and metabolic syndrome, in addition to being stimulated by physical exercise.[15] Beige adipocytes are seen interspersed in the TAA, especially in the subcutaneous part of it, and have a morphology similar to brown adipocytes.[14,16] In addition, beiges express the distinct cell surface markers Tmem26 and Cd137, which when stimulated show increased capacity for fuel oxidation and thermogenesis.[14,16,17] Recently, studies have begun to analyze the adaptations introduced by physical exercise in adipose tissue.[14]

Physical exercise can induce the development of beige adipose tissue (BAD) in the TAA, increasing mitochondrial biosynthesis, which contributes to the improvement of oxidative and thermogenic capacity.[18,19] Irisin, a peptide hormone, stimulates this transformation. First, it is secreted by skeletal muscle and adipocytes, and activated due to the exercise of coactivator-1α (PGC-1α), in which it promotes the secretion of the fibronectin type 3 containing 5 (FNDC5) domain into skeletal muscle; then it is cleaved and then mature irisin is produced.[19]

After the end of exercise, TAB can maintain the metabolization of fuels, thus contributing to increased energy expenditure.[5] Studies in mice have shown that irisin at high levels after exercise induces UCP1 mRNA, thereby promoting the darkening of yellow adipose tissue.[19.20]

Adaptive thermogenesis, a process in which the body regulates heat production in response to changes such as temperature and caloric intake, is primarily mediated by UCP1.[15] TAM is the only one that contains UCP1 under normal conditions, allowing energy to be dissipated as heat instead of being stored as ATP.[15] Several modalities and durations of exercise (voluntary running in a wheel, forced running on a treadmill and swimming) were investigated in a study with rodents, in which they identified a significant increase in subcutaneous TAA at baseline, measured by the increase in brown and beige adipocyte markers (UCP1, Prdm16, Cidea, Elovl3, Dio2, Ppary, Pgc1α Cox8b and otopetrin), in addition to the increase in immunofluorescence of UCP1 and the presence of multilocular cells.[18,20-22] These studies indicate that the duration of exercise influences the change in UCP1 expression.[14]

AAT is induced to transform into BAD through the practice of exercises, a process that involves the mechanism of Crosstalk – mechanism that controls the contractile apparatus, blood pressure and circulating volume – between skeletal muscle and adipose tissue.[18] Therefore, regular physical activity increases mitochondrial biosynthesis, which contributes to the improvement of oxidative capacity and the increase in the number of beige adipocytes in the TAA, and also, these cells have the ability to discard excess caloric intake in heat; This effect may be beneficial against obesity and metabolic syndrome.[18,19] TAB also has UCP1 and can mimic the metabolic function of TAM when stimulated.[15] It is reported that the hormone irisin, myokine stimulated by physical exercise, acts by transforming yellow adipose tissue into beige.[15]

Beige and brown adipose tissues and their relationship to oxidative metabolism

Exercise increases the production of reactive oxygen species (ROS). While acute exercise causes increased oxidative stress in skeletal muscles, chronic exercise tends to decrease this stress.[18] Reactive oxygen species increase in obese and aging individuals. Excessive levels of ROS lead to inadequate oxidative defense, causing oxidative stress, which is related to diseases such as obesity, diabetes, cardiovascular and neurodegenerative.[18]

Free radicals, including ROS, are the main causes of aging and are produced primarily by mitochondria. However, physical exercise increases the production of beige adipose tissue (TAB) and improves the function of brown adipose tissue, which can protect the body from oxidative stress.[18] Exercise induces the appearance of BAD in yellow adipose tissue (AAT), mediated by myokines, proteins secreted by contracted muscles that transmit information from skeletal muscle.[18]

According to studies, TAA transplantation submitted to physical exercise in sedentary mice resulted in improved glucose uptake in skeletal muscles and in the metabolism of the body as a whole. This is likely due to the altered profile of adipokines – including adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha, among others – in white adipose tissue after exercise.[23] It is also reported that the expression of adiponectin receptors in white adipose tissue increases significantly in humans after 4 to 12 weeks of exercise training, as does the expression of UCP1.[23]

Other exercise-induced myokines, such as fibroblast growth factor 21 (FGF21), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), adiponectin, leptin, β-aminoisobutyric acid, follistatin, meteorin-like, interleukin-6, lactate, and succinate, have a stimulating effect on thermogenic gene expression in TAA cells, inducing the onset of BAD or promoting brown adipose tissue (TAM) function.[18] Myokines, therefore, can play a central role as mediators of the effects of physical exercise on thermogenic adipose tissues.[18]

Uncoupling in mitochondrial respiration protects against oxidative stress, as UCPs (uncoupling proteins) are involved in controlling the production of reactive oxygen species (ROS) in mitochondria.[18] Thus, it can be stated that adipose tissues adapt to physical exercise in many ways, such as releasing adipokines, producing beige fat, promoting brown fat function and, depending on the intensity and duration of exercise, increasing ROS.[18] The antioxidant effect of physical exercise is due to antioxidant enzymes that are induced by post-workout oxidative stress.[18]

CONCLUSION

Adipose tissue plays important roles in human physiology, being essential for energy regulation and thermogenesis. Yellow adipose tissue is responsible for energy storage and thermal insulation, but it also acts in the regulation of metabolism. On the other hand, brown adipose tissue is essential in thermogenesis, especially in newborns, and in the maintenance of body temperature. In addition, beige adipose tissue has intermediate characteristics between the 2 previous tissues, highlighting its therapeutic potential in obesity and metabolic diseases. In addition, the practice of regular exercise has a great impact on the modulation of adipose tissue, promoting the conversion of yellow adipose tissue into beige. Physical exercise increases the production of myokines, which induce the formation of beige adipose tissue, contributing to the improvement of metabolic health and protection against diseases associated with oxidative stress. Thus, understanding the characteristics and functions of adipose tissues, as well as the mechanisms of regulation, is essential for the development of effective therapeutic strategies for the treatment of obesity and other metabolic diseases.

Authors' contributions:
Aglatha Maalli Santana – Conceptualization
Alana Caroline Carvalho Chagas – Research
Laura de Andrade Mazia – Methodology
Luana de Almeida Chagas da Silva – Formal analysis
Rebeca Medeiros da Silva – Writing – Conceptualization
Irlena Monica Wisniewska de Moura – Supervision, project administration

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Pathophysiology of anxiety related to nicotine use

Fisiopatologia da ansiedade relacionada ao uso de nicotina

Izabela Bereza Cray da Costa[1], Luana Mattos Vasconcellos[1], Mariana Latronico Baena[1], Pietra Delgado Piluski[1], Jaciele Defavari[1], Irlena Wisniewska de Moura[1]

ABSTRACT

Introduction: Although the rate of tobacco use has decreased in recent years, tobacco-related diseases remain the leading cause of preventable death. Smoking can worsen or trigger symptoms of anxiety during withdrawal. Nicotine dependence is highly comorbid with neuropsychiatric and mood disorders.

Objective: To report the effects of nicotine on the central nervous system, its relationship with anxiety, and confrontation methods. Method: A narrative review of nicotine and anxiety was conducted in the PubMed, Google Scholar, Scielo, and Capes Periódicos databases, using the descriptors "anxiety due to lack of nicotine," "nicotine," and "anxiety." Twenty-two articles published between 2000 and 2024 were included.

Result: Nicotine binds to nicotinic acetylcholine receptors, releasing dopamine and causing dependence. Furthermore, prolonged exposure dysregulates the hypothalamic-pituitary-adrenal system, resulting in cortisol hypersecretion and altered stress response. With continued use, neuronal changes can occur that make nicotine anxiogenic, due to the wide range of nicotinic receptors and their varying sensitivities.

Conclusion: Treatment should include both an approach to nicotine dependence and management of anxiety symptoms. Nicotine modulates neurotransmitters essential for mood and anxiety, and withdrawal makes users dependent.

KEYWORDS: Nicotine. Anxiety. Tobacco. Addiction.

RESUMO

Introdução: Embora a taxa de usuários de tabaco tenha reduzido nos últimos anos, as doenças relacionadas ao seu uso ainda são a principal causa de morte evitável. O tabagismo pode agravar ou desencadear sintomas de ansiedade na abstinência. Sua dependência apresenta alta comorbidade com distúrbios neuropsiquiátricos e transtornos de humor.

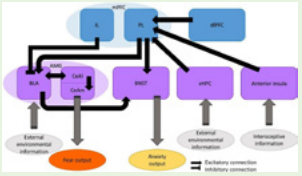
Objetivo: Relatar os efeitos da nicotina no sistema nervoso central, sua relação com a ansiedade e métodos de enfrentamento.

Método: Realizou-se revisão narrativa sobre a nicotina e a ansiedade nas bases PubMed, Google Acadêmico, Scielo e Capes Periódicos, usando os descritores "anxiety due to lack of nicotine", "nicotine" e "anxiety". Foram incluídos 19 artigos publicados entre 2000 e 2024.

Resultado: A nicotina liga-se a receptores nicotínicos de acetilcolina, liberando dopamina e causando dependência. Além disso, a exposição prolongada desregula o sistema hipotálamo-hipófise-adrenal, resultando em hipersecreção de cortisol e alteração na resposta ao estresse. Com a manutenção do uso, podem ocorrer mudanças neuronais que tornam a nicotina ansiogênica. devido à grande gama de receptores nicotínicos e suas diferentes sensibilidades.

Conclusão: O tratamento deve incluir tanto a abordagem para a dependência de nicotina quanto a gestão dos sintomas de ansiedade. A nicotina modula neurotransmissores essenciais para o humor e ansiedade e sua abstinência, torna os usuários dependentes.

PALAVRAS-CHAVE: Nicotina. Ansiedade. Tabaco. Vício.



Anxiety circuit diagram

Central Message

Nicotine directly affects the central nervous system by modulating neurotransmitters involved in anxiety and mood. Although the substance can provide momentary relief from anxiety, its use and especially abstinence favors the appearance of anxious symptoms, making smoking cessation even more difficult. Therefore, smoking cessation treatment should address both chemical dependence and associated neuropsychiatric disorders, combining pharmacological and behavioral therapies to increase the chances of success in quitting tobacco use and minimize mental health impacts.

Perspective

Considering not only chemical dependence, but also the impacts of nicotine on neuropsychiatric disorders such as anxiety, is very relevant for clinical practice aimed at the treatment of smoking. Understanding the neurobiological mechanisms involved can aid in the development of more effective strategies, such as the use of specific pharmacological therapies and targeted behavioral interventions. Thus, integrating anxiety management into smoking cessation treatment can enhance therapeutic results.

[1]Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

While global tobacco addiction rates have steadily declined in recent years with the fall from 1.362 billion people using one or more tobacco products in 2020 to 1.245 billion in 20241, tobacco-related diseases remain the leading global cause of preventable mortality. According to the WHO, smoking is responsible for 63% of deaths related to chronic non-communicable diseases, 85% of deaths from chronic lung disease, 30% of deaths from various types of cancer (lung, mouth, larynx, pharynx, esophagus and others), 25% of deaths from coronary heart disease and 25% of deaths from cerebrovascular diseases.[2] And in addition to the well-known physical diseases caused by the habit of smoking, such as cardiovascular and pulmonary problems, smoking can also cause mental disorders, such as anxiety.[3]

Nicotine, the main substance present in tobacco that causes dependence, is a psychostimulant that, from the first puff, reaches the central nervous system, acting on the reward system, causing the release of the neurotransmitter dopamine, generating a sensation of momentary pleasure that has little durability, causing the individual to repeat the act of smoking and then enter the addiction.[4] Furthermore, it is well established that nicotine can modulate several neurotransmitter systems involved in the regulation of mood and anxiety, including dopamine, GABA, glutamate, serotonin (5-HT), and acetylcholine. And, also, nicotine dependence shows exceptionally high comorbidity with variety of neuropsychiatric disorders, including schizophrenia, mood and anxiety disorders.[5]

Anxiety disorder is related to the neurophysiological mechanisms of nicotine in active smokers, but anxiety is also one of the main symptoms of withdrawal syndrome, which occurs in those smokers who are trying to quit smoking.[6]

Despite the decrease in the number of smokers in the world population, smoking cessation treatment has not achieved the desired therapeutic success rates. In this context, there are smokers with a greater degree of difficulty in quitting the habit and others with a lower degree. Many of them quit smoking spontaneously, while others are unable to quit even with the use of medication. The latter are generally the most dependent, have a higher smoking history and have several failed attempts to quit.[7]

The objective of this review was to report the effects of nicotine on the central nervous system and its relationship with neuropsychiatric disorders, with emphasis on anxiety, seeking to understand the neurobiological mechanisms involved in nicotine dependence, the impacts of the substance during its use and abstinence, in addition to discussing therapeutic approaches to minimize anxiety symptoms and optimize smoking cessation treatment.

METHOD

Narrative review carried out from the search for information contained in selected and credited scientific articles. The search was initiated in the Pubmed, Scielo, Google Scholar and Capes Periódicos databases, through descriptors related to the theme, which were identified through DeCS using the following terms: "Anxiety", "Nicotine", "Withdrawal", "Addiction", "Central Nervous System" with AND or OR search, considering title and/or abstract. A total of 31 articles were found and read in full, of which 19 were published in the last 20 years (2004/2024), in English and Portuguese, which were more related to the theme and the proposed objective.

DISCUSSION

Nicotine and its effect on the body

Nicotine is part of the organic group of closed-chain amines, and for this reason it is liquid at room temperature. It can be acidic or alkaline. The first cannot penetrate the mucous membranes of the mouth, reaching the alveoli, where it becomes alkaline and is diffused in the blood by the action of the lungs. The second is easily absorbed in the oral mucous membranes, diffusing directly into the blood.

This substance is a psychoactive agent found in some plants, such as tobacco leaves, and in some fungi. It is known to have a bitter taste and high toxicity, in addition to inducing neoangiogenesis, responsible for cell proliferation.[8]

In the form of cigarettes, nicotine is the biggest cause of dependence on smokers, because, when burned, it reaches the brain in about 9 seconds, binding to nicotinic acetylcholine receptors, which facilitate the release of neurotransmitters, such as dopamine, acting on the feeling of well-being and acting as a physiological stimulant (increases blood pressure and respiratory and heart rates).[8]

In addition to the action on the brain, which is permanent, this substance affects the tissues and lungs, causing yellowing of the dentition, premature aging, reduced respiratory and circulatory capacity.

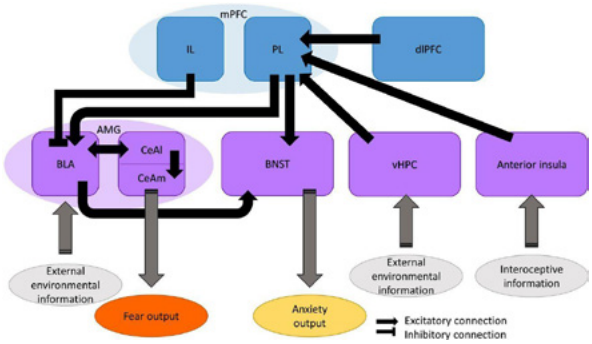
Nicotine is metabolized in the liver, by cytochrome 450, in about 15 minutes and the substance of each cigarette takes about 2 hours to decompose in the body.

Nervous system and anxiety

Anxiety is a state of apprehension about the threat of the future, more diffuse and uncertain than that of fear. However, there is a big difference between the natural feeling of anxiety, related to daily life commitments, and the disorders that affect individuals. These are characterized by the expression of symptoms in an excessive way, such as those found in generalized anxiety disorder, panic syndrome, social phobia and OCD. The most common symptoms, for example, are shortness of breath, sweating, tremors, and rapid heart rate.

The neural circuit of anxiety works from the arrival of external environmental information to the ventral hippocampus (vHPC) and interoceptive information to the anterior insula of the brain. Subsequently, these

two areas of the brain, together with the dorsolateral prefrontal cortex (dlPFC), transmit signals to the medial prefrontal cortex (mPFC), more precisely to the infralimbic (IL) and paralimbic (PL) cortexes, and will be routed to the 2 nuclei of the cerebral amygdala (AMG and BLA) and to the nucleus of the stria terminalis bed (BNST), conditioning the sensation of anxiety9 (Figure).



Source: Robinson et al.9

FIGURE — Anxiety circuit diagram

Anxiety caused during nicotine use

In many cases of nicotine dependence, it is possible to identify an association between smoking and symptoms of anxiety or panic attacks. Such conditions may predispose individuals to smoke cigarettes, when the diagnosis occurs prior to smoking, or they may be potentiated by nicotine withdrawal syndrome. However, anxiety symptoms often reach their peak during nicotine use.[10]

Smoking has adrenergic effects and consequently pulse rate, blood pressure and lactate and pyruvate levels increase. Nicotine crosses the blood-brain barrier and activates several pathways of the central nervous system, leading to the release of norepinephrine, acetylcholine, dopamine, and serotonin, effects that may be related to the development of anxiety. The presence of anxiety may alter the pharmacokinetics of nicotine and contribute to even more severe manifestations of panic syndromes.[10,11]

Prolonged exposure to nicotine dysregulates the hypothalamus-adrenal pituitary system, leading to cortisol hypersecretion and changes in the activity of the associated monoamine neurotransmitter system, whose function is to regulate stressful reactions, generating a predisposition to anxiety. The medial habenula, an interpeduncular nucleus (a circuit composed of neurons that project to the midbrain) has a high density of nicotinic acetylcholine receptors, which controls acute nicotine responses. Recent studies affirm a relationship between this circuit and symptoms of anxiety and fear. Levels of dependence are significantly correlated with anxious symptoms, i.e., the greater the smoking dependence, the higher the levels of anxiety.[4-12]

Nicotine withdrawal syndrome

Nicotine withdrawal syndrome is a preponderant factor for the maintenance of smoking habits in young people and adults. This condition generates a series of symptoms due to the abrupt withdrawal of the drug nicotine present in cigarettes, vapes, hookahs and several other vectors. This condition has physical and mental effects on its symptoms, with regard to the physiological effects, it is possible to mention bradycardia, gastrointestinal discomfort and increased appetite. In the psychological aspect, the consequences can be depressed mood, anxiety, irritability, dysphoria and concentration difficulties.[13]

Anxiety caused by nicotine withdrawal

Nicotine withdrawal may be accompanied by an increase in anxiety, a factor that makes it difficult to stop smoking habits. Animal and clinical studies create hypotheses about the pathophysiology of correlation of this disease with the lack of this drug, the action of GABAb1 receptors, the use of nicotine for self-medication of pre-existing anxiety and the action of nicotinic receptors are some of them.[14-17]

Nicotine as self-medication for pre-existing anxiety

There is a wide range of patients who use tobacco in this way. Nicotine, as an escape valve for existing anxiety, would bring a feeling of calm, reducing the symptoms of the disease. Data show that the smoking rate in the American population increased from 22% to 54.6% comparing those not affected and those affected by anxiety disorder. However, with the maintenance of smoking habits, making it chronic, there may be changes in the neuronal mechanisms that transform the hitherto anxiolytic drug into anxiogenic one within the body, which is due to the wide range of nicotinic receptors and their great expression, since some neurotransmitters released by them are more sensitive to nicotine withdrawal than others. In this way, the drug would initially combat those symptoms and start to increase them in moments of abstinence. In addition, patients with psychological disorders already present are more likely to have withdrawal symptoms, which makes the cessation process more complex, leading many patients to even give up. Making the comparison between healthy people and those with anxiety disorders, the propensity rate to quit smoking drops by almost half, from 42.5% to 23.2/32%. Some studies also show that withdrawal symptoms, especially psychological, are greater in patients with these disorders when pre-existing; however, the physiological relationship is not clearly described in the literature.[5-17]

Action of nicotinic receptors on anxiety during withdrawal

Nicotinic acetylcholine receptors play a certain role in the response to stress, anxiety and depression, with the use of nicotine these responses can be exacerbated, causing cases of anxiety disorder. Nicotinic receptors are formed by subunits , being the most affected by nicotine 4 and 2. This drug will encourage the release of several neurotransmitters such as dopamine, GABA, glutamate, acetylcholine,

norepinephrine and serotonin. However, this action depends on which nicotinic receptor is being activated, since they can be stimulators, modulators, and inhibitors, causing the different effects of nicotine on the nervous system. It is possible that nicotine does not have an anxiolytic role in itself, it only generates relief for the anxiety caused by withdrawal, which would justify the paradox that exists in the action of the drug, since in the physiological action the cigarette would have a sympathetic excitement effect and in the physiological part the users would be more relaxed and calm. Thus, if the emotional part is justified by the relief of the withdrawal situation, the physiology of cigarettes would make sense. However, this would be a reason for anxiety to increase for a period of time with smoking cessation due to the expectation of relief from the feeling of abstinence. 17

Ways to reverse or alleviate anxiety symptoms and forms of treatment for nicotine-dependent patients

After the smoking cessation process, many individuals find it difficult to reverse the symptoms of anxiety arising from nicotine addiction. Therefore, it is important that they are aware of some ways to alleviate such anxious symptoms and some forms of treatment for nicotine dependence.[10]

Sudden cessation of smoking in patients with anxiety may exacerbate symptoms of panic attacks or generate withdrawal symptoms, similar to panic attacks. It is possible that pharmacological treatment of this disorder decreases nicotine withdrawal symptoms in smokers. Therefore, in addition to nicotine withdrawal treatments, it is necessary to control anxiety symptoms. The probable mechanism that associates smoking with anxiety is noradrenergic. Clonidine, an a-adrenergic agonist with some anti-panic properties, may improve tobacco withdrawal symptoms. In addition, pharmacological interventions are necessary when symptoms are severe and disabling. Selective serotonin reuptake inhibitors can be effective for relieving anxiety symptoms and are considered the medication of choice due to their side effect profile, greater safety, easy administration, and when there is comorbidity with mood disorder.[10-18]

Regarding the treatment of nicotine addiction, dialogue with the patient is the first step towards quitting smoking. It should be evaluated whether or not the patient is dependent on nicotine, how much he smokes, if he is willing to quit smoking, if he has associated diseases and what are the forms of treatment most accessible to him. Then, it proceeds to pharmacotherapy, which is indicated for nicotine-dependent people. It is divided into first-line drugs (bupropion and nicotine replacement therapy) and second-line drugs (clonidine and nortriptyline). Another form of treatment involves alternative methods such as acupuncture, cognitive behavioral therapy, and self-help groups.[19]

CONCLUSION

The literature review showed that nicotine exerts profound effects on the central nervous system, modulating neurotransmitters critical for mood and anxiety, such as GABA. Not only does this substance have addictive effects, that make tobacco addictive, but it is also associated with increased anxiety symptoms, both during continuous use and withdrawal, due to the paradox that exists in its physiology. These findings reinforce the need for integrated therapeutic approaches that simultaneously treat nicotine dependence and anxiety disorders, using both pharmacological interventions and alternative therapies, to increase the chances of smoking cessation and promote sustainable recovery.

Authors' contributions

Izabela Bereza Cray da Costa - Conceptualization
Luana Mattos Vasconcellos - Formal analysis
Mariana Latronico Baena - Methodology
Pietra Delgado Piluski - Writing (original draft)
Jaciele Defavari - Writing (proofreading and editing)
Irlena Wisniewska de Moura - Supervision

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Can premature aging be related to Williams Syndrome?

Envelhecimento precoce pode estar relacionado com a Síndrome de Williams?

Fernanda Ritt de Souza[1], Maria Eduarda Hammerschmidt[1], Gabriela van Erven[1], Julia Daniela de Sá[1], Evelyn Mazur[1], Liya Regina Mikami[1]

ABSTRACT

Introduction: Williams syndrome (WS) is a rare, autosomal dominant genetic condition caused by a heterozygous microdeletion in 7q11.23. It presents diverse clinical manifestations, including multisystemic premature aging symptoms, such as the early development of diseases typically associated with older age. The haploinsufficiency of the ELN gene, oxidative stress triggered by the overexpression of the NCF1 gene, and mitochondrial dysfunction are identified as key factors contributing to aging-related manifestations.

Objective: To analyze the clinical and biological aspects of Williams syndrome related to premature aging, aiming to understand its causes and mechanisms of action.

Method: This study is a narrative review, including 25 articles obtained from databases such as Scielo, PubMed, ProQuest, and Google Scholar. Studies published between 1996 and 2024 in Portuguese and English were included, using the descriptors "Williams syndrome," "aging," "NCF1," and "ELN."

Result: ELN gene haploinsufficiency, high angiotensin II levels, NCF1 gene overexpression, and alterations in mitochondrial cellular respiration in individuals with Williams syndrome lead to oxidative stress and, consequently, premature aging. Individuals with the syndrome may experience hearing loss, early puberty, early-onset cataracts, and impaired cognitive development, often manifesting attention deficit disorder and anxiety.

Conclusion: Premature aging in Williams syndrome involves multisystemic manifestations associated with the ELN gene haploinsufficiency and the NCF1 gene overexpression, which promote oxidative stress and cellular dysfunction.

KEYWORDS: Williams syndrome. Aging. Elastin.

RESUMO

Introdução: A síndrome de Williams (SW) é condição genética rara, autossômica dominante causada por uma microdeleção heterozigótica em 7q11.23. Apresenta manifestações clínicas diversas, incluindo sintomas de envelhecimento precoce multissistêmicos, como o desenvolvimento precoce de doenças de idades mais avançadas. A haploinsuficiência do gene ELN, o estresse oxidativo, desencadeado pela superexpressão do gene NCF1 e disfunção mitocondrial, são apontados como responsáveis por manifestações ligadas ao envelhecimento.

Objetivo: Analisar aspectos clínicos e biológicos da síndrome de Williams relacionados ao envelhecimento precoce, buscando entender suas causas e mecanismos de ação.

Método: Trata-se de revisão narrativa, sendo utilizados 25 artigos obtidos nas bases de dados Scielo, PubMed, ProQuest e Google Acadêmico. Foram incluídos estudos publicados entre 1996 e 2024, nos idiomas português e inglês, utilizando os descritores "síndrome de Williams", "envelhecimento", "NCF1" e "ELN".

Resultado: Haploinsuficiência do gene ELN, aumento da angiotensina II, superexpressão do gene NCF1 e alterações na respiração celular mitocondrial nos portadores da síndrome de Williams geram estresse oxidativo, e consequentemente, envelhecimento precoce nos afetados. Os portadores da síndrome podem apresentar perda auditiva, puberdade e catarata precoces e desenvolvimento cognitivo prejudicado, manifestando transtorno de déficit de atenção e ansiedade.

Conclusão: O envelhecimento precoce na síndrome de Williams envolve manifestações multissistêmicas associadas à haploinsuficiência do gene ELN e à superexpressão do gene NCF1, que promovem estresse oxidativo e disfunção celular.

PALAVRAS-CHAVE: Síndrome de Williams. Envelhecimento. Elastina.

Central Message

Williams-Beuren syndrome or Williams syndrome is a rare autosomal dominant, multisystemic, genetic condition caused by the heterozygous microdeletion of part of the long arm of chromosome 7, in the 7q11.23 region, involving between 21 and 28 genes. Most cases are sporadic occurring, the result of a de novo deletion. This condition has an estimated incidence of 1:7500 and 1:20000 live births, with no prevalence between sex and ethnicity or a given geographic region. This article aims to update the knowledge about the disease, emphasizing mainly the side effects on its development.

Perspective

Premature aging in Williams syndrome has complex and multisystemic manifestations, involving complex biological mechanisms of genetic and biomolecular action. The causes of this premature aging are not yet widely known, but the role of haploinsufficiency of the ELN gene and overexpression of the NCF1 gene in increasing oxidative stress and consequent reduction of tissue function and cell apoptosis is highlighted. Ongoing research is essential to better understand the underlying mechanisms of the syndrome and develop interventions that can improve the prognosis and quality of life of those affected.

[1]*Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.*

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INTRODUCTION

Williams-Beuren syndrome or Williams syndrome (WS) is a rare autosomal dominant, multisystemic, genetic condition caused by the heterozygous microdeletion of part of the long arm of chromosome 7, in the 7q11.23 region, involving between 21 and 28 genes. Most cases are sporadic occurring, the result of a de novo deletion. This condition has an estimated incidence of 1:7500 and 1:20000 live births, with no prevalence between sex and ethnicity or a given geographic region.[1,2]

Although the mechanisms of action of all the genes involved are not widely known, the main clinical manifestations of those affected are linked to the haploinsufficiency of the genes ELN, GTF2I, BAZ1B, LIMK1. Because it affects several genes, the syndrome triggers clinical manifestations in almost all systems of the body. These complications vary from one affected to another and can also appear or disappear over time.[3]

The main complications occur in the endocrine, cardiac, and central nervous systems; however, there are also gastrointestinal, musculoskeletal, and other body system manifestations. Those affected usually have moderate cognitive deficit, anxiety disorders and hypersociability, which characterizes the neurological profile of the syndrome. Other commonly found features are craniofacial dysmorphology (wide forehead, periorbital fullness, large lips and wide mouth, and dental problems (microdontia and missing teeth, enamel hypoplasia, dental malocclusion), which triggers a typical facial phenotype of WS.[3-5]

Its diagnosis is usually given at birth or in early childhood by the perception of signs and/or symptoms suggestive of the condition in these 2 age groups, especially facial dysmorphism. However, there is no specific neonatal screening. Although the characteristic facial phenotype facilitates diagnosis in childhood, there are no significant studies on symptoms and complications of the syndrome in adulthood, since this information was unknown not long ago, as many affected did not reach adulthood. With the improvement in treatment and development of new drugs, the life expectancy of patients has become very similar to that of unaffected individuals.[4]

With increasing age, multisystem signs of premature aging began to be observed in patients along with early manifestations in adolescence and early adulthood with diseases characteristic of advanced ages, such as cataracts, diabetes, and emphysema. Marked cognitive decline and increased impairment of the digestive, endocrine, musculoskeletal and other systems affected by the syndrome were observed, as well as sleep regulation, possibly linked to changes in the methylation patterns of certain genes.[6]

The causes of this aging are not yet widely understood, the main ones being related to the haploinsufficiency of the ELN gene and the intensification of oxidative stress in those affected. This haploinsufficiency triggers the impairment of tissues rich in elastic fibers and consequently signs of premature aging, especially in the skin and in the cardiac and pulmonary systems. Meanwhile, the increase in oxidative stress occurs due to the increase in NOX activity, due to the increase in the compound angiotensin II and the overexpression of the NCF1 gene, which suffers an increase in its copy number due to polymorphism with pseudogenes.[7]

Studies on the symptoms of Williams syndrome in adults are scarce, being more focused on the clinical signs already apparent in children in early childhood. Thus, this study aimed to review the clinical and biological aspects of Williams syndrome related to premature aging, seeking to understand its main causes.

METHOD

This is a narrative review that used original review articles, meta-analyses and case reports in Portuguese and English, applying the following descriptors: Williams syndrome, Premature aging, Genetics and their counterparts in Portuguese. Information obtained from scientific articles from the following databases was used: Scielo, PubMed, ProQuest and Google Scholar. As inclusion criteria, articles focusing on symptoms, aging, pathophysiological cause, and diagnosis, published from 1996 to 2024, totaling 25 selected studies, were used.

DISCUSSION

Williams syndrome (WS) is caused by a microdeletion in 7q11.23, mainly involving the ELN gene, which encodes tropoelastin - a precursor protein of elastin, responsible for the elasticity of tissues, considered a structural protein of elastic fibers. This molecule acts on the flexibility and resistance of organs such as the skin and joints. Thus, the loss of function of this protein causes complications, especially in tissues that have a greater amount of elastic fibers, such as the cardiovascular, pulmonary, and connective fibers in regions such as bladder diverticula and hernias. Also, a peculiar characteristic of the syndrome is the development of premature aging of the carriers, resulting both from the haploinsufficiency of the ELN gene, as well as from other biological mechanisms not yet fully understood. This aging is due to phenotypic characteristics such as aging of facial features and early reduction in tissue function.[4,8]

The recruitment of older adults with WS for research has been an arduous task, due to the relatively low incidence of the condition, in addition to the low interest of family members in letting their child participate in a study whose diagnosis, prognosis and treatment have already been carried out in childhood, as they do not have good expectations about the progression of the disease. For the researchers, studies on adult patients with WS are of great interest, since they evaluate functional and aging changes associated with age, as they present characteristics that suggest premature aging in those affected by the syndrome.[9]

In the 7q11.23 region, deleted in the WS, at least 26 genes (MLXIPL, BAZ1B, STX1A, WTSF, GTF2L, FZD9, ELN, NCF1, LIMK1, ABHD11, ABHD11-AS1, BCL7B, BUD23, CLDN3, CLDN4, CLIP2, DNAJC30, EIF4H, FKBP6, FZD9, LAT2, METTL27, MIR590, MLXIPL, NSUN5 and GTF2IRD) have already been identified; however, their individual contributions to patient phenotypes are not yet completely established.[10] So far, only the deletion of the ELN gene has its effect well clarified, and the heterozygosis of the variant in ELN is necessary, but not sufficient to cause, alone, the syndrome and all the symptoms related to premature aging. Another cause already identified, although not completely understood, is the overexpression of the NCF1 gene and its role in intensifying oxidative stress.[11]

The signs of accelerated aging in patients manifest themselves in the most diverse systems of the body. Among the main ones are: cataracts, the appearance of gray hair during adolescence, reduced high-frequency sensorineural hearing, continuous weight loss, senile emphysema, and a considerable reduction in episodic memory.[6]

Other characteristics of this aging are dementia, progressive hearing loss, and skin aging, linked to the damage caused by oxidative stress.[6] There is also the development of diverticulosis in the walls of the colon, diabetes mellitus and hypertension. With advancing age, adults are also prone to joint contractures and hyperreflexia, and often become even more unstable in performing motor tasks such as going up or down stairs.[12]

Gagliardi et al.[13] In 2007, when analyzing patients between 3 and 14 years of age, they observed that symptoms related to the cerebellar system did not show significant changes between the different age groups, and mild extrapyramidal signs tended to increase with advancing age, with an increase in dystonic and involuntary movements. The study suggested the existence of mild and complex neurological dysfunctions in all cases of patients with the syndrome in different age groups.[13]

It is common knowledge that cognitive development is impaired in WS. Concomitantly, there are deficiencies in skills related to verbal comprehension, planning, problem-solving, and spatial cognition. In addition, they may have attention deficit hyperactivity disorder (ADHD), generalized anxiety, and affective disorders.[14] Even with these deficits, the average verbal intelligence quotient of patients between 20 and 30 years of age is slightly higher than the average performance intelligence quotient. However, from the age of 40, this quotient begins to deteriorate rapidly, while the average performance intelligence ratio continues to improve until approximately 50 years of age, when it also begins to decrease.[12]

Pober and Morris[15] reported in 2007 that there was a delay in the acquisition of motor landmarks and deficits in motor coordination, with muscle tone increasing with age, and older children developing progressive joint limitation and hypertonia. These authors also reported that mild to moderate high-frequency sensorineural hearing loss is present in most individuals with WS, possibly caused by cochlear dysfunction.

Still, Bódizs at al.[16,] 2014, also reported that the prevalence of GAD (generalized anxiety disorder) in the syndrome increased significantly with age.[16] The authors, when studying older adults with WS, observed that they developed age-related declines in explicit processing and, therefore, it is important to understand the cognitive processes that come with normal aging in patients. However, more research is needed to gain a clearer picture of the robustness of implicit processes, especially in people with the syndrome and in individuals with intellectual disabilities in general.

Adult memory profiles show age-associated alterations parallel to those observed in the general population. Regarding explicit memory, adults showed a marked reduction with advancing age.[16] However, it is not yet possible to determine with certainty whether the magnitude of the observed change in the performance of adults with WS is consistent with "normal" aging or with preclinical dementia. The study by Axelsson et al.[17,] which analyzed the sleep of children with WS, indicated that those affected by the syndrome have sleep problems throughout their lives, but more present in infants and young children (6-12 years). Some of the complications that arise at younger ages (6-12 years) and persist into adulthood are: dispersion throughout the night, poor sleep quality, longer sleep time in stages 3 and 4, and nocturnal restlessness (evident by breathing patterns). In addition, many children, adolescents and young adults (17-35 years) with WS complain of sleepiness during the day, which persists throughout life. Adolescents in particular have nocturnal discomfort in the legs and younger children, when compared to typical children, have a higher incidence of episodes of dispersion and consequent nocturnal agitation, taking time to fall asleep. However, these symptoms are not as common in other age groups of affected individuals. A certain discrepancy in the phonological development scores of affected children compared to normal ones may also be linked to sleep quality.[17]

Advanced puberty is characterized by atypical neurodevelopmental processes in WS, since the delays in the age-dependent decrease in sleep depth are not in tune with the hormonal changes inherent to puberty. The origin of this abnormal pattern of development/aging of individuals with WS may arise from compensatory processes of increased wakefulness and decreased sleep efficiency. The possible neurocognitive consequences of this apparent developmental disharmony should be the focus of specific investigation in the near future. In summary, the list of bodily functions and anatomical signs that reflect mildly accelerated aging can be supplemented with premature sleep impairment, characterized by accelerated reductions in sleep efficiency.[16]

In individuals with WS, there is also manifestation of hypersensitivity and distress in response to selected sounds (called hyperacusis or phonophobia); in

addition, the voice is typically described as hoarse and/or low, another finding presumably attributed to elastin deficiency (specifically of the vocal cords, in this case).[15]

Cherniske et al.[18] In 2004, when studying 20 patients with the syndrome, between 30 and 51 years of age, they observed that all of them had visual problems, including strabismus and cataracts. Cardiovascular abnormalities were reported in 70% of individuals, with supravalvular aortic stenosis present in approximately 93%; in addition, 60% had hypertension. In addition, 50% of individuals had elevated PTH levels, but the thyroid function of 75% of patients was considered normal; 75% of the individuals had a similar pattern of high-frequency sensorineural hearing loss; 65% had moderate to severe anxiety levels and 15% had mild or subclinical anxiety.

The causes of these multisystem signs of aging are not yet widely known, but it is known that WS leads to alterations in the regulation of the oxidation-reduction state (redox) by ELN haploinsufficiency and to the overexpression of the NCF1 gene that encodes the p47phos protein, which regulates NOX family members present in the vasculature. Changes in the redox state are capable of generating oxidative stress in the cells and tissues of those affected, so that excess free radicals, without enough antioxidants, triggers inflammation, altered cell signaling, and oxidative damage.[19]

Oxidative stress, therefore, occurs in the imbalance between the anabolism of oxidative compounds and the antioxidant defense system and when there is excessive production of reactive oxygen species. This can lead to serious consequences, such as tissue necrosis and cell apoptosis, determining a greater predisposition to cellular aging, carcinogenesis, increased development of autoimmune diseases, and less muscle mass. However, the role of oxidative stress is less well known than in other genetic diseases.[19]

Micangeli et al.[19] in 2022, reported a correlation between elastin insufficiency in WS and cardiovascular and respiratory diseases. For the cardiovascular system, the greatest impact of reactive oxygen species seems to be related to the predisposition to hypertension, since elastin is a crucial component of the vascular wall, providing retreat to elastic vessels.

In WS, haploinsufficiency of the ELN gene occurs, so that a single copy of the gene cannot meet the body's need for tropoelastin. Thus, the production of elastic fibers is impaired. These allow distension to tissues that suffer repeated deformities, such as blood vessels, skin and lungs, for example. Elastin is the main component of elastic fibers; In this way, syndromes that impact the production of elastin directly affect the function of these fibers. This alteration is widely linked to heart problems, skin aging, and lung problems, since elastin is responsible for maintaining the elasticity and resistance of these tissues.[20]

Patients with WS have vascular characteristics similar to patients with supravalvular aortic stenosis (ASE), but have other phenotypes due to deletion of other genes. Patients with SW/SVAS mutations deposit less total elastin, but elastic fibers usually appear normal but less organized. 21 Regarding vascular alterations, a study carried out by Brengle et al.[22] in 2023 with mice, showed changes in the vascular structure related to haploinsufficiency of the ELN gene. There was an increase in the number of smooth muscle cells, vascular stiffness and consequent increase in blood pressure.

Hypertension is more prevalent in individuals with the syndrome compared to unaffected individuals, and its etiology is multifactorial, possibly due to elastin haploinsufficiency. Also, presumably, due to the haploinsufficiency of the ELN gene, about 50% of affected adults have chronic constipation, which generates a greater probability of developing diverticulosis before old age (about 60 years).[15] The authors also showed that elastin insufficiency leads to increased stiffness of the great arteries. Thus, the mice achieved maximum dilation at lower pressures than those that had the 2 elastin genes. The study shows that pressure changes occurred due to the elastin gene independently of increased plasma renin levels and activation of the renin-angiotensin system, despite elevated renin levels contributing to systolic and diastolic hypertension.[22]

Also, in relation to elastin deficiency, Gagliardi et al.[13] in 2007, reported accelerated aging in facial and somatic features in the patients studied, in addition to altered glucose tolerance and decreased bone mineral density, and this deficiency of elastic fibers triggers the loss of skin elasticity and the early formation of wrinkles.

In the respiratory system, individuals with WS with haploinsufficient ELN may be more predisposed to the early development of pulmonary emphysema, since elastin is a key component of elastic fibers in the lung.[6]

The NCF1 gene is also present in the deleted region in the WS. However, there is a change in its number of copies in those affected, which can have from 1 to 4 copies of this gene. This occurs because next to the deleted region, there are regions with low number of gene copies, including NCF1 and 2 of its pseudogenes - NCF1B and NCF1C - which differ from this by the absence of 2 base pairs at the beginning of exon 2. Thus, polymorphism can occur in which there is a conversion of the gene with its pseudogenes, triggering overexpression of the NCF1 gene. This genomic instability is attributed to the location of the gene and its pseudogenes and favors chromosomal rearrangements.[23,24]

NCF1 is responsible for the production of the protein p47phox, which regulates the activation of NADPH (enzyme complex involved in the creation of reactive oxygen species). Thus, while the heterozygosity of this gene leads to the reduction of this process by the significant decrease of the encoded protein, an increase in the number of copies of NCF1 is linked to the intensification of oxidative stress due to the greater production of ROS. The increase in the number of copies of the NCF1 gene generates an increase in the individual's NOX activity and an increase in the

expression of p47phox, generating overexpression of this gene.[7,23]

In addition, elastin haploinsufficiency triggers vascular stiffness and fragmentation of elastic fibers, favoring an increase in blood pressure. analysis by Kozel et al.[23] in 2015 with 103 patients with WS verified, by comparing the speed of the pulse wave in the vessels in common individuals (with diabetes, hypertension and those using anti-hypertension medications) and in individuals affected by the syndrome, an increase in vascular stiffness in those affected. Pulse wave velocity was higher in those who had 2 or more copies of the NCF1 gene when compared to those who had only 1 copy. In this way, it was possible to identify that 1 single copy of this gene confers protection against hypertension, while 2 or more favored the development of the condition. In other words, a reduced number of the NCF1 gene confers not only lower oxidative stress, but also protection against a higher risk of hypertension in WS.[23,25]

Vascular stiffness and narrowing of the vessels predispose to the elevation of angiotensin II, which acts to regulate blood pressure. The stiffness of the vessels usually occurs with aging and is greater in diabetics and hypertensives; however, in WS it is more favored and intense due to the haploinsufficiency of the gene.[23,25]

The haploinsufficiency of elastin triggers increased stiffness of the blood vessel wall, also increasing blood pressure. This triggers increased angiotensin II and NADPH activation. Oxidative stress and the response of cells to angiotensin II depends on the copy number of the NCF1 gene.[6,7,23]

On the other hand, a reduced number of copies of NCF1 is related to a lower risk of hypertension and lower oxidative stress, even with vascular stiffness caused by elastin deficiency. Thus, cell damage is decreased, but it still exists and, also, triggers the characteristics of premature aging, even if more slowly and controlled. Increased oxidative stress generates cell damage, apoptosis, and loss of cellular function, causing multisystem premature aging symptoms.[7,23]

Mitochondrial dysfunction is also observed, which also contributes to the increase in oxidative damage. Due to the haploinsufficiency of the ELN gene, the fibroblasts of affected individuals show changes in the capacity for basal respiration, so that there is a decrease in ATP production and an increase in the production of reactive oxygen species. This dysfunction may have its origin in the deletion of the DNAJC30 gene, also present in the critical deleted region and is mainly involved with lung damage, disturbances of cellular homeostasis and mitophagy associated with chronic lung disease and activation of cell necrosis and apoptosis pathways.[20]

Mitochondrial dysfunction may also be related to problems in brain development. Characteristics of the mitochondria of the patients show that the integrity of oxidative phosphorylation supercomplexes and ATP-synthase dimers are decreased in WS.[20]

CONCLUSION

Premature aging in Williams syndrome has complex and multisystemic manifestations, involving complex biological mechanisms of genetic and biomolecular action. The causes of this premature aging are not yet widely known, but the role of gene haploinsufficiency is highlighted ELN and gene overexpression NCF1 in the increase of oxidative stress and consequent reduction of tissue function and cell apoptosis. Ongoing research is essential to better understand the underlying mechanisms of the syndrome and develop interventions that can improve the prognosis and quality of life of those affected.

Authors' contributions

Fernanda Ritt de Souza: Conceptualization
Maria Eduarda Hammerschmidt: Formal analysis
Gabriela van Erven: Investigation
Liya Regina Mikami: Methodology
Julia Daniela de Sá: Project administration
Evelyn Mazur Writing: (original draft)
Liya Regina Mikami: Writing (proofreading and editing)

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Critical analysis of the calcium intake in pregnant women with high-risk pregnancy

Análise crítica da ingestão de cálcio em gestantes com gravidez de alto risco

Mariana de Souza Bissoli[1], Nathalia Arndt Costa[1], Viviane Dombroski[1], Naiara Bozza Pegoraro[1], Arthur Rodrigues Caetano de Sousa[1], Jan Pawel Andrade Pachnicki[1]

ABSTRACT

Introduction: Preeclampsia is a multifactorial syndrome of pregnancy characterized by increased blood pressure from 20 weeks of gestation, which may or may not be associated with proteinuria or target organ damage. Studies indicate that dietary calcium deficiency acts as an important contributing factor, and adequate calcium intake can reduce the incidence of preeclampsia.

Objective: To determine whether pregnant women seen in outpatient clinics consume the recommended daily amount of calcium, to determine their sociodemographic profile, and to estimate the population at risk.

Method: This observational, cross-sectional, prospective study was conducted by administering a questionnaire on the consumption of calcium-rich foods to estimate the ingested amount in pregnant women seen in an obstetrics outpatient clinic.

Result: A total of 381 pregnant women were included, with a mean age of 29.29 years, and 52 were diagnosed with preeclampsia during pregnancy. Regarding calcium intake, the average was 282.9 mg/day. The average consumption by monthly family income bracket was 219.82 mg in the lowest bracket and 301.86 mg in the highest, but there was no significant difference (p = 0.36) between the average daily calcium intake across salary brackets.

Conclusion: The pregnant women analyzed did not consume the recommended amount of calcium, demonstrating the importance of health education, especially for high-risk pregnant women, as calcium is a nutrient recognized as important in preventing preeclampsia.

KEYWORDS: High-risk pregnancy. Pre-eclampsia. Calcium deficiency.

RESUMO

Introdução: A pré-eclâmpsia é síndrome multifatorial da gravidez caracterizada por aumento da pressão arterial a partir das 20 semanas de gestação, podendo estar associada ou não à proteinúria ou lesão de órgãos-alvo. Estudos apontam que a deficiência de cálcio na dieta atua como importante fator contribuinte, e sua ingestão adequada pode reduzir a incidência de pré-eclâmpsia.

Objetivo: Verificar se gestantes atendidas ambulatorialmente ingerem a quantidade diária recomendada de cálcio, traçar seu perfil sociodemográfico e estimar a população de risco.

Método: Estudo observacional, transversal e prospectivo, realizado por meio da aplicação de questionário sobre consumo de alimentos ricos em cálcio, para estimativa da quantidade ingerida, em gestantes atendidas em ambulatório de obstetrícia.

Resultado: Foram incluídas 381 gestantes, com média de idade de 29,29 anos, e 52 foram diagnosticadas com pré-eclâmpsia durante a gravidez. Em relação à ingestão de cálcio, obteve-se média de 282,9 mg/dia. O consumo médio dele por faixa de renda familiar mensal foi de 219,82 mg na faixa mais baixa e 301,86 mg na mais alta, mas sem diferença significativa (p = 0,36) entre a ingestão média diária de cálcio entre as faixas salariais.

Conclusão: As gestantes analisadas não ingeriam a quantidade recomendada de cálcio, demonstrando a importância da educação em saúde principalmente às gestantes de alto risco, pois o cálcio é nutriente reconhecidamente importante na prevenção da pré-eclâmpsia.

PALAVRAS-CHAVE: Gravidez de alto risco. Pré-eclâmpsia. Deficiência de cálcio.

Central Message

Low calcium intake can cause arterial hypertension by stimulating PTH or renin, increasing the intracellular concentration of the mineral in muscle fibers, causing vasoconstriction. In this way, calcium supplementation alters uteroplacental blood flow, decreasing the resistance of the uterine and umbilical arteries and preventing endothelial damage common in preeclampsia

Perspective

Even though no differences were found in the amount of calcium ingested through the correlation between maternal characteristics, such as socioeconomic level and diagnosis of preeclampsia, calcium supplementation is an effective strategy to reduce its incidence and severity, and it is interesting to think about universal calcium supplementation during pregnancy, as is done with iron. The dissemination of health education to this public, especially high-risk pregnant women, will have a positive impact on what pregnant women understand about preeclampsia and on how they accept and comply with recommendations for its prevention.

[1]*Evangelical Mackenzie Faculty of Paraná, Curitiba, PR, Brazil*

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INTRODUCTION

Preeclampsia is a multifactorial syndrome, dependent on inflammatory activity, impacting several systemic components. The diagnosis, made after the 20th week of gestation in a previously normotensive pregnant woman, is made based on the association of arterial hypertension with proteinuria or target organ damage (liver dysfunction, kidney injury, pulmonary edema, among others).[1]

Low calcium intake can cause arterial hypertension by stimulating PTH or renin, increasing the intracellular concentration of the mineral in muscle fibers, causing vasoconstriction. Thus, calcium supplementation alters uteroplacental blood flow, reducing the resistance of the uterine and umbilical arteries and preventing endothelial damage common in preeclampsia (PE).[2]

Thus, it is impossible to dissociate the current scenario of Brazilian food insecurity, in which 55.2% of the population is in some degree of food insecurity - which includes everything from frank hunger to the ingestion of foods low in nutrients - with changes in human rights and high impact on maternal health.[3] The 2008/2009 Household Budget Survey (POF) provided data indicating insufficient calcium intake throughout the country, with even lower consumption by individuals with lower socioeconomic and educational levels.[4]

Thus, the lack of screening for calcium intake during pregnancy, as well as the non-establishment of calcium supplementation for pregnant women with low intake as a public policy for the prevention of PE, corroborates the maintenance of the maternal mortality rate, since PE is the second leading cause of maternal death in Brazil. affecting mainly black women aged 20-29 years, and which may have its aggravation due to inadequate intake.[5]

As a result, there is also an overload of the Unified Health System (SUS), implying greater expenses, since the treatment of this condition requires human, structural and, consequently, financial resources. As pointed out by research, calcium deficiency can generate the occurrence of [144,941] cases of PE per year in Brazil, which means an annual cost of approximately R$ 203,659,371.00.6

The objective of this study was to verify whether pregnant women treated at the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil, ingest the recommended daily amount of calcium, to trace their sociodemographic profile, and to estimate the population at risk for PE with signs of severity through a previously known protection factor.

METHOD

This is an observational, cross-sectional and prospective study, based on the application of a questionnaire on the intake of calcium-rich foods, to estimate the amount ingested, in pregnant women treated at the hospital's obstetrics outpatient clinic. The inclusion criteria were pregnant women, at any gestational age, aged 16-45 years attending the outpatient clinic. Patients under follow-up for osteoporosis or diseases that alter calcium metabolism were excluded.

The study was approved by the Research Ethics Committee of Faculdade Evangélica Mackenzie do Paraná, Curitiba PR, Brazil, included on Plataforma Brasil under number 58327622.8.0000.0103 and CAAE registered. Because it is prospective, there was a need for the Informed Consent Form (ICF) applied to pregnant women over 18 years of age and the Informed Consent Form (TALE) applied to pregnant women aged 16-17 years.

The research was carried out through a questionnaire on the daily intake of calcium-rich foods, adapted from Coutinho7, which covered the main calcium-rich foods in the diet of the Brazilian population and their amounts ingested during the day. In addition, a sociodemographic questionnaire translated and adapted from Castro and Frías8 was included, which contained full name, date of birth, marital status, education, number of living children, occupation, profession, monthly income, and residential environment. The questionnaires and the ICF/TALE were applied in person by the research participants through the Google Forms platform on the days of operation of the outpatient clinic, with an estimated time of 10 min, and the entire process took place in a private and silent environment, in order to avoid embarrassment.

In addition, the research used a nutritional table that contained the amount of calcium in each food described in the questionnaire adapted from Coutinho7 and completed by the researchers themselves after data collection at the outpatient clinic.

The amount of calcium in each food was calculated according to the data provided by the Brazilian Food Composition Table9, with the amount estimated at 100 g of each product. The following foods were evaluated in the research: whole milk 107.34 mg, skim milk 103.69 mg, semi-skimmed milk 103.69 mg, Minas cheese 1020 mg, mozzarella cheese 774.54 mg, prato cheese 802.19 mg, ricotta cheese 253.34 mg, yogurt 207.04 mg, sour cream 82.73 mg, butter 5.78 mg, sardines 198.21 mg and egg yolk 117.40 mg. The density of some foods such as semi-skimmed milk 1.027 g/mL, whole milk 1.032 g/mL, skim milk 1.035 g/mL, yogurt 1.028 g/mL, and sour cream 0.99 g/mL were also necessary, since the research quantified the intake of pregnant women in milliliters.

The authors' contacts were available at the outpatient clinic and shared in the social groups of the service members. From this, through an active and voluntary search, the participants were able to participate in the study and conduct the interview.

Statistical analysis

The collected data were studied using the ANOVA and Chi-square tests, and p-values below 0.05 were considered statistically significant.

RESULT

Of the universe of 384 responses, 381 met all the inclusion criteria and 3 met at least 1 of them. The sociodemographic profile (Table 1) indicates a mean age of 29.[29±6.41] years, and there was no significant difference when comparing the mean between those who had and did not have a diagnosis of PE, being 29.77 and 29.21 years, respectively.

Regarding self-declared color/ethnicity, 14 (3.67%) were yellow, 196 (51.44%) white, 130 (34.12%) brown, 37 (9.71%) black, and 4 (1.05%) chose not to declare. The predominant marital status was married with 205 answers (53.81%); divorced with 14 (3.67%), single 161 (42.26%) and widowed with 1 answer (0.26%). Regarding education, 19 (4.99%) had incomplete primary education, 28 (7.35%) completed primary school, 38 (9.97%) had completed high school, 189 (49.61%) had completed high school, 47 (12.34%), and 59 (15.49%) had completed higher education, and 1 (0.26%) had no schooling. Regarding the occupation retired, it was n=1 (0.26%), self-employed/liberal professional n=58 (15.22%), unemployed n=39 (10.24%), housewife n=87 (22.83%), employed with a formal contract n=152 (39.90%), employed without a formal contract n=42 (11.02%), pensioner n=2 (0.52%).

The data collected regarding the monthly family income in minimum wages indicated that 25 (6.56%) reported income below 1 (<R$1212.00), 114 (29.92%) between 1 and 1.5 (R$1212.00 - 1818.00), 207 (54.33%) between 2 and 5 (R$2424.00 - 6060.00), 32 (8.40%) between 6 and 10 (R$6060.00 - 12,120.00) and only 3 (0.79%) income above 10 minimum wages (+R$12,120.00).

In addition, the absence of live births was reported by 145 (38.06%), 125 (32.81%), 1 live birth, 74 (19.42%), 2 live births, 26 (6.82%), 3 live births, 8 (2.10%) 4 live births, 2 (0.52%) 5 live births, and 1 (0.26) reported 6 live births. Thus, the average was 1.05±1.09 live births.

Regarding the number of inhabitants per household, the study obtained an average of 3.21±1.20. The last item related to the sociodemographic aspect was related to the area of housing, with 4 (1.05%) reporting living in rural areas and 377 (98.95%) in urban areas.

Regarding the diagnosis of the disease, 52 had PE in the current pregnancy and 329 did not at the time of the interview. In addition, 58 patients (15.22%) reported a diagnosis of PE in a previous pregnancy, 320 (83.99%) denied the presence of this diagnosis, and 3 (0.79%) could not say. When comparing the groups with and without current and previous PE, it was found that 23 (6.04%) of the interviewees had been diagnosed previously and in the current pregnancy, 35 (9.19%) had a previous PE but not in the current pregnancy, 29 (7.61%) did not have PE in a previous pregnancy, but obtained the diagnosis in the current one, 291 (76.38%) had no previous or current diagnosis and 3 (0.79%) did not know if there was a previous diagnosis, but it does not have it in the current pregnancy.

TABLE 1 – Sociodemographic profile of the patients

Average age	29.29 ±6.41)	%
Color/ethnicity		
Yellow	14	3,67
White	196	51,44
Brown	130	34,12
Black	37	9,71
Not declared	4	1,05
Marital status		
Married woman	205	53,81
Divorced	14	3,67
Single	161	42,26
Widow	1	0,26
Schooling		
Incomplete elementary school	19	4,99
Complete elementary school	28	7,35
Incomplete high school	38	9,97
High School	189	49,61
Incomplete higher education	47	12,34
Complete higher education	59	15,49
No schooling	1	0,26
Occupation		
Retired	1	0,26
Self-employed/liberal professional	58	15,22
Unemployed	39	10,24
From home	87	22,83
Maid with a formal contract	152	39,90
Maid without a formal contract	42	11,02
Pensioner	2	0,52
Monthly family income		
<1 minimum wage (<R$1212.00)	25	6,56
1-1.5 minimum wages (R$1212.00 - 1818.00)	114	29,92
2-5 minimum wages (R$2424.00 - 6060.00)	207	54,33
6-10 minimum wages (R$6060.00 - 12,120.00)	32	8,40
+10 minimum wages (+R$12,120.00)	3	0,79
Average number of live births	1.05 (±1.09)	
Average number of people per household	3.21 (±1.2)	
Residence environment		
Rural	4	1,05
Urban	377	98,95

When comparing the ages of pregnant women with and without current PE, the mean age with the current diagnosis was 29.77±6.57 years, while the mean and standard deviation of those without the current diagnosis were 29.21±6.44, respectively, and there was no significant difference between the groups.

Regarding calcium intake, the average was 282.9±255.96 mg/day. When evaluating each food questioned, it was observed that the average daily intake of milk was 171.62 ml (±187), with 279 (73.22%) of the interviewees consuming whole milk, 22 (5.77%) semi-skimmed milk and 15 (3.93%) skim milk and 65 (17.06%) did not ingest any type of milk, with the average daily calcium ingested by the pregnant women in milk being 190 mg.

The daily intake of mozzarella cheese/plate obtained was 15.93 g (±22.8) and the average daily calcium was 0.12 mg (±0.18), and 136 (35.69%) did not eat this type of food. As for Minas cheese/ricotta, an average daily intake of 2.98 g (±11.72) and 0.0221 mg (±0.0871) of calcium was observed on this occasion, but only 58 (15.22%) of the interviewees consumed this type of cheese.

In addition, 161 (42.25%) patients consumed natural

yogurt, with a daily mean of 37.58 ml (±65.7) and a mean daily calcium intake of 80.[23] mg (±140.24). Only 95 (24.93%) used condensed milk, with a mean intake of 2.84 ml/day (±8.4) and the mean daily calcium intake was 9.05 mg (±26.8); 152 (39.89%) of the interviewees reported ingesting heavy cream, with an average daily consumption of 4.04 ml (±7.95) and, consequently, 3.31 mg (±6.51) calcium/day.

Regarding butter, 182 (47.76%) did not use the food, with the average daily consumption of 8.31 g (±12.13) and 0.00048 mg (±0.0007) of calcium for this food. As for sardines, 327 (85.82%) interviewees did not use it in their meals, with an average daily consumption of 5.28 g (±19.12) of the food and an average of 0.02 mg (±0.075) per day; 134 (35.17%) of the pregnant women did not consume boiled egg yolk, and the mean daily intake was 129.25 g (±2310.79) and calcium intake through yolk intake of 0.14 mg (±2.64).

TABLE 2 – Daily calcium intake

Total daily calcium intake (mg)	
Average	282,90
Median	238,58
DP	255,96
n	381,00
mg of calcium ingested by food	
Milk	
Average	190,00
Median	138,37
DP	206,29
Mozzarella cheese/plate	
Average	0,12
Median	0,03
DP	0,18
Minas cheese/ricotta	
Average	0,0221
Median	0,0000
DP	0,0871
Natural yogurt	
Average	80,23
Median	0,00
DP	140,24
Condensed milk	
Average	9,05
Median	0,00
DP	26,80
Heavy cream	
Average	3,31
Median	0,00
DP	6,51
Butter	
Average	0,0004804
Median	0,0001237
DP	0,0007011
Sardine	
Average	0,0208
Median	0,0000
DP	0,0752
Yolk	
Average	0,1479
Median	0,0057
DP	2,6442

DP=standard deviation

When comparing the average daily calcium intake between pregnant women with and without the current diagnosis of PE, no significant difference was found, being 293.9 mg (±261.8) and 281.16 mg (±255.39), respectively, as shown in Table 3A.

TABLE 3 – Comparisons of daily calcium intake between pregnant women with and without a current diagnosis of preeclampsia (A) and daily calcium intake between the monthly family income ranges (B)

A		With PE	Without PE			
	Average	293,90	281,16			
	Median	226,17	239,60			
	DP	261,80	255,39			
	n	52	329			
	p	0,36				
B	SM	<1	1 to 1.5	2 to 5	6 to 10	>10
	Average	219,82	268,19	291,13	329,64	301,86
	Median	166,45	191,62	260,09	278,60	276,80
	DP	212,19	260,11	258,46	262,94	168,61
	n	25	114	207	32	3
	p	0,36				

PE=preeclampsia; SM=minimum wage

Finally, Table 3B shows the mean calcium intake by monthly family income range, with 219.82 mg in the range below 1 minimum wage; 268.19 mg between 1 and 1.5 minimum wages; 291.13 mg between 2 and 5 minimum wages; 329.64 mg between 6 and 10 minimum wages, and 301.86 mg above 10 minimum wages. When applying the ANOVA test with the mean daily calcium intake of the first 4 salary ranges, there was no significant difference (p = 0.36).

DISCUSSION

The present study found that the mean calcium intake of the pregnant women interviewed was lower than recommended,[2] establishing an association with risk factors for preeclampsia. This research evaluated the epidemiology, the sociodemographic context of the interviewees, ethnicity, marital status, education, occupation, number of live births, in addition to the factors listed as risk for the development of PE, such as diagnosis of the disease in previous and/or current pregnancy and calcium intake profile.[10]

The literature shows that a diet with low calcium intake correlates with an increase in the incidence of PE, justifying the supplementation of this nutrient throughout prenatal care.[10] A review of 12 studies, published in Cochrane in 2010, showed that dietary calcium supplementation reduced the risk of pregnant women developing both PE and hypertension, with an even more considerable reduction when high-risk pregnant women with deficient calcium intake were observed, which was the predominant situation in the present study.[11]

Among the risk factors, advanced maternal age (over 40 years) is of considerable importance because it favors gestational complications, including PE. In this study, the mean age of the women was 29.29 years, and most of the interviewees were below the age range at risk, following a result mostly seen in other studies on the disease and reinforcing the intermediate character in terms of the importance of evidence of this risk factor.[12]

With regard to self-declared ethnicity, although the

majority considered themselves white (51.44%), the risk of black women developing hypertensive diseases during pregnancy is slightly higher.[13] In the meantime, it is necessary to point out that, although only 1% of the participants are black, this minority has greater difficulty in accessing public health in Brazil and suffers from health problems resulting from unfavorable socioeconomic conditions. In line with this aspect, a 2018 study found that black or brown women, when compared to white women, have access to fewer prenatal consultations.[14] In addition, the same study pointed out that the darker the skin color of the pregnant woman, the greater the chance of low level of education and the later the start of prenatal care, which limits the patient's understanding of the disease, compromising the prevention and treatment of PE.[14]

Regarding the marital status of the interviewees, although most declared themselves married/in a stable union, another large group declared themselves single (42.26%). The literature shows that adherence to the minimum number of prenatal consultations is higher in the group of married or legally separated women.[15] Therefore, from this, it can be inferred that single pregnant women form a vulnerable group, in many cases without the necessary emotional and financial support, making the process of pregnancy even more regretful.[16] Regarding the impact of the level of education, it is known that the low level of education is directly associated with the increase in complications during the gestational period, since pregnant women belonging to this group are less educated about the indispensability of well-done prenatal care to reduce complications in the maternal-fetal binomial.[16] Although the study was conducted in a high-risk outpatient clinic of the SUS, most of the interviewees had at least completed high school, and theoretically did not have the level of education as a limiting factor for access to information and habits necessary for a healthier pregnancy.

Still, with regard to the sociodemographic profile, the fact that approximately half of the sample is composed of employed women with or without a formal contract, brings some relief when analyzing the possibility of financial independence. However, more than 30% of the interviewees stated that the monthly family income did not exceed 1.5 minimum wages, which was insufficient to maintain a house in an urban area with about 4 residents (average profile of the interviewees) in dignified and healthy housing conditions. In the meantime, it is known that the lower the patient's purchasing power, the lower the possibility of a diet rich in essential nutrients, such as calcium-containing foods, due to the high market value.[16] A 2015 study by Borges et al.[17] indicated that, when trying to follow the diet recommended in the "Food Guide for the Brazilian Population", there would be a daily cost of R$3.47, compromising a considerable portion of the family income at the end of the month.

Thus, when imagining an unfortunate progression of this scenario in the last decade, the difficulty in maintaining an adequate diet is indisputable, in addition to all the costs in the process of living (or surviving, in some cases) on about R$2,000.00 per month - a reality of most of the sample studied. Therefore, when analyzing the foods (eggs, fish, dairy products) that have calcium in their composition and that would bring benefits to the pregnant woman in the prevention of PE, it is noted that these are in the background, being purchased only if there is a "positive balance" at the end of the month, while the priority becomes the monthly responsibilities (water, energy, rent) and industrialized foods with few nutrients, however, more accessible.[16]

Regarding the diagnosis of PE, only 13.65% of the pregnant women had already been diagnosed at the time of the interview, and it is important to highlight that the gestational age was heterogeneous and, therefore, it should be considered that some of them were still less than 20 weeks pregnant, and it is not possible to confirm the presence or absence of PE. Regarding recurrence, 15.22% of the sample reported 1 previous episode of the condition and, although the literature states a chance of recurrence of around 15% in cases diagnosed with PE in previous pregnancies, many articles still associate the disease with primiparous, since the bad experience during pregnancy influences the choice to avoid the next one.[10,14] In the present study, 6% of the interviewees were diagnosed with PE in the previous and current pregnancies, in accordance with what has been found in the literature. Also, it is known that women who had PE in the first 2 pregnancies, approximately 30% will have the disease in a next pregnancy.[13] This risk is even greater if the previous PE had an early onset, had associated severity factors, or progressed to eclampsia or HELLP syndrome.

Regarding calcium intake, it was found that the daily average was 289.[2] mg - well below the amount considered adequate by the Estimated Average Requirement for adult pregnant women (800 mg/day).[2] In the present study, when talking to the interviewees, it was noted that they did not have the ideal intake due to a series of factors, but mainly due to the difficulty of buying foods rich in this micronutrient. According to data from the Brazilian Institute of Geography and Statistics (IBGE), dairy products are the food source with the highest bioavailability of calcium, according to this, the food with the highest calcium content (190 mg/day) ingested by the interviewees was milk.[7] However, this amount of calcium is still lower than that found in 200 ml of the drink (300 mg), proving insufficient intake. In addition, the most ingested type was whole milk (73.22%), suggesting that the pregnant women were not instructed that this is not the best choice in terms of calcium content and low fat percentage, as skimmed or semi-skimmed milk would be healthier and more beneficial options.[7]

Another dairy product addressed in the research was cheese (mozzarella, prato, minas and ricotta). As for the first 2, more than 60% of the patients ingested them, with a daily average of 15.93 g (less than 1 slice) - a better result than that presented in the study by Coutinho[7]. However, the minas and ricotta types, which have a higher calcium content, were consumed by less than 16%, bringing to light, once again, the socioeconomic influence, since these products are more expensive and

seen as superfluous in food. In addition, natural yogurt was also present in the diet of almost half of the sample (42.25%), with an average daily amount of calcium of 80.23 mg - lower than that found in 200 ml of the product and below the daily portion recommended by the Ministry of Health.[18] The proportion of interviewees who consumed yogurt was similar to that found in the study by Coutinho[7], however, emphasizing that it was carried out 10 years ago, alerting us that there has been no considerable progress in the acceptance of the recommendations for dairy intake.

Regarding the consumption of condensed milk, less than 1/4 of the pregnant women approached reported consumption. This data is consistent with the reality of the high-risk outpatient clinic in which the study was applied, since most patients are referred due to previous diabetes or gestational diabetes and are advised by health professionals to drastically reduce the consumption of foods rich in carbohydrates and sugars. Thus, this data enables the discussion about this important risk factor for PE. The Hyperglycemia and Adverse Pregnancy Outcomes - HAPO study, which involved about 25,000 pregnant women in several countries, highlighted the positive and linear correlation between altered blood glucose values and the higher occurrence of unfavorable maternal-fetal outcomes, including PE.[19] With regard to the consumption of heavy cream, although approximately 40% of the interviewees ingest it, the average amount of daily calcium (3.31 mg) is small compared to what is necessary, and this low consumption can be justified by the same factor presented in the previous topic.

Regarding the intake of butter, sardines and egg yolks, most of the pregnant women did not consume them: 47.7%, 85.82% and 35.17%, respectively. When questioned about the reasons for the absence from the food menu, the answers ranged from association with episodes of nausea to the financial difficulty in buying such foods in order to eat them with adequate frequency. About butter, another point in common among the pregnant women interviewed is that many consumed margarine: according to data from the United States Department of Agriculture (USDA), 100 g of the product contains 3 mg of calcium, while the same amount of butter has 8 times more calcium.[20] In addition, despite its lower cost, margarine has a higher amount of trans fats in its composition, favoring an increased risk of other health complications, such as dyslipidemia and obesity. Although some of the interviewees included butter, sardines, and egg yolks in their diets, the amounts ingested were small, resulting in an average daily calcium intake of 0.00048 mg, 0.02 mg, and 0.14 mg, respectively.

This scenario of deficiency in calcium consumption is not exclusive to Brazil and, therefore, the World Health Organization (WHO) recommended in the document "Prenatal Care for a positive experience in pregnancy", from 2017, calcium supplementation in regions with low intake. In this context, the recent Cochrane study (2018) showed that supplementation, from the 20th week of gestation, reduced the risk of PE by 64% in populations with a low-calcium diet, such as in Brazil.[2] For pregnant women at high risk for PE, supplementation should start even earlier, from the 12th week.[10] Thus, it has been proven that with a low cost for the SUS (about R$0.10 per unit) and easy adherence to use, calcium carbonate replacement (1 g/day) becomes the main route of intervention to prevent PE, in addition to other fetal conditions, such as prematurity and fetal malformations. When comparing the annual cost of supplementation for pregnant women with that of the treatment of complications generated by PE (more than 200 million), it is evident that, once again, prevention is the best choice.[6]

Regarding the comparison of the mean calcium intake between pregnant women with and without a diagnosis of PE at the time of the interview, no significant difference was found (293.9 mg and 281.16 mg, respectively). This information corroborates the hypothesis that, even with the diagnosis of the disease, pregnant women do not receive or do not follow guidance to improve calcium intake, proving how challenging it is to propose dietary changes. Furthermore, it can be noted that both groups are ingesting only 1/3 of the recommended daily amount of calcium and 1/2 of the average Brazilian consumption, making supplementation with calcium carbonate even more essential to prevent not only PE, but also other consequences of hypertensive diseases during pregnancy.[2,10,21] In addition, when comparing the amount of calcium ingested according to the salary range, the present study showed that the higher the income, the higher the average daily consumption of the nutrient, reiterating the influence of the financial factor. However, the low intake cannot be justified only in this association, since other poorer populations, such as Guatemala and Ethiopia, have diets that are poor in calories and proteins, but rich in calcium.[21]

CONCLUSION

The present study demonstrates that the pregnant women submitted to the study did not ingest the recommended amount of calcium, as initially expected. In addition, it was also able to trace the sociodemographic profile of the patients, associating these data with difficulties in understanding the disease and adherence to behavioral changes, including dieting, to establish a protective factor during pregnancy. Since no differences were found in the amount of calcium ingested through the correlation between maternal characteristics such as socioeconomic level and diagnosis of preeclampsia, even though calcium supplementation is an effective strategy to reduce the incidence and severity of the disease, it is interesting to think about universal calcium supplementation during pregnancy, as is done with iron. Continuity in studies and dissemination of health education for this public, especially in places of care that receive mostly high-risk pregnant women, will have a positive impact on what pregnant women understand about preeclampsia and on the way they accept and comply with recommendations for its prevention.

Authors' contributions

Mariana de Souza Bissoli - Conceptualization
Nathalia Arndt Costa - Formal analysis
Viviane Dombroski - Research
Naiara Bozza Pegoraro - Methodology
Arthur Rodrigues Caetano de Sousa - Validation
Jan Pawel Andrade Pachnicki - Project Management

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CYP2D6 polymorphisms in drug therapy in autism spectrum disorder (ASD) in children and adolescents

Polimorfismos da CYP2D6 na terapia medicamentosa no transtorno do espectro autista (TEA) em crianças e adolescentes

Fernanda Arissa Takii[1], Isadora Kertscher[1], Rafael Fortaleza de Souza[1], Naiara Bozza Pegoraro[1], Maria Regina Pinheiro de Andrade Tizzot[1], Jaqueline Carvalho de Oliveira[1], Mariane Wehmuth Furlan Eulálio[1,3], Mauricio Marcondes Ribas[1,3], Liya Regina Mikami[1,4]

ABSTRACT

Introduction: Autism spectrum disorder (ASD) impairs neuropsychomotor development, hindering cognition, language, and social interaction. It is genetic in origin, and severe behavioral symptoms related to it are currently treated with antipsychotics, primarily risperidone and aripiprazole.

Objective: To describe the influence of genetic polymorphisms of the CYP2D6 enzyme on the treatment with risperidone and aripiprazole in ASD.

Method: Electronic search from January 2023 to December 2023 in the main scientific databases, using combinations of MeSH/DeCS descriptors and free terms related to ASD ("Autism Spectrum Disorder", "Autism"), drugs ("risperidone", "aripiprazole"), clinical manifestations ("disruptive behavior", "irritability", "stereotypies"), and pharmacogenomics ("CYP2D6*3 and CYP2D6*4 alleles, "metabolizers").

Result: Seventy-two articles were included in Portuguese, English, and Spanish, published between 2010 and 2024.

Conclusion: ASD manifests itself in diverse ways, and understanding its clinical characteristics, drug treatment, and knowledge of drug pharmacogenetics is of great importance for adequate disease control and improved quality of life.

KEYWORDS: Autism spectrum disorder. Risperidone. Aripiprazole

RESUMO

Introdução: O transtorno do espectro autista (TEA) compromete o desenvolvimento neuropsicomotor, dificultando a cognição, linguagem e interação social. É de etiologia genética e atualmente, o tratamento de sintomas comportamentais graves relacionados a ele é realizado com antipsicóticos, principalmente com a risperidona e o aripiprazol.

Objetivo: Descrever no TEA a influência dos polimorfismos genéticos da enzima CYP2D6 no tratamento com risperidona e o aripiprazol.

Método: Busca eletrônica de janeiro/2023 a dezembro/2023 nas principais bases de dados científicas, utilizando combinações de descritores MeSH/DeCS e termos livres relacionados ao TEA ("Transtorno do Espectro Autista", "Autismo"), aos fármacos ("risperidona", "aripiprazol"), às manifestações clínicas ("comportamento disruptivo", "irritabilidade", "estereotipias") e farmacogenômica ("alelos CYP2D6*3 e CYP2D6*4, "metabolizadores").

Resultado: Foram incluídos 72 artigos nos idiomas português, inglês e espanhol, publicados entre 2010 e 2024.

Conclusão: TEA se manifesta de forma diversificada, e o entendimento de suas características clínicas, tratamento medicamento e conhecimento da farmacogenética dos medicamentos é de grande importância para controle adequado da doença e melhora da qualidade de vida.

PALAVRAS-CHAVE: Transtorno do espectro autista. Risperidona. Aripiprazol.

Central Message

ASD is a neurodevelopmental disorder characterized by behavioral signs accompanied by persistent deficits in communication and social interaction, repetitive and stereotyped behavior patterns, and a restricted repertoire of interests. Its diagnostic characteristics classify it into 3 levels, I, II and III, according to the severity and level of support required. Currently, the treatment of severe behavioral symptoms related to ASD is carried out with antipsychotics, especially with risperidone and aripiprazole

Perspective

It was observed that ASD manifests itself in a diversified way, and the understanding of its clinical characteristics, drug treatment and knowledge of applied pharmacogenetics is of great importance for adequate disease control and improvement of patients' quality of life. A better understanding of the influence of CYP2D6 enzyme genetic polymorphisms on treatment with risperidone and aripiprazole in children and adolescents is necessary to evaluate their relationship with pharmacogenomics and the improvement of the clinical picture presented by patients.

[1] Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil;
[2] Federal University of Paraná, Curitiba, PR, Brazil;
[3] Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil;
[4] Genetika - Genetics Counseling Center and Laboratory, Curitiba, PR, Brazil.

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INTRODUCTION

Historically, the term autism was coined by Swiss psychiatrist Eugen Bleuler in 1908. In 1943, another psychiatrist, Leo Kanner, made a diagnostic categorization with characteristics and complications that delimit the clinical picture for autism.[1]

In 2013, the nomenclature currently used "Autism Spectrum Disorder" (ASD) emerged after changes resulting from years of revision by the Neurodevelopmental Disorders Committee created specifically for this purpose, which originated the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) and defined the ASD criteria currently used.[2] In addition, the subdivisions formerly known as "Classic Autism, Atypical or Not Otherwise Specified Autism, and Asperger's Syndrome" were grouped into a single group known as the autism spectrum.[2,3]

The U.S. Food and Drug Administration (FDA) recommends the use of second-generation antipsychotics, such as risperidone and aripiprazole, for the treatment of behavioral symptoms of ASD in children and adolescents, including aggression, irritability, and disruptive behaviors.[4] Although these drugs demonstrate efficacy in controlling symptoms, in many cases significant variability in therapeutic response and incidence of adverse effects is observed, limiting their benefit in a considerable part of patients.[5]

One of the main factors influencing this variability is the genetic diversity in the cytochrome P450 enzyme CYP2D6.[6] This enzyme plays an important role in the metabolism of both risperidone and aripiprazole, regulating their plasma concentrations and, consequently, their efficacy and safety profile.[6] Thus, genetic polymorphisms in CYP2D6 can lead to marked differences in the way each individual responds to treatment, requiring individual strategies to optimize clinical outcomes.[7]

The aim of this review was to describe the influence of genetic polymorphisms of the CYP2D6 enzyme on treatment with risperidone and aripiprazole in children and adolescents with ASD, evaluating their relationship with pharmacogenomics.

METHOD

An electronic search was performed from January 2023 to December 2023 in the main databases, including PubMed/MEDLINE, SciELO, LILACS, EMBASE, and Cochrane Library, using combinations of MeSH/DeCS descriptors and free terms related to ASD, drugs ("risperidone", "aripiprazole"), clinical manifestations ("disruptive behavior", "irritability", "stereotypies"), and pharmacogenomics ("CYP2D6*3 and CYP2D6*4 alleles"), "metabolizers"). Articles in Portuguese, English, and Spanish, published between 2010 and 2024, were included. The inclusion criteria established were: studies describing the clinical manifestations of ASD in children and adolescents; to evaluate the use of risperidone or aripiprazole in the treatment of these manifestations; gene variants and CYP2D6 polymorphisms; randomized controlled trials, observational studies, or systematic reviews; and full-text articles available. Isolated cases, anecdotal reports, and publications without a clearly described methodology were excluded.

The article selection process took place in 3 stages: 1) initial screening by title and abstract; 2) full reading of the pre-selected articles; and 3) extraction of the relevant data. Two independent reviewers conducted this process, with a third reviewer being consulted in case of disagreement.

Thus, in the end, 72 articles were included

DISCUSSION

Characteristics of ASD

According to the DSM-5, it is a neurodevelopmental disorder characterized by behavioral signs accompanied by persistent deficits in communication and social interaction, repetitive and stereotyped behavior patterns, and a restricted repertoire of interests. Its diagnostic characteristics classify it into 3 levels, I, II and III, according to the severity and level of support required.[2,8,9]

At level I, there is notable social impairment in the absence of support and difficulties in initiating interactions, sometimes they seem to have reduced interest in them, with unsuccessful attempts at social contact, in addition to difficulty in organizing, planning and a certain inflexibility of behaviors.[8,10] Level II requires substantial support with apparent social impairments, limitations in initiating and maintaining interactions, inflexibility in behavior, and difficulty in dealing with change.[8,10] Level III requires a lot of substantial support, with severe deficits in social communication skills, inflexibility of behavior, and extreme difficulty with change. Thus, the lower the degree of impairment of the level, the better the prognosis tends to be.[8-10]

A striking and consistent characteristic of ASD is that it is diagnosed more frequently in males. According to the DSM-5 and statistics from the CDC (Centers for Disease Control and Prevention), ASD is 4 times more frequent in men than in women.[2,11]

Loomes, Hull and Mandy[12], showed that girls with ASD face a higher risk than boys of having their diagnosis neglected or made late, possibly due to the female ASD phenotype, which differs subtly from conventional conceptualizations of the disorder. In addition, girls with ASD are less likely to exhibit obvious restricted interests, making it difficult to identify. In addition, the authors demonstrated emerging evidence that girls are more likely to mask their difficulties, making early and accurate diagnosis more challenging. The persistence of female stereotypes among professionals and contact with these individuals, such as teachers, pediatricians, psychiatrists, and psychologists, may contribute to this diagnostic bias, reducing their sensitivity to symptoms when they occur in girls.[11,12]

Diagnosis of ASD

CDC stipulates that the steps in the process of diagnosing ASD begin with follow-up and surveillance, which consists of monitoring development, seeking its milestones in all children through tools with validity to

identify if they are acquiring basic skills that can help determine possible delay. Then, perform comprehensive developmental assessment by thorough review of how the child plays, learns, communicates, acts, and moves, and how these traits are over time. This evaluation may include clinical observation, parental reports on development and health history, psychological testing, and speech and language assessments. To rule out other disorders, neurological and genetic testing can be used.[11]

There are also other screening tests, including: 1) the Autism Classification Scale in Childhood; 2) Clinical Risk Indicators for Child Development, and 3) the Modified List for Autism in Children.[8]

The diagnosis of ASD is defined as being early, when it is made before the age of 6 and late, after the age of 6. It is important to note that the sooner the child is diagnosed, the sooner they can access services and support, providing better adaptation for the individual and their family.[11,13]

Prevalence of ASD

WHO (World Health Organization) estimates that autism affects 1:100 children in the world.[14] In the United States, data from the CDC show that there are approximately 1:36 children at the age of 8 years with ASD.[11]

In the last 30 years, there has been a 20-fold increase in its prevalence, reaching an annual rate of more than 2% of autistic people in the United States alone.[15] The reason for the increase in incidence in the last 20 years has not yet been clarified. King et al.[16] and Schieve et al.[17] analyzed the effect of changes in the age of the parents and certain perinatal risk factors on the prevalence of ASD, under the hypothesis of a causal pathway, concluding that the contribution of these factors to the increase in ASD incidence is probably minimal. On the other hand, the studies by Parner et al.[18] and King and Bearman19, by focusing on non-etiological factors, concluded that the earlier age at the time of diagnosis and the expanded access to diagnostic methods are some of the factors responsible for the increasing prevalence of ASD.

Etiology of ASD

Currently, it is considered a disease of complex interaction between genes and environment, that is, of multifactorial inheritance, with a genetic component that varies between 40-80%.[20,21]

The involvement of chromosomal regions and variants in specific genes were associated with increased risk for their development.[22] Among the main causes, copy number variants (CNVs), cytogenetically observable chromosomal abnormalities, and monogenic disorders can be mentioned.[23,24] However, it is unclear whether the involvement required to result in the ASD phenotype is single-gene in combination with non-genetic factors, multiple genes through locus heterogeneity, or allelic. The association of multiple genes in combination with non-genetic factors is also suggested.[25]

More than 800 genes have already been related to the disorder, and some of those reported with strong association are: DRD4, SCN2A, CHD8, GRIN2B, DMPK, FXN, CA2, DDHD1, NSUN2, PAH, NLGN3, SHANK3, RARB, ROGDI, SLC1A1, USH2A, CHD2, HDAC4, GDI1. 26-29 In addition, many ASD-related genes are located on the X chromosome, and are involved in chromatin remodeling, synaptic function, neuronal signaling, and brain neurodevelopment.[30]

There are also reports of the presence of chromosomal microdeletions or duplications in children with ASD in chromosomal regions 1q24.2, 1p36.22, 2p13.1, 2q13, 2q37.3, 3p26.2, 4q34.2, 6q27, 6q24.3, 7q35, 8q24.22, 9p21.3, 9q31.2, 12p13.31, 13q13.2-q22, 15q11-q13, 15q11.2, 15q22, 16p11.2, 16p13.2, 17p11.2, 18q21.1, Xp2 and 22q11.[31-34]

Just as genetic variations are related to the etiology of the disorder, the body's response to a given pharmacological treatment is also influenced by the genetic profile.[35]

Treatment of ASD

The heterogeneity of ASD is extremely important to define the types of interventions needed; after all, its wide phenotypic variability directly reflects on different responses to the treatments established as standard.[36] The use of naturalistic behavioral approaches of early onset is recommended; however, there are controversies that show different levels of effectiveness for each modality of therapy. Likewise, no medication is effective in isolation for the treatment of ASD, and it is recommended to individualize drug treatment and interventions according to the target behaviors to be worked on.[36]

Therapeutic interventions, including behavioral strategies and habilitative therapies, are the cornerstones of ASD management and address communication, social, daily living, play, and leisure skills, and maladaptive or maladaptive behaviors.[37]

Pharmacological treatment is prescribed for certain patients, aiming to alleviate some specific symptoms, and not the disorder itself, such as aggressiveness, irritability, significant sleep changes, self-injurious behavior, repetitive behaviors (e.g., perseverance, obsessions, compulsions, and stereotyped movements), mood lability, anxiety, hyperactivity, lack of attention, destructive behavior, or other disruptive behaviors.[38,39]

Recent research indicates that approximately 45% of children and adolescents and up to 75% of adults with ASD are treated with antipsychotic medication. They are drugs with psychotropic action, which inhibit psychomotor function by acting on the nerve cells that regulate psychic processes.[40]

Atypical antipsychotics

Atypical antipsychotics (AAPs), or second-generation antipsychotics, are called "atypical" because they are considered safer and better tolerated than "conventional" or first-generation antipsychotics, including risperidone and aripiprazole.[41]

These medications are widely used in the other generalized developmental disorders (PDDs) to treat maladaptive behaviors. PACs are available in several forms of application, and the main use in ASD is the oral route.[41]

These AAPs are all potent antagonists of dopamine D2 receptors and, also, have additional properties, as they are antagonists of 5-HT2A and 5-HT1A receptors, belonging to the serotonin receptor family, inhibiting the reuptake of serotonin and/or norepinephrine.[42]

AAPs with action of D2 receptor antagonists combined with 5-HT2A receptor antagonism have greater efficacy for symptoms of mania and depression. Antipsychotics also exhibit histamine, muscarinic (cholinergic), and alpha-adrenergic antagonism.[43]

Risperidone

Since 2006, the FDA has approved risperidone to treat ASD-related irritability.[4] Approximately 1 in 9 young people with ASD use this medication.[2,44]

Its effect on aggression, stereotypies, irritability, and restlessness is attributed to dopamine antagonism, while its effect on restricted activity patterns, communication, social, and emotional skills, such as difficulty maintaining eye contact and attention, is attributed to serotonin antagonism.[4] This drug also blocks alpha-1 adrenergic receptors and, to a lesser extent, histamine H1 and alpha-2 adrenergic receptors.[5]

The major route of metabolization of risperidone is in the liver, where it undergoes hydroxylation producing 9-hydroxyrisperidone, or paliperidone, as its active metabolite, this reaction is catalyzed primarily by the enzyme CYP2D6, and to a lesser extent by CYP3A4 and CYP3A5.[45]

Although there are no mandatory requirements for monitoring of therapeutic drugs (TDM) with risperidone, monitoring of plasma concentrations of this drug is strongly recommended by European guidelines. Therapeutic monitoring can help assess compliance and identify drug concentrations, which may be low, resulting in therapeutic failure.[46] In addition, monitoring the level of the drug can help in the evaluation of potential drug interactions and side effects.[46]

Safety, efficacy, acceptability, and tolerability have been evaluated in several clinical studies for the treatment of ASD symptoms. According to Hutchinson et al.[47,] and Mano-Souza et al.[4,] risperidone has demonstrated a response rate of 70% in efficacy for the treatment of maladaptive symptoms of ASD, both short-term (up to 8 weeks) and long-term (after 8 weeks) use.

On the other hand, Maneeton et al.[48,] showed that the acceptability, defined as the overall discontinuation rate, of risperidone treatment was comparable to placebo, and no difference in treatment was found between risperidone and placebo for tolerability.

In another study, Mano-Souza et al.[4,] on the use of risperidone, both in the short and long term in children with ASD showed general improvement in maladaptive behaviors.

Aripiprazole

Aripiprazole is an FDA-approved atypical antipsychotic used for the management and treatment of schizophrenia, mania associated with bipolar disorder, irritability associated with ASD, major depressive disorder, and Tourette's syndrome.[49] He is a partial agonist of dopamine D2 and serotonin 5HT-1a receptors and an antagonist of the serotonin 5HT-2a receptor. It has a high affinity for D2, D3, 5HT-1a, and 5HT2a receptors and moderate affinity for D4, 5HT-2c, 5-HT7, alpha-1 adrenergics, and H1 receptors. This drug demonstrates functional selectivity in intracellular signaling pathways, requiring an occupancy rate greater than 90% in D2 receptors to be clinically active, thus not producing so many extrapyramidal symptoms.[50]

The half-life of oral administration is approximately 75 h. Constant serum concentration doses (based on 15-30 mg per day) should occur in approximately 14 days and therefore it may take up to 2 weeks to fully assess tolerability.[49]

Aripiprazole metabolism occurs by hepatic dehydrogenation, hydroxylation, and N-dealkylation via CYP2D6 and CYP3A4, genes of the CYP450 family.[51] Taking this medication require monitoring for any side effects, and antipsychotic switching should be considered if weight gain is greater than or equal to 5% of initial weight.[49]

The main route used in ASD is oral and its dosage is available in tablets of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg.[49] The study by Hirsch and Pringsheim52 demonstrated that the short-term use of aripiprazole in ASD resulted in a decrease in irritability, hyperactivity, and stereotypies.

Adverse effects of antipsychotics

PAOs can cause adverse effects such as weight gain, hyperlipidemia, diabetes mellitus, prolongation of the QTc interval on the electrocardiogram, extrapyramidal symptoms, myocarditis, agranulocytosis, cataracts, and sexual side effects.[53] Treatment with these drugs can contribute to weight gain and, subsequently, to metabolic syndrome with hyperglycemia, hypertension, hyperlipidemia, and hypertriglyceridemia, which are risk factors for stroke, myocardial disease, and diabetes mellitus.[53]

Weight gain, metabolic changes, and sleepiness are significant concerns when using risperidone. This drug may also produce extrapyramidal symptoms (EPS), including acute dystonia, akathisia, tardive dyskinesia, and parkinsonian symptoms.[54,55]

Regarding aripiprazole, although its side effects are similar to those found in typical and atypical antipsychotics, the degree of EPS and metabolic syndrome are lower due to the specificity of its receptor.[49] Aripiprazole is associated with lower incidences of weight gain, hypercholesterolemia, hyperglycemia, and cardiovascular abnormalities. Other possible side effects include drowsiness, nausea, vomiting, akathisia, and dizziness. Rare adverse effects may include neuroleptic malignant syndrome, liver function abnormalities and jaundice, seizures, and agranulocytosis.[49,56]

Pharmacogenomics

Pharmacogenomics is the science that studies the interaction between genes and drugs.[57] From the analysis of specific regions of DNA, it is possible to verify genetic markers such as single-nucleotide polymorphisms (SPN),

microsatellite insertions, deletions and repeats, and RNA splicing.[57,58] The main targets of pharmacogenomics are the genes that encode enzymes responsible for the pharmacokinetics (events of absorption, distribution, metabolism, and excretion of the substance at its systematic concentration) and pharmacodynamics (relationship between the administered dose and the effects produced) of licit and illicit drugs.[57,58]

CYP2D6

The cytochrome P450 (CYP) superclass is a family of enzymes found in several species and are named for their ability to absorb light at a frequency of 450 nm.[6,59]

The human genome contains 57 CYP genes, of which 12 of the enzymes produced are associated with the metabolism of about 80% of the drugs most commonly used by the population.[60] The CYP2D6 gene is located at 22q13.[1] and is composed of 9 exons, with 1491 base pairs encoding 497 amino acids and 8 introns.[61]

CYP2D6 is responsible for metabolizing approximately 25% of drugs by encoding monooxygenase proteins, which participate in phase I metabolism.[61,62] These enzymes metabolize drugs such as antivirals, opioids, beta-blockers, antidepressants, antipsychotics, antiarrhythmics, antihistamines, and β blockers, among others.[61,63]

Deficiency of CYP2D6 activity is inherited as an autosomal recessive trait and its genetic variants may be CNVs or SNPs.[7] Are natural variations found in genes and CYP2D6 and can have significant influence on metabolism, clinical efficacy, and side effects in drug therapy, depending on whether it modifies the amino acid sequence of the encoded protein and whether it has physiological consequences.[64] If several SNPs occur in the same gene, the resulting genotypes can form haplotypes, which would be when different genetic variants segregate together in the formation of gametes, which would characterize linkage imbalance. There are many functional patterns of CYP family polymorphism that result in mutations such as nucleotide substitution, change in reading matrix, splicing defects, insertion/deletion, tandem rearrangement, gene deletion, and duplication.[65]

This significant alteration of polymorphisms in the CYP2D6 gene alters the pharmacokinetics and pharmacodynamics of drugs such as risperidone and aripiprazole, which may lead to the occurrence of toxic effects and therapeutic failure, which could explain why drug therapy is ineffective in some individuals.[65]

According to the Human Cytochrome P450 Allele Nomenclature Committee (CYP), from 2010, the CYP2D6 gene is highly polymorphic, with more than 90 allelic variants, which can significantly affect enzymatic activity, generating 4 different phenotypes of metabolizers: 1) non-functional isoforms (weak); 2) isoforms with reduced function (intermediate); 3) functional isoforms (normal) and 4) isoforms with increased function (ultra-fast).[65]

Genetically, individuals who have 2 normal alleles or one normal and one altered are classified as normal metabolizers (NMs).[65] Individuals with 2 inactive copies of the CYP2D6 gene are called slow metabolizers (PMs) and have slow breakdown of medications, that is, they have decreased metabolization capacity, making side effects more exacerbated and the standard dose of certain drugs may not work as expected and up to 15% of the population fits into this subgroup.[66] Intermediate metabolizers (MIs) may somehow have the metabolism of drugs altered, causing effects similar to PMs, but not as pronounced.[65] Ultrafast (UMs) metabolize drugs very quickly, because they have alleles that produce enzymes with high activity or have extra copies of alleles (e.g., gene duplications or triplications).[58]

Globally, NMs and IMs phenotypes are the most common, comprising 43-67% of populations.[67] PMs and UMs are less common, but these individuals are at higher risk for adverse reactions or treatment failure when treated with a drug that is metabolized or bioactivated by CYP2D6.[67]

Lopes et al.[68] reported that the CYP2D6*3 variant exerts an influence on opioid metabolization. Regarding the importance of the CYP2D6*4 variant, Scantamburlo et al.[69] showed that this allele leads to the change in the reading matrix at position 259 of the protein, generating an enzyme with little or no metabolizing function.

The CYP2D6*3 and CYP2D6*4 alleles are the most important null variants of the protein, responsible for the absence of enzymatic activity, thus causing poor metabolism.[70] These alleles are the most prevalent of Eurodescendants, *3 appears in 1.6% and *4 in 18.5% of this population.[67]

The alleles of CYP2D6*1, CYP2D6*2, CYP2D6*33, and CYP2D6*35 are normal; while CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6 express isoenzymes with no activity, and CYP2D6*10, CYP2D6*17, CYP2D6*29, and CYP2D6*41 encode enzymes with reduced activity.[71,72] The CYP2D6*1 allele is considered the reference allele and is often inferred when no variant is detected by genotyping test.[70]

CONCLUSION

From this review, it is concluded that autism spectrum disorder manifests itself in a diversified way, and the understanding of its clinical characteristics, drug treatment and knowledge of pharmacogenetics applied to these drugs is of paramount importance for adequate disease control and improvement of patients' quality of life.

Authors' contributions
Fernanda Arissa Takii – Conceptualization, methodology
Isadora Kertscher - Formal Analysis
Rafael Fortaleza de Souza - Formal analysis
Naiara Bozza Pegoraro - Project Administration
Maria Regina Pinheiro de Andrade Tizzot - Project Administration
Jaqueline Carvalho de Oliveira - Supervision
Mariane Wehmuth Furlan Eulálio - Supervision
Mauricio Marcondes Ribas - Writing (original draft)
Liya Regina Mikami - Writing (proofreading and editing)

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BioSCIENCE Review Article
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Vitiligo: discoveries in its pathogenesis and new therapies

Vitiligo: descobertas em sua patogênese e novas terapias

Carolina Silva Poiani[1], Gisele Moss Troiano[1], Inácio Skraba Silva[1], Johann Costa Migliorini[1], Maria Clara Messias Gomes[1], Rafaela Precoma Erdmann[1], Irlena Monica Wisniewska de Moura[1]

ABSTRACT

Introduction: Vitiligo is an autoimmune disease characterized by the progressive loss of melanocytes, resulting in hypochromic and achromic skin patches. It affects 0.4–2% of the global population and is more prevalent in women and Africans, and less in Europeans and Asians.

Objective: To review its mechanisms and analyze the main hypotheses underlying its manifestation and existing treatments.

Method: Narrative review searching for articles published between 2008 and 2023 in PubMed, Researchgate, Google Scholar, and SciELO.

Result: Ten articles were selected, emphasizing new pathophysiological hypotheses and current therapeutic approaches.

Conclusion: Vitiligo is an autoimmune disease involving genetic predisposition, oxidative stress, and abnormal immune responses. Therefore, the complexity of the mechanisms underlying the disease presents a challenge for therapeutic strategies. Current therapies aim to halt lesion progression and promote repigmentation depending on the clinical manifestation and location of the patches.

KEYWORDS: Vitiligo. Therapeutics. Pathology. Autoimmunity.

RESUMO

Introdução: Vitiligo é doença autoimune caracterizada pela perda progressiva de melanócitos no organismo, resultando em manchas cutâneas hipocrômicas e acrômicas. Apresenta-se em 0,4-2% da população mundial, é mais prevalente em mulheres e nos africanos, e menos em europeus e orientais.

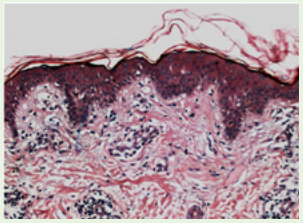
Objetivo: Revisar os seus mecanismos e analisar principais hipóteses atribuídas à sua manifestação e tratamentos existentes.

Método: Revisão narrativa com busca de artigos publicados entre 2008 e 2023 no Pubmed, Researchgate, Google Acadêmico e SciELO.

Resultado: Foram selecionados 10 artigos com ênfase nas novas hipóteses fisiopatológicas e abordagens terapêuticas atuais.

Conclusão: Vitiligo é doença autoimune que envolve predisposição genética, estresse oxidativo e respostas imunológicas anômalas. Portanto, a complexidade dos mecanismos subjacentes à doença é desafio frente às estratégias terapêuticas. As terapias atuais visam interromper a progressão das lesões e promover a repigmentação conforme a manifestação clínica e localização das máculas.

PALAVRAS-CHAVE: Vitiligo. Terapêutica. Patologia. Autoimunidade.



Marchioro et al.[3]

Central Message

Vitiligo is an autoimmune disease characterized by the progressive destruction of melanocytes caused by the presence of excess cytotoxic lymphocytes (TCD8+), which leads to the appearance of hypochromic and achromic spots on the skin. Thus, examining its pathophysiological mechanisms, exploring the main hypotheses about its causes, and analyzing the currently available treatments is pertinent to the present day.

Perspective

Vitiligo is a multifactorial disease involving genetic factors, oxidative stress, and abnormal immune responses. Its treatment follows 3 main approaches: use of topical corticosteroids, nbUVB therapy and excimer laser. These therapies aim to interrupt the progression of lesions and promote repigmentation, varying according to the clinical manifestation and location of the macules.

[1]*Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.*

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INTRODUCTION

Vitiligo is an autoimmune disease characterized by the progressive loss of melanocytes in the body, resulting in the appearance of hypochromic and achromic spots in various regions of the skin.[1-3] This is a chronic condition that has 2 main clinical manifestations, divided into segmental vitiligo (SV) and non-segmental vitiligo (VNS).[2,4] The first form is usually presented in a linear or block area of the body.[2,4] VNS, on the other hand, includes other forms such as focal, mucous, acrofacial, generalized, universal, mixed, and other rare forms whose main characteristic is the presence of bilateral macules or spots on the body.[2,4] Vitiligo affects 0.[4-2%] of the world population and its prevalence is very variable, being higher in Africans and Europeans and lower in Orientals.[2,3] According to the Brazilian Society of Dermatology, in 2019, population prevalence in some countries in the world was: China, 0.09%; Denmark, 0.38%; United States, 0.40-2%; India, 1.13%.[5]

The objective of this study was to review and update the pathophysiological mechanisms of vitiligo, analyzing the main hypotheses attributed to the manifestation of the disease and the existing treatments.

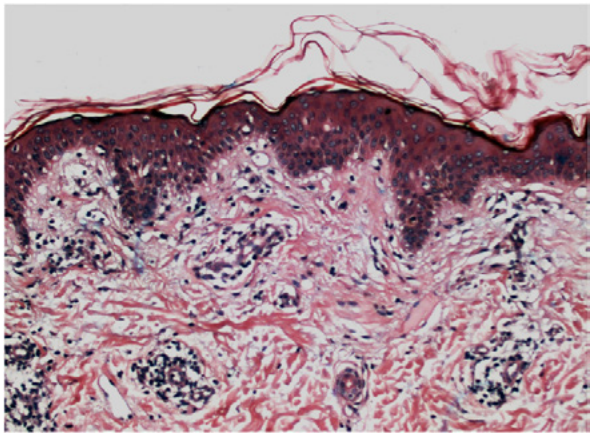
METHOD

Narrative review with search of articles published between 2008 and 2023 in the following databases: Pubmed, Researchgate, Google Scholar and SciELO. After reading the titles and abstracts, those that did not adequately meet the objectives of this research were excluded, and 10 articles were selected with an emphasis on those that presented the pathophysiological hypotheses and therapeutic approaches from the years 2015 to 2023. The inclusion criteria involved in the selection of articles were articles published in the last 10 years and that addressed the desired content of pathophysiology and therapy. The research involved the descriptors "vitiligo", "therapeutics", "pathology" and "autoimmunity".

DISCUSSION

Vitiligo is chronic acquired dyschromia that results in the loss of melanocytes in the basal layer of the epidermis and the consequent loss of pigmentation of the affected areas.[3,6,7] The characteristic lesions are calcareous, amelanotic, non-scaly white macules with varied borders.[7] They can be found all over the skin and areas of the mucous membrane, including the possible involvement of hair follicles, and may be accompanied by systemic manifestations such as sensorineural deafness, uveitis, thyroiditis.[3] The distribution patterns and clinical characteristics of vitiligo allow us to classify its manifestation into SV and VNS.[4] While SV is present in a unilateral body area, in a linear fashion or in blocks tending to stabilization, the other type is more predominant and manifests symmetrically, usually on the extensor and flexor surfaces, and the lesions tend to evolve over time.[4] VNS can also present itself in various forms such as acrofacial, mucosal, generalized, and universal.[4]

From the histopathological point of view, its lesions affect both the epithelium and the superficial portion of the dermis.[3] In the basal layer of the epidermis, there is a significant reduction in melanin and melanocytes present, as well as the presence of lymphocytic inflammatory infiltrate, with TCD3+ and TCD8+ lymphocytes predominating in perivascular areas of the dermis (Figure 1).[3] In addition, there is an increase in the number of Langerhans cells in the epidermis, melanocytes with short dendrites and few melanosomes, and vacuolization of melanocytes in the basal layer of the epidermis.[3] Among other alterations found are the thickening of the basement membrane and stratum corneum of the epidermis, with larger corneocytes as a way of compensating for the decrease in keratinocytes in areas with vitiligo.[3] Lesions may also present acanthosis and defects in the adhesion elements between keratinocytes and/or melanocytes, such as E-cadherins, hindering cell adhesion.[3]

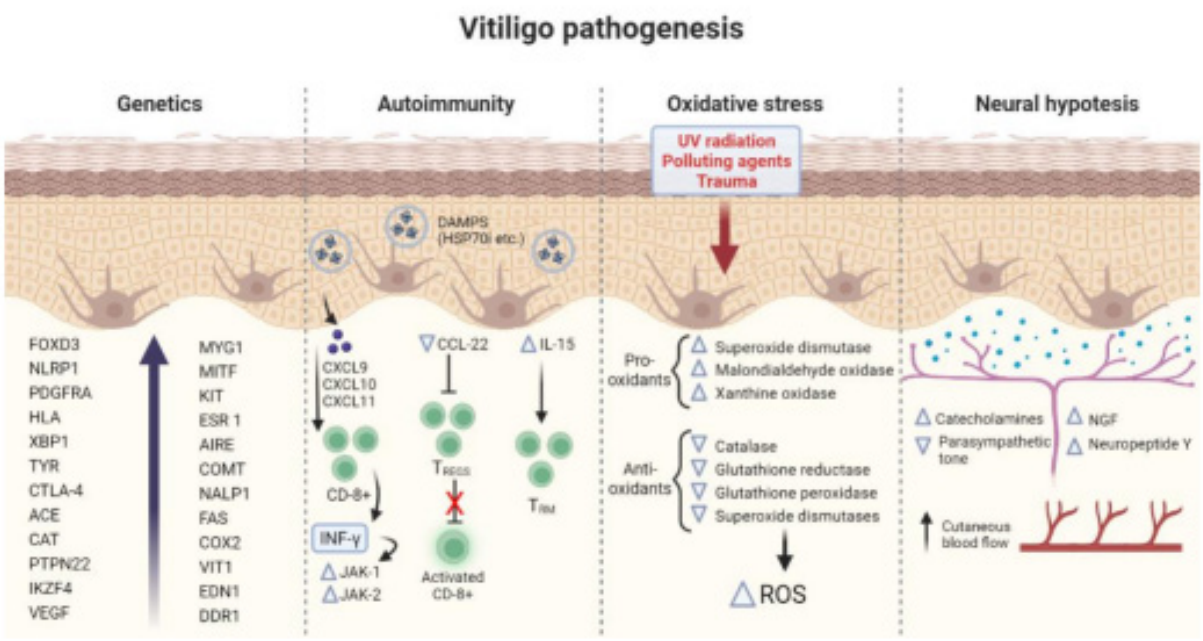


Source: Marchioro et al.[3]

FIGURE 1 — Active vitiligo (H&E×40)

The pathophysiology of vitiligo is multifactorial, encompassing several factors, including genetic, autoimmune, environmental, and neural, resulting in the elaboration of several hypotheses to try to explain its pathogenesis (Figure 2).[6]

One hypothesis suggests that genetics plays a significant role in the incidence.[3] It is estimated that between 75-83% of affected individuals have components of genetic inheritance.[3] Because it is a multifactorial disease with polygenic pattern inheritance, the genetic mapping for the analysis of risk factors is extensive and covers several genes whose expression may be associated with vitiligo.[3] Among these genes, the transcription factor XBP1 located on chromosome 22q12 stands out.[3,8,9] It regulates the expression of genes such as HLA class II, which is often related to autoimmune diseases, vitiligo being an example.[3,8,9] In residues 135 for HLA-DQB1 and 46 for HLA-B, changes in amino acids were found that indicate increased susceptibility in the Chinese population.[3,8,9] In addition, 3 loci in 1p31.[3] – p32.[2,] 7q21.[11] and 8p12 were associated with increased vulnerability in Europeans and loci 4q13-q21 in the Asian population.[3,8,9] Of these described, FOXD3 was the gene present at loci 1p31.3–p32.2 and PDGFRA



Source: Diotallevi et al.[6]

FIGURE 2 — Theories of the pathogenesis of vitiligo

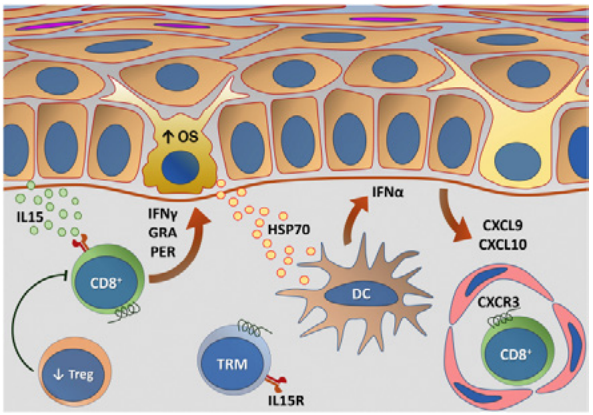
at loci 4q13–q21.[3,8,9] In addition to those mentioned above, HLA-A*33, HLA-Aw*31, HLA-DR4, HLA-DR7 and HLA-DQB1*0303 have been identified as risk factors for vitiligo in different populations.[3,8,9]

Another hypothesis to explain the pathogenesis of vitiligo, determining a crucial point at the beginning of the symptomatology, would be the interaction of melanocytes with reactive oxygen species (ROS), such as O2- and H2O2, in a process of oxidative stress.[2] From the perspective of the affected organism, the accumulation of ROS occurs both by external factors, such as exposure to ultraviolet radiation (UV) and medications, and by internal factors, due to genetic propensities that stimulate the production of these molecules in metabolic reactions with high mitochondrial demand.[2] In particular, melanocytes act as instigators and victims of oxidative stress, as the process of melanogenesis results in significant amounts of O2- and miscoiled proteins, favoring a pro-oxidative environment.[2] Consequently, there is hyperactivity of the enzyme superoxide dismutase 2 responsible for degrading the O2 into H2O2 and O2.[2] This enzyme is also related to the reaction of unfolded proteins, while the main lines of defense against the imbalance between oxidants and antioxidants, such as glutathione and NFR2, have limited effects on the disease.[1] In addition, in vitiligo there is a dysregulated redox balance associated with low expression of catalase, an enzyme that protects cells from ROS.[2] Thus, the state of oxidative stress and continuous inflammation increase the cytotoxicity of melanocytes, causing apoptosis of these cells at pathological levels even in the subclinical period.[2] The accumulation of reactive oxygen species can trigger changes in the endoplasmic reticulum of the melanocyte, resulting in the accumulation of defective proteins and activating the cellular stress phenomenon known as the misfolded protein reaction.[2,6]

Additionally, one of the main hypotheses widely investigated in the pathophysiology of vitiligo is the relationship with autoimmunity.[2,3] The pathogenesis of this disease is marked by the participation of the innate immune system. In vitiligo lesions, dendritic cells, macrophages and Natural Killer cells can be found.[3] In addition, there is the presence of pro-inflammatory cytokines characteristic of innate immunity, such as interleukins 6, 8, 12, and 15 and tumor necrosis factor alpha.[2,3] One of the major hypotheses is that oxidative stress in melanocytes stimulates the secretion of exosomes containing chaperone proteins and molecular patterns associated with damage, and thus delivering self-antigens to dendritic cells that undergo maturation into antigen-presenting cells.[2,3] The molecular pattern associated with damage with greater relationships with vitiligo is Heat Shock 70 chaperone.[2,3] They are extracellular proteins that prevent protein misfolding and have the potential to induce the maturation and activation of dendritic cells.[2,3] However, under conditions of physiological stress, they can be secreted by cells and released into the extracellular medium.[3] Thus, its recognition by immune cells results in signaling for the release of cytokines such as interferon-alpha (IFN-alpha).[3]

This participation of the innate immune system also promotes the activation of the adaptive immune system.[3] IFN-gamma produced by dendritic cells stimulates the production of chemokines such as CXCL9 and CXCL10 by keratinocytes, resulting in the recruitment of T cells.[3,8] TCD8+ lymphocytes recruited to the epidermis and dermis cause damage to melanocytes through the release of perforins, granenzymes, and proinflammatory

cytokines such as TNF-alpha and interferon-gamma, resulting in the destruction of these melanin-producing cells (Figure 3).[3] Cytokines such as IFN-gamma, considered central to vitiligo autoimmunity, and TNF-alpha are significantly important in this context.[3] IFN-gamma promotes the recruitment of autoreactive TCD8+ cells to the skin.[3] These cells secrete greater amounts of this cytokine, which induce the production of CXCL9 and CXCL10 receptors by keratinocytes to recruit more T cells and promote the progression of vitiligo.[2-4,8] When IFN-gamma is neutralized by antibody treatment or when T cells lack CXCR3 expression, autoreactive T cells are unable to migrate to the skin and therefore do not cause vitiligo.[2-4,8] IFN-gamma regulation involves chemokine receptors and their ligands, such as CXCL9, CXCL10, and CXCL11.[4,8]



Source: Marchioro et al.[3]

FIGURE 3 — Representation of changes related to the adaptive immunity of vitiligo

There is also the participation of neurological factors in vitiligo, both in clinical aspects, due to its presentation following the dermatomes in segmental vitiligo, and in general pathological mechanisms.[3,6] Studies comparing the activity of the sympathetic nervous system in the skin between individuals with both presentations of vitiligo and patients without the condition concluded that segmental lesions showed up to 3 times greater activity of the local microcirculation, suggesting dysfunction of the sympathetic nervous system that would contribute to the pathophysiology of VS.[3,6,10] Another factor would be the increased action of neuropeptides and neuronal growth factors around the areas of injury, which is associated with stressful situations.[3,6,10] As a consequence, the joint occurrence of vitiligo and severe emotional stress can cause exacerbation of the condition, linking to other hypotheses about pathogenesis to explain the complex correlations in the affected metabolism.[3,10]

The treatment of vitiligo depends on the manifestation of the disease.[7] Treatments differ according to location and evolution, requiring follow-up and evaluation of 3-6 months after the beginning of the line of action.[7] For its treatment, there are the 2021 British Association of Dermatologists guidelines, the 2023 German S1 guidelines, and the 2012 European Dermatology Forum consensus.[7] They establish that both non-segmental and segmental vitiligo must follow 3 lines of treatment, with some changes depending on the manifestation of the disease, in addition to psychotherapy and self-care with UV protection.[7]

For VNS, there are 3 possible objectives during the therapeutic procedure, which are stabilization, repigmentation and depigmentation.[7] The first line consists of the use of topical corticosteroids (CTs) once daily.[7] The second line provides nbUVB (narrowband UV-B) with or without CTs.[7] In the third line, there are options such as excimer laser or light, plus CTs for localized disease.[7] For adults with VNS in the hands and feet with inefficient response to other treatments, the third line is based on CO2 laser (1 time per month for 5 months) in combination with 5-fluorouracil (1 time per day for 7 days per month for 5 months).[7]

For VS, there are 2 main objectives, namely stabilization and repigmentation.[7] The first line of treatment is the use of CTs once daily for up to 3 months.[7] The second also consists of localized therapy with nbUVB.[7] In case of progression under topical treatment, monochrome excimer or laser lamp is recommended.[7] Otherwise, the laser or excimer is considered to be of the third line of treatment.[7]

CONCLUSION

Vitiligo is a complex and multifactorial autoimmune disease, characterized by the loss of pigmentation due to the decrease of melanocytes in the basal layer of the epidermis. It has 2 classifications: VS and VNS. Its etiology involves genetic predisposition, especially the transcription factor XBP1 located on chromosome 22q12; oxidative stress, resulting from the interaction between melanocytes and reactive oxygen species (ROS); and anomalous immune responses, marked by the presence of dendritic cells, macrophages, Natural killer and pro-inflammatory cytokines characteristic of innate immunity. In addition, sympathetic nervous system dysfunction may contribute to the pathophysiology of VS. Current therapies such as topical corticosteroids, narrow-band UVB phototherapy, and Excimer Laser, aims to interrupt the progression of lesions and promote repigmentation according to the clinical manifestation and location of the macules.

Authors' contributions

Carolina Silva Poiani – Research, Project Writing (original draft)
Gisele Moss Troiano – Research, Project Writing (original draft)
Inácio Skraba Silva – Methodology, Project Writing (original draft), Project Writing (review and editing)
Johann Costa Migliorini – Conceptualization, Project Writing (original draft), Project Writing (review and editing)
Maria Clara Messias Gomes – Research, Project Writing (original draft)
Rafaela Precoma Erdmann – Conceptualization, Project Writing (original draft)
Irlena Monica Wisniewska de Moura - Project Administration, Project Writing (proofreading and editing)

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Temporal-spatial analysis of mortality from Lupus in Brazil, between 2011 and 2021

Análise têmporo-espacial da mortalidade por Lupus Eritematoso Sistêmico no Brasil, entre 2011 e 2021

Thelma Larocca Skare[1], Vitor Hugo Mariano[1], Davi Canteri Mendelski[1], Fernanda Ritt de Souza[1], Isadora Candotti Sperotto[1], Leonardo Moreira Dias[1], Pedro Canteri Mendelski[1], Tailla Cristina de Oliveira[1]

ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) has a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. It predominantly affects women of childbearing age. Studies have shown that its prevalence is higher in Black and Asian populations, while white populations have lower rates.

Objective: To analyze mortality from in Brazil between 2011 and 2021, taking into account its temporal-spatial distribution.

Method: It was developed under the descriptive epidemiological scope and based on data extracted from the Mortality Information System (SIM/DATASUS). Variables such as sex, age group, ethnicity, marital status, education, place of death, and residence were analyzed. The temporal trend was assessed by joinpoint regression, and the spatial distribution was assessed by Global and local Moran indices.

Result: Between 2011 and 2021, 11,195 deaths from SLE were recorded, representing an average mortality rate of 0.49/100,000 inhabitants, with a predominance of women (89%) and a higher incidence in individuals aged 40-49 years (19.46%). The highest rates were in the South, Southeast, and Central-West regions. The analysis demonstrated positive autocorrelation and significant clusters in the aforementioned regions.

Conclusion: Regional disparities exist, and specific strategies to expand access to early diagnosis and appropriate treatment are needed, especially in vulnerable regions.

KEYWORDS: Systemic lupus erythematosus. Mortality. Epidemiology. Spatial distribution. Brazil.

RESUMO

Introdução: LES apresenta epidemiologia global marcada por variações na prevalência que podem ser atribuídas a fatores genéticos, ambientais e socioeconômicos. Afeta predominantemente mulheres em idade fértil. Estudos demonstraram que a prevalência dele é maior em populações negras e asiáticas, enquanto populações de etnia branca apresentam taxas menores.

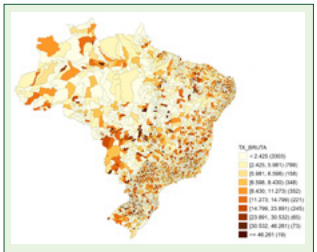
Objetivo: Analisar a mortalidade por Lúpus Eritematoso Sistêmico (LES) no Brasil entre 2011 e 2021, levando em consideração sua distribuição têmporo-espacial.

Método: Desenvolveu-se sob o escopo epidemiológico descritivo e baseado em dados extraídos do Sistema de Informação sobre Mortalidade (SIM/DATASUS). Foram analisadas variáveis como sexo, faixa etária, etnia, estado civil, escolaridade, local do óbito e residência. A tendência temporal foi avaliada por regressão joinpoint, e a distribuição espacial, por índices de Moran Global e local.

Resultados: Entre 2011 e 2021, foram registrados 11.195 óbitos por LES, dado este que representa taxa de mortalidade média de 0,49/100 mil habitantes, com a predominância de mulheres (89%) e maior incidência em indivíduos de 40-49 anos de idade (19,46%). As maiores taxas foram nas regiões Sul, Sudeste e Centro-Oeste. A análise demonstrou autocorrelação positiva e aglomerados significativos nas regiões mencionadas.

Conclusão: Existem disparidades regionais e estratégias específicas para ampliar o acesso ao diagnóstico precoce e tratamento adequado são necessárias, especialmente nas regiões vulneráveis.

PALAVRAS-CHAVE: Lúpus eritematoso sistêmico. Mortalidade. Epidemiologia. Distribuição espacial. Brasil.



Crude mortality rate from lupus in Brazil (2011-2021)

Central Message

SLE has a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. It presents with a wide range of signs and symptoms. Clinically, patients may experience dermatologic manifestations such as rashes and photosensitivity, as well as arthritis or arthralgia. Systemic symptoms include fatigue, fever, and weight loss. It is a complex disease that presents diagnostic challenges due to its wide range of clinical manifestations and overlaps with other conditions.

Perspective

SLE predominantly affects women of childbearing age, with a ratio of approximately 9:1 to men. Studies have shown that its prevalence is higher in black and Asian populations, while white populations have lower rates. Differences in prevalence also reflect the influence of environmental factors and access to medical care, impacting the diagnosis and management of the disease.

[1] *Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting multiple body systems, characterized by clinical heterogeneity and significant potential morbidity and mortality. Recent advances include new classification criteria from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), as well as new biomarkers and definitions of remission and low disease activity. The International Classification of Diseases (ICD) for SLE is M32 (disseminated lupus erythematosus) and L93 (lupus erythematosus). These developments are guiding new therapeutic strategies and disease management.[1]

It presents a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. SLE predominantly affects women of childbearing age, with a ratio of approximately 9:1 to men.[2] Studies have shown that its prevalence is higher in black and Asian populations, while white populations have lower rates. Differences in prevalence also reflect the influence of environmental factors and access to medical care, impacting the diagnosis and management of the disease.[3]

SLE is of multifactorial origin, whose etiology involves a complex combination of genetic, environmental, and hormonal factors. Genetic predisposition is evidenced by a higher incidence in individuals with a family history. Environmental factors such as exposure to ultraviolet light also play a significant role in development. In addition, because it predominantly affects women, SLE suggests a hormonal component, with estrogens potentially modulating the immune response and contributing to increased risk in women of reproductive age.[4]

It presents with a wide range of signs and symptoms. Clinically, patients may experience dermatologic manifestations such as rashes and photosensitivity, as well as arthritis or arthralgia. Systemic symptoms include fatigue, fever, and weight loss. In more severe cases, there may be renal involvement (lupus nephritis), neurological manifestations (such as seizures and psychosis), and hematological complications, such as anemia. The clinical presentation is highly variable and may overlap with other conditions, complicating the diagnosis.[5]

In addition, it is a complex disease that presents diagnostic challenges due to its wide range of clinical manifestations and overlaps with other conditions. Its classification follows the 2019 ACR/EULAR criteria that consider a combination of clinical and laboratory findings, such as skin rashes, arthritis, kidney dysfunction, the presence of specific autoantibodies, among others, to which different weights are assigned. It is necessary to present at least 10 points for classification as SLE.[1]

Treatment aims to achieve disease remission or a state of low activity, improving quality of life. Recent advances include the use of new biological therapies, such as belimumab and anifrolumab, monoclonal antibodies that have shown efficacy in clinical trials, mainly by generating a decrease in corticosteroid consumption. The management of SLE also involves the use of traditional immunomodulatory agents, such as hydroxychloroquine, which has a favorable safety profile and can reduce the risk of thrombosis and reduce disease outbreaks, and corticosteroids, which have a very rapid effect on reducing disease activity, but generate significant side effects with prolonged use, to control inflammation and prevent organ damage.[6] The new therapeutic options are expanding the personalized treatment strategies for him.[7]

Lupus nephritis is one of the most serious and common manifestations; cardiovascular manifestations, such as pericarditis, myocarditis, and increased risk of atherosclerosis, which can result in myocardial infarction or stroke; pulmonary events, involving pleuritis, lupus pneumonitis, and pulmonary hypertension; oral problems; risks during pregnancy, and neurological and psychiatric impacts, including depression, anxiety, seizures, psychosis, Peripheral neuropathy and other neurological disorders are manifestations that affect the quality of life and survival of these patients.[8]

The objective of this study was to analyze SLE mortality in Brazil between 2011 and 2021 taking into account its temporospatial distribution.

METHOD

The data used to compose the survey are available on the internet for free consultation. Thus, there is no possibility of causing physical or moral damage from the perspective of the individual and the collectivity. Therefore, the present study did not need to be approved by an ethics committee.

This is an epidemiological study of secondary data analysis in health with a focus on temporospatial analysis. Data on cases of death were obtained from the Mortality Information System (SIM) of the Department of Informatics of the Unified Health System (DATASUS) of the Ministry of Health (MS), via Tabnet, through the place of death and place of occurrence. The population data used as denominator for the purpose of calculating mortality rates come from DATASUS.

Statistical analysis

For the analysis of the SLE mortality trend in Brazil, the period from 2011 to 2021 was selected, in order to better understand the outcome in this historical series. For the population, individuals were selected according to the data available in DATASUS for adults who were registered with deaths from lupus. The following variables were considered for the analysis: sex, age group, color/race, marital status, education, deaths by residence, year of death, place of death, and place of occurrence.

For the underlying cause of these deaths, ICD

L93 AND M32 of chapter IX of the International Classification of Diseases (ICD-10) was adopted. Information on the epidemiological profile and frequency of deaths were tabulated using the Microsoft Excel for Microsoft 365 MSO software. Thus, the nominal variables were analyzed by means of the absolute frequency and percentage of occurrence in the study population. Annual mortality was calculated using the total number of deaths in the state as the numerator and the population of the state in that year as the denominator, taking 100 thousand inhabitants as a reference for this coefficient. The mortality of each municipality was calculated based on standardization by the indirect method, using the average number of cases in the period, divided by the average population between 2001 and 2021, multiplied by 100 thousand inhabitants.

Initially, the temporal trend of SLE mortality was analyzed (Figure 1). Thus, the Annual Percent Change (APC) of the studied trend was evaluated, with a 95% confidence interval (95%CI) and statistical significance $p < 0.05$. The temporal pattern analysis was performed using the Joinpoint Regression Program 5.0.2 2023 software. Next, the spatial distribution of mortality in Brazil was analyzed. Initially, the mean mortality of SLE in the municipalities of Brazil was created (Figure 1). As there is a probability of identifying a heterogeneous pattern between municipalities, the municipal values were smoothed by the local empirical Bayesian method. This method weights the value of the municipal tax in relation to the municipalities that border it by means of a spatial proximity matrix. The spatial analyses were carried out in the GeoDa 1.22.0.4 2023 program, as well as the creation of the thematic maps.

For the identification of spatial clusters, the Global Moran and Local Index was used, which measures the correlation between first-order neighbors and was used to test the hypothesis of spatial dependence. The method identifies spatial autocorrelation and can vary between -1 and +1, in which values close to zero indicate the absence of spatial dependence, considering a significant $p < 0.05$. If the hypothesis of dependence is accepted, the Local Index of Spatial Association (LISA) is used to observe the presence of spatial aggregates, given $p < 0.05$. The results of the analyses described above were demonstrated by Moran Map and LISA Map (Figures 4 and 5). The Moran Map graphically demonstrates the degree of similarity between neighbors, being represented by 4 quadrants: 1) high-high (upper right quadrant): corresponds to municipalities that have high mortality rates and are close to municipalities that also have high mortality rates; 2) low-low (lower left quadrant): corresponds to municipalities that have low mortality rates and are close to others that also have low mortality rates; 3) high-low (lower right quadrant): correspond to municipalities that have high mortality rates and are close to municipalities that have low mortality rates; 4) low-high (upper left quadrant): corresponds to municipalities that have low mortality rates and are close to municipalities that have high mortality rates.

RESULT

As shown in Table, the analysis of the profile of SLE victims in the period from 2011 to 2021 revealed a higher incidence among individuals aged between 40-49 years, representing 19.46% of all cases. This percentage is close to that observed in the 20-29 age group, which concentrated 17.74% of the cases. In addition, a significant predominance of females was found, which corresponded to 89%. Regarding the ethnic distribution, most of the affected individuals belonged to the white ethnicity, representing 43.43% of the total. Regarding marital status, 45.06% were single, indicating a relevant prevalence within this specific group.

Regarding educational level, it was observed that most deaths occurred among individuals with 8-11 years of complete schooling, corresponding to 32.21% of the cases. Secondarily, in 21.13%, the educational level was 4-7 years. It is also noteworthy that most deaths due to SLE occurred in a hospital environment, representing 87.23% of the cases.

From 2011 to 2021, 11195 deaths from SLE were recorded in Brazil. The average mortality in this period was (0.49/100 thousand inhabitants), with the lowest mortality recorded in 2013 (0.46/100 thousand inhabitants) and the highest in 2019 (0.53/100 thousand inhabitants). The analysis of the temporal pattern of mortality in the period from 2011 to 2021 showed a significant average increase of 0.74% per year in the mortality rate per 100 thousand inhabitants ($p < 0.05$, Figure 1). Pearson›s correlation coefficient was 0.7955125531 with $p =/< 0.05$, indicating that there is a significant linear correlation and, directly proportional over the years, there was a significant increase in the mortality rate.

Through the spatial analysis, which can be seen in Figure 2, there is dispersion of mortality, with a focus of incidence in the South, Southeast and Midwest regions. Jacutinga (83/100 thousand inhabitants), Herdeiras (66.2/100 thousand inhabitants), Tupanci do Sul (65.9/100 thousand inhabitants) and Coqueiro Baixo (65.7/100 thousand inhabitants) were the 4 municipalities that had the highest number of SLE mortality in Brazil between 2011 and 2021, all of these municipalities located in Rio Grande do Sul.

With the smoothing of the crude rates by the local empirical Bayesian method (Figure 3), it is possible to observe a more apparent spatial pattern, with aggregation of municipalities with higher mortality rates in the South, Southeast and Midwest regions. Spatial autocorrelation was identified using the Global Moran›s Index ($I = 0.482$; $p = 0.01$), demonstrating evidence of positive autocorrelation.

The application of the local Moran›s Index allowed the identification of spatial clusters with both high and low values (Figure 4). The pattern of high values (high-high) was predominant in the north, central-west, and

south, as well as small clusters in the southeast and northeast. The low-low pattern was identified in the north, northeast, and south regions. Figure 4 illustrates the degree of statistical significance of the clusters, as indicated by the LISA Map.

TABLE — Epidemiological profile of individuals who died from SLE in Brazil between 2011-2021

Education (years)	n	%
No	431	3.85%
1 to 3	1594	14.24%
4 to 7	2365	21.13%
8 to 11	3606	32.21%
12 or more	1233	11.01%
Silenced	1996	17.56%
Marital status	**n**	**%**
Single	5044	45.06
Married	3386	30.25
Widowed	731	6.53
Separate	733	6.55
Other	502	4.48
Silenced	799	7.14
Place of occurrence	**n**	**%**
Hospital	9.765	87.23
Other		
Health center	489	4.37%
Domicile	832	7.43%
Public road	24	0.21%
Other	79	0.71%
Ignored	6	0.05%
Age group (years)	**n**	**%**
(-) 1	4	0.04%
1 to 4	11	0.10%
5 to 9	44	0.39%
10 to 14	268	2.39%
15 to 19	698	6.23%
20 to 29	1986	17.74%
30 to 39	224	2.00%
40 to 49	2179	19.46%
50 to 59	1709	15.27%
60 to 69	1197	10.69%
70 to 79	588	5.25%
(+) 80	271	2.42%
Sex	n	%
Male	1265	11%
Female	9930	89%
Color/Race	**n**	**%**
White	4862	43.43%
Black	1142	10.20%
Yellow	56	0.50%
Brown	4657	41.60%
indigenous	39	0.35%
Silenced	439	3.92%

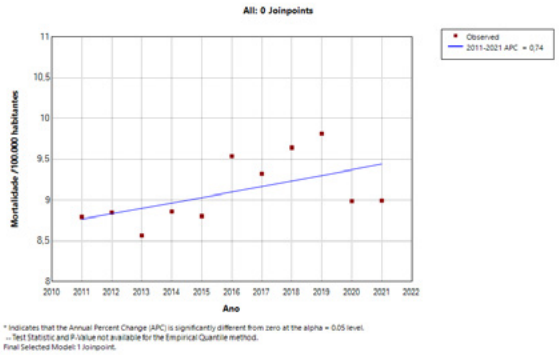

FIGURE 1 — Time pattern of SLE mortality in Brazil between 2011 and 2021.

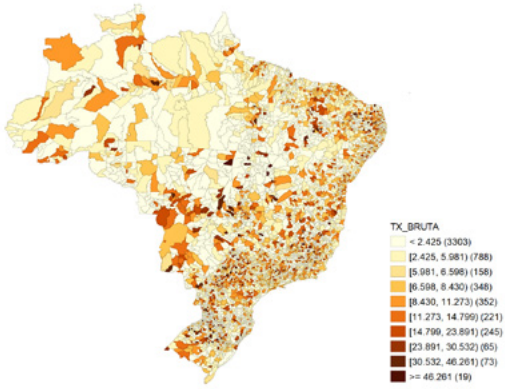

FIGURE 2 — Crude mortality rate from lupus in Brazil (2011-2021)

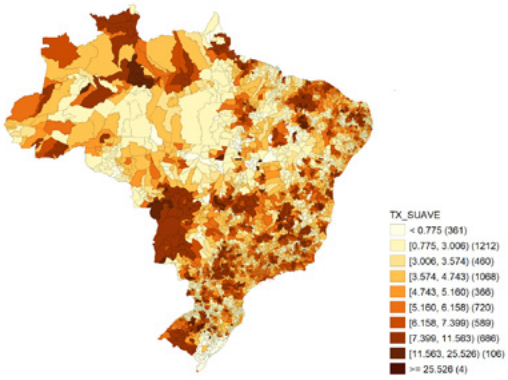

FIGURE 3 — Mortality rate smoothed by the local empirical Bayesian method for lupus in Brazil (2011-2021).

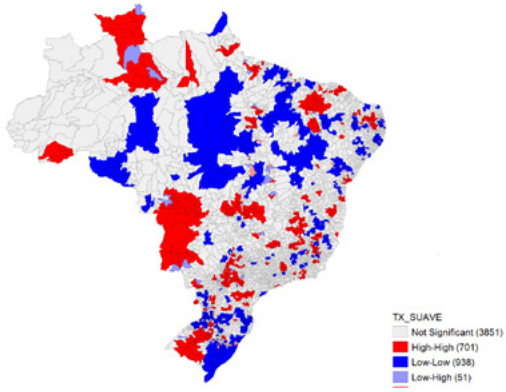

FIGURE 4 — Spatial clusters of lupus mortality in Brazil (2011 to 2021)

DISCUSSION

The temporal and spatial analysis of SLE mortality in Brazil between 2011 and 2021 reveals a complex mosaic of determinants and public health challenges. Its incidence reflects a higher prevalence in the South, Southeast, and Midwest regions of the country, where cities such as Jacutinga, Herdeiras, Tupanci do Sul, and Coqueiro Baixo are the most affected by mortality. Such a spatial pattern is indicative of variations in living conditions, health habits, and access to medical services. Regional studies in Brazil have already shown how health disparities can be rooted in socioeconomic differences, shaping the risk of autoimmune diseases and the responsiveness of the health system. The Southeast region, on the other hand, stands out as the most affected by the disease due to greater access to health and because of its higher population density, which is reflected in a higher prevalence of diagnoses.[9] In other regions such as the South and Midwest there are no conclusive studies on why they have the highest mortality.

Total mortality from SLE requires careful analysis, given the relevance of autoimmune diseases in Brazil. Comparing SLE mortality rates with other diseases is critical to prioritizing health interventions and policies. SLE often presents with serious complications such as lupus nephritis, thromboembolic events, cardiovascular involvement, and infective endocarditis, reflecting the significant impact of autoimmune diseases as a growing public health challenge.[10]

This reality does not occur in a vacuum, but rather in a context where social and economic factors play crucial roles. Autoimmune diseases, such as SLE, are often associated with inequalities in access to early diagnosis and appropriate management. The interaction between genetic, environmental, and social factors can influence both the manifestation and progression of these conditions. Individuals in situations of socioeconomic vulnerability are more likely to have delays in diagnosis and greater exposure to triggering factors, such as infections and chronic stress, aggravating clinical outcomes and disease burden. Regarding access to health services, there is a greater concentration of resources and better results in the diagnosis and management of SLE in the more developed regions of the country. This fact raises questions about equity in access to specialized care and high-complexity treatments throughout Brazil, especially in less financially favored regions.[11]

The demographic characteristics of those affected by SLE point to a predominance of women (89%) aged between 40 and 49 years (19.46%); this is due to hormonal issues, which are much more present in women, thus favoring the emergence of autoimmune disease.[12] In contrast to what was stated by Luquetti et al.[3] regarding the prevalent ethnicity in the cases (blacks and Asians), the analysis of the DATASUS platform revealed a higher prevalence in the white population (43.43%). However, Brazil is a country characterized by a high rate of racial miscegenation, in which the phenotype does not always correspond to the genetic load, justifying the need for local studies that reflect this Brazilian peculiarity.

The mortality and morbidity associated with SLE in Brazil are of concern. The lack of specialized centers, late diagnosis, and difficulty in managing the complications of the disease may be contributing to these statistics. This reinforces the need to strengthen local health systems, ensuring access to rheumatologists and specialized treatments for the population.[13] The management of SLE, which ranges from immunomodulatory and immunosuppressive therapies in general to specific treatment of certain forms of manifestation, such as lupus nephritis or cardiovascular complications, can be a costly and complex process. Education about the disease and its treatment are essential to control its progression and avoid serious complications. However, adherence to treatment can be hampered by factors such as the high cost of medications, lack of access to diagnostic tests, and difficulty in finding specialists.[14]

Finally, the intersection between these factors demonstrates the intricate network of influences that shapes the clinical outcomes of SLE in Brazil. The unequal distribution of morbidity and mortality associated with it in the country reflects the disparity in the distribution of health resources and variations in demographic and genetic profiles. Intervention programs should therefore be multifaceted, ranging from training professionals for early diagnosis to expanding access to specialized treatments and raising awareness of the disease among the population. The central question is not limited to understanding the causes of the high burden of SLE, but also how to intervene. The creation of more robust health care systems, education campaigns aimed at early recognition of symptoms and healthy lifestyles, and policies that reduce economic barriers to treatment may be the key to improving the quality of life and clinical outcomes of patients with SLE in Brazil.[15]

The secondary data used in this research are a limiting factor, which can generate biases, such as underreporting, lack of information, and inconsistencies in filling in the causes of death. The results found for the general population may not be reflected at the individual level, due to the effects of data aggregation, characteristic of the ecological fallacy. It is noteworthy that the mortality analysis was based only on the underlying cause of death and not on multiple causes. Thus, there may be an underestimation of deaths from SLE.

CONCLUSION

The temporospatial analysis allowed the identification of the municipalities in the state with high mortality from SLE. In this way, the need for strategies that are in line with the reality and particularities of these places is exposed. This research serves as a scientific subsidy for the organization and planning

of actions aimed at improving health care in the most vulnerable places, especially Primary Health Care (PHC), aiming to ensure access and care for this population and consequently promote health and prevent SLE diseases.

Authors' contributions

Thelma Larocca Skare – Conceptualization, writing, project management
Vitor Hugo Mariano - Formal analysis, methodology
Davi Canteri Mendelski – Software
Fernanda Ritt de Souza – Validation, conceptualization
Isadora Candotti Sperotto – Validation, methodology
Leonardo Moreira Dias – Research, validation
Pedro Canteri Mendelski – Methodology
Tailla Cristina de Oliveira – Research, writing

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Effects of creatine supplementation on postoperative wound healing: mechanisms and evidence

Efeitos da suplementação de creatina na cicatrização pós-operatória: mecanismos e evidências

Gabriel Mathias Vitoreti[1], Homero Grein Neto[1], Mariana Tiboni Nacamura[1], Luiz Eduardo Latorre Guimarães[1]

ABSTRACT

Introduction: Tissue healing and repair processes are complex and require adequate energy and nutritional supply to occur efficiently. Creatine, a nitrogenous compound widely known for its role in muscle energy metabolism and its use as an ergogenic supplement, has emerged as a potential therapeutic agent in several conditions beyond sports.

Objective: This narrative review aimed to synthesize the main information on the influence of creatine supplementation on healing and postoperative recovery.

Method: A narrative search was conducted in the PubMed, Scopus, Web of Science, and LILACS databases, using the DeCS/MeSH descriptors: Creatine, Wound Healing, Postoperative period, Tissue Repair, and Dietary supplements. Original and review articles published since 2000, in Portuguese and English, were included.

Result: Seventeen articles were selected.

Conclusion: Creatine has robust theoretical potential to aid healing and postoperative recovery, inducing favorable cellular responses and attenuating catabolism. Understanding the biological mechanisms that mediate the effects of creatine on tissue repair is essential for the development of effective nutritional intervention strategies in the perioperative period.

KEYWORDS: Creatine. Wound healing. Postoperative period. Dietary. Supplements.

Central Message

Creatine, widely known for its role in muscle energy metabolism and its use as an ergogenic supplement, has emerged as a potential therapeutic agent in several conditions, in addition to sports. Evidence indicates that metabolic stress induced by surgical procedures increases the demand for ATP, and creatine, through the phosphocreatine system, acts in the rapid regeneration of this compound.

Perspective

The mechanisms by which creatine supplementation may positively affect postoperative recovery include optimizing energy metabolism, modulating inflammation and oxidative stress, and influencing protein synthesis and cellular hydration. Surgery imposes metabolic stress that can deplete cellular energy reserves, leading to impairment of cellular function and repair processes.

RESUMO

Introdução: Os processos de cicatrização e reparo tecidual são complexos e demandam suprimento energético e nutricional adequado para ocorrerem de forma eficiente. A creatina, um composto nitrogenado amplamente conhecido por seu papel no metabolismo energético muscular e seu uso como suplemento ergogênico, tem emergido como potencial agente terapêutico em diversas condições além do esporte.

Objetivo: Revisão narrativa a fim de sintetizar as principais informações sobre a influência da suplementação de creatina nos eventos de cicatrização e recuperação pós-operatória.

Método: Realizou-se busca nas bases de dados PubMed, Scopus, Web of Science e LILACS, utilizando os descritores DeCS/MeSH: Creatine, Wound healing, Postoperative period, Tissue repair e Dietary supplements. Foram incluídos artigos originais e de revisão publicados a partir de 2000, em português e inglês.

Resultado: Foram selecionados 17 artigos.

Conclusão: A creatina possui potencial teórico robusto para auxiliar na cicatrização e recuperação pós-operatória, induzindo respostas celulares favoráveis e atenuando o catabolismo. A compreensão dos mecanismos biológicos que mediam os efeitos da creatina sobre o reparo tecidual é essencial para o desenvolvimento de estratégias de intervenção nutricional eficazes no perioperatório.

PALAVRAS-CHAVE: Creatina. Cicatrização. Período pós-operatório. Dieta. Suplementos.

Supplementary material for the articles included in this publication[1-17]

[1]*Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brasil.*

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INTRODUCTION

Adequate recovery in the postoperative period is essential for the prognosis and quality of life of patients, and is a constant challenge in clinical practice.[1] The processes of healing and tissue repair are complex and require adequate energy and nutritional supply to occur efficiently.[2] Creatine, a nitrogenous compound widely known for its role in muscle energy metabolism and its use as an ergogenic supplement.[3] has emerged as a potential therapeutic agent in several conditions beyond sports. Evidence indicates that metabolic stress induced by surgical procedures increases the demand for ATP, and creatine, through the phosphocreatine system, acts in the rapid regeneration of this compound.[4]

Surgical interventions often lead to a catabolic state, with loss of muscle mass and impaired function, in addition to a systemic inflammatory response that, if exacerbated or prolonged, can impair healing.[5] The search for nutritional strategies that can modulate these responses and optimize recovery is, therefore, of great relevance. The relationship between creatine supplementation and the optimization of postoperative recovery is multifaceted, impacting the body through several biological mechanisms.[6] It is known that, in addition to energy supply, creatine can influence cellular hydration, protein synthesis, inflammatory response, and oxidative stress, all of which are crucial processes for tissue repair and wound healing.[7,8]

This review aimed to synthesize and critically analyze the available scientific evidence on the potential effects of creatine supplementation on wound healing and tissue recovery in the postoperative period.

METHOD

This is a narrative review of the literature, carried out in the PubMed, Scopus, Web of Science and LILACS databases. The search used the following keywords (DeCS/MeSH) and their correspondents: "Creatine", "Wound Healing", "Postoperative Period", "Tissue Repair", and "Dietary Supplements". The inclusion criteria included original articles (clinical trials, observational studies, studies in animal models) and review articles (systematic, meta-analyses) published from the year 2000 to December 2023, in Portuguese and English, available in full text. Articles that did not address the topic of creatine supplementation in the context of healing or post-trauma/surgery recovery, or that focused exclusively on sports performance unrelated to injury, were excluded. The selection process followed the PRISMA[9] guidelines for identification, screening, and inclusion of studies. In total, 17 articles were selected for this review (See table in supplemental material at the end).

DISCUSSION

The mechanisms by which creatine supplementation may positively affect postoperative recovery include optimizing energy metabolism, modulating inflammation and oxidative stress, and influencing protein synthesis and cellular hydration. Surgery imposes metabolic stress that can deplete cellular energy reserves, leading to impairment of cellular function and repair processes.[1]

Biochemical and physiological mechanisms of creatine in tissue repair

The fundamental mechanisms that contribute to the potential benefits of creatine in the postoperative period are associated with several pathways. These include the primary role in the ATP-phosphocreatine system for rapid energy resynthesis in tissues with high demand, the attenuation of protein catabolism often observed after surgical procedures[9], the possible modulation of the inflammatory response[10] and the antioxidant capacity.[11] In terms of direct impact, systemic inflammation and exacerbated oxidative stress in the postoperative period can delay healing. Creatine has been shown in some contexts to reduce inflammatory markers such as TNF-α and IL-6 and protect against oxidative damage.[10,11]

Preservation of muscle mass and functional recovery

The preservation of muscle mass in the postoperative period is crucial, especially in patients undergoing major operations or requiring immobilization. Hespel et al.[1] demonstrated that creatine supplementation attenuated muscle atrophy and facilitated rehabilitation after immobilization in humans. This effect is attributed both to the improvement of energy availability to muscle fibers and to possible direct effects on the expression of myogenic factors. The loss of muscle mass not only affects mobility, but also reduces the reserve of amino acids available for the synthesis of new proteins necessary for healing. Other mechanisms related to creatine supplementation include cell volumization. Creatine attracts water into the cell, which can act as an anabolic signal, stimulating protein synthesis and inhibiting proteolysis.[12]

Creatine in the healing of specific tissues

Studies indicate that creatine supplementation may be particularly beneficial in tissues with a high metabolic rate or in regeneration. Antolic et al.[13] demonstrated in rats that creatine supplementation accelerated bone healing. Although direct transposition to humans and other tissues requires further studies, the principle of providing additional energy substrate for the cells involved in repair (osteoblasts, fibroblasts, keratinocytes) is promising. In the context of skin wound healing, direct evidence of oral creatine supplementation is still limited. However, fibroblasts, central cells in collagen production and extracellular matrix, are metabolically active and could benefit from increased ATP availability. The topical application of creatine has been explored in cosmeceuticals, suggesting improvement in skin bioenergetics[2], but oral supplementation for surgical wound healing requires specific investigation.

Dosage and safety

Considering safety, creatine supplementation is generally well tolerated in healthy subjects at recommended doses (saturation phase of ~20g/day for 5-7 days, followed by maintenance of 3-5 g/day).[3,7] However, in surgical patients, especially those with

compromised pre-existing renal function or at risk of acute kidney injury, supplementation should be considered with caution and under monitoring.[14]

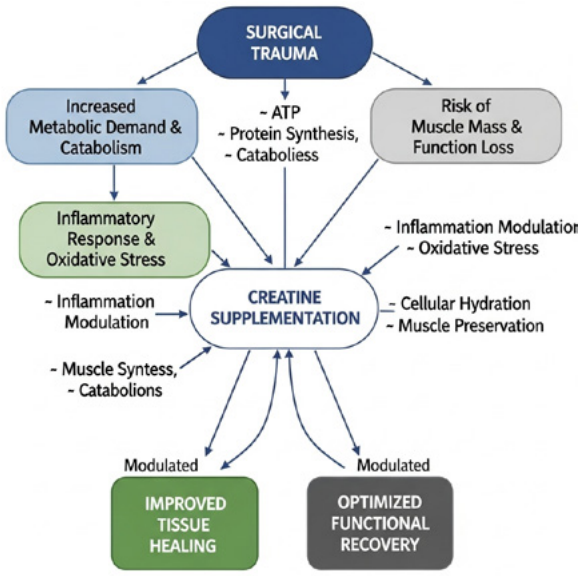

FIGURE — Potential effect of creatine supplementation on postoperative recovery.

CONCLUSION

Creatine supplementation has robust theoretical potential and some indirect evidence of benefit for postoperative recovery, particularly in attenuating muscle loss and improving function. Its mechanisms of action, centered on the optimization of cellular bioenergetics and possible anabolic and anti-inflammatory effects, are congruent with the needs of the tissue repair process. However, direct evidence on the impact of creatine on the healing of specific surgical wounds in humans is currently limited. Future research should prioritize well-controlled randomized controlled trials to elucidate the efficacy, safety, and optimal protocols of creatine supplementation in this context. If proven effective, creatine could become a valuable adjuvant tool to improve surgical outcomes.

Authors' contributions

Gabriel Mathias Vitoreti – Conceptualization, Supervision
Homero Grein Neto – Formal Analysis, Revision
Mariana Tiboni Nacamura – Investigation, Writing (revision and editing)
Luiz Eduardo Latorre Guimarães – Methodology, Project Management

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Evaluation of the clinical impact of smart oximeters in patients with chronic obstructive pulmonary disease (COPD)

Avaliação do impacto clínico de oxímetros inteligentes em pacientes com doença pulmonar obstrutiva crônica (DPOC)

Gabriel Mathias Vitoreti[1], Homero Grein Neto[1], Mariana Tiboni Nacamura[1], Luiz Eduardo Latorre Guimarães[1]

ABSTRACT

Introduction: Chronic obstructive pulmonary disease is a global public health challenge, being one of the leading causes of morbidity and mortality worldwide. Its effective management is essential to improve quality of life and reduce the burden on healthcare systems.

Objective: To critically evaluate the scientific literature to determine the clinical impact of the use of smart oximeters in the control of this disease.

Method: Systematic review of PubMed and ScienceDirect databases, selecting original studies and reviews published since 2015, in Portuguese or English, with full text available, that investigated the use of smart oximeters in patients.

Result: 10 studies were included.

Conclusion: Monitoring with smart oximeters is associated with a reduction in the frequency of acute exacerbations, hospitalization rates, and improved quality of life. Thus, they demonstrate significant potential to improve disease management. However, future studies should address implementation challenges, such as data integration and technological accessibility.

KEYWORDS: Oximetry. Chronic obstructive pulmonary disease. COPD. Clinical effectiveness.

Central Message

Traditionally, continuous monitoring of oxygen saturation has occurred in clinical settings or by home visits, which may be limited in terms of frequency and access. With the advancement of technology and the popularization of wearable devices, smart oximeters emerge as tools capable of performing continuous measurements and transmitting data to health platforms, enabling remote and proactive monitoring.

Perspective

The implications of these findings suggest that the adoption of smart oximeters can transform COPD care, leading to more proactive management, reduced healthcare costs associated with exacerbations and hospitalizations, and substantial improvement in patient well-being and autonomy.

RESUMO

Introdução: A doença pulmonar obstrutiva crônica é desafio de saúde pública global, sendo uma das principais causas de morbidade e mortalidade em todo o mundo. Sua gestão eficaz é essencial para melhorar a qualidade de vida e reduzir a carga sobre os sistemas de saúde.

Objetivo: Avaliar criticamente a literatura científica para determinar o impacto clínico do uso de oxímetros inteligentes no controle dessa doença.

Método: Revisão sistemática nas bases PubMed e ScienceDirect selecionando estudos originais e revisões publicados a partir de 2015, em português ou inglês, com texto completo disponível, que investigaram o uso de oxímetros inteligentes nos pacientes.

Resultado: Foram incluídos 10 estudos.

Conclusão: O monitoramento com oxímetros inteligentes está associado à redução na frequência de exacerbações agudas, nas taxas de hospitalização e melhora na qualidade de vida. Assim, os eles demonstraram potencial significativo para melhorar o manejo da doença. Contudo estudos futuros devem abordar desafios de implementação, como a integração de dados e a acessibilidade tecnológica.

PALAVRAS-CHAVE: Oximetria. Doença pulmonar obstrutiva crônica. DPOC. Efetividade clínica.

[1]*Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global public health challenge, being one of the leading causes of morbidity and mortality worldwide. Characterized by persistent airflow limitation, usually progressive, it is associated with chronic inflammatory response of the airways and lung parenchyma to harmful particles or gases. Their effective management is essential to improve quality of life and reduce the burden on health systems. One of the pillars of this management is the continuous monitoring of oxygen saturation (SpO_2), a vital indicator of respiratory function that can early signal acute exacerbations.[1]

Traditionally, SpO_2 monitoring has taken place in clinical settings or by home visits, which can be limited in terms of frequency and access. With the advancement of technology and the popularization of wearable devices, smart oximeters emerge as tools capable of performing continuous measurements and transmitting data to health platforms, enabling remote and proactive monitoring. These devices represent a promising frontier in telemedicine, transforming the follow-up of patients with COPD. The incorporation of smart oximeters into the COPD routine is relevant because it provides real-time data, facilitating the early identification of clinical deteriorations and exacerbations. This can lead to rapid interventions, reducing hospitalizations, emergency room visits, and promoting self-management of the disease. In addition, continuous monitoring provides valuable information to adjust treatment plans and optimize oxygen therapy.[2-5]

The objective of this systematic review was to critically evaluate the scientific literature in order to determine the clinical impact of the use of smart oximeters in patients with COPD, investigating outcomes such as frequency of exacerbations, hospitalizations, quality of life, treatment adherence, and patient satisfaction, in order to support clinical decisions and future research.

METHOD

This systematic review was designed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The search was conducted in the PubMed (including Medline) and ScienceDirect databases. The strategy used controlled descriptors (DeCS/MeSH) and free terms, combined with Boolean operators (AND, OR). The descriptors included: "Smart oximeters" OR "Wearable oximeters" OR "Remote pulse oximetry"; "COPD" OR "Chronic obstructive pulmonary disease"; "Remote monitoring" OR "Telemonitoring" OR "Telemedicine"; "Clinical outcomes" OR "Hospitalization" OR "Exacerbation" OR "Quality of life" OR "Patient reported outcomes". The search string has been adapted for each base, maintaining the essence of the terms.

Eligibility criteria

Articles that met the following types of studies were included: originals (randomized clinical trials, cohorts, case-control, prospective observational) and systematic reviews. They followed the following PICO guidance:

- Population: Adult patients (>18 years) with a confirmed diagnosis of COPD.
- Intervention: Use of smart oximeters or remote pulse oximetry devices for
- home monitoring.
- Comparator: Usual care, absence of remote monitoring, or other forms of
- Monitoring.
- Outcome: Frequency of exacerbations, hospitalizations, emergency room visits, quality of life (assessed by validated instruments), treatment adherence, patient satisfaction, or healthcare costs.

The publication period should be from January 1st 2015 to May 2025. The accepted languages were Portuguese and English. It should be available as full text. Articles that did not address smart oximeters or COPD, studies focused only on technical aspects of the devices, letters to the editor, conference abstracts without full text, and duplicate publications were excluded.

The selection was carried out in stages: 1) identification: titles and abstracts imported into reference management software (Mendeley) for removal of duplicates; 2) screening: evaluation of titles and abstracts, applying the inclusion/exclusion criteria; 3) Eligibility: full texts; 4) inclusion: articles that met all criteria. The quality of randomized controlled trials was assessed using the Cochrane Risk of Bias tool; observational studies were assessed using the Newcastle-Ottawa Scale (NOS); discrepancies were resolved by consensus among 2 reviewers.

Statistical analysis

The data were synthesized narratively, grouped by outcome and characteristics of the intervention. When possible, a meta-analysis was performed using the DerSimonian and Laird random-effects model. Heterogeneity was assessed by the I^2 test (0–40% = insignificant; 30–60% = moderate; 50–90% = substantial; 75–100% = considerable) and by the Cochran Q test, where $p<0.10$ indicates significant heterogeneity. Results were presented with 95% confidence intervals (95% CI) and $p<0.05$ for significance. Sensitivity analyses were conducted when necessary.

RESULT

The search, carried out in May 2025, retrieved 1,237 articles (PubMed: 689; ScienceDirect: 548). After removing 412 duplicates, 825 articles were screened by title and abstract. Of these, 765 were excluded, leaving 60 for evaluation of the full text. After applying the criteria, 10 studies were included: 2 randomized controlled trials (RCTs), 3 observational/cohort studies, 2 systematic reviews, 2 guidelines/statements, and 1 opinion article, all published between 2015 and 2024. Methodological quality revealed a low to moderate risk of bias in RCTs. Observational studies have obtained good quality in the NOS scale.

TABLE — Preferred metadata of the review carried out[1-10]

Author (Year)	Title/Type	Goals	Conclusion/Relevance
Ambrosino et al. 2016[1]	Declaration (ERS)	Provide a statement on telemonitoring for ventilator-dependent patients.	Telemonitoring is feasible and effective for subgroups of patients, including COPD, improving adherence and allowing for early intervention.
Aranburu-Imatz et al. 2022[2]	Systematic Review	To evaluate nurse-led interventions in patients with COPD.	Telemonitoring interventions (including oximetry) reduce hospitalizations and improve quality of life.
GOLD 2024[3]	Global Guideline	Strategy for diagnosing, managing, and preventing COPD.	It defines the management of COPD, highlighting the importance of monitoring symptoms and exacerbations.
Hardinge et al. 2015[4]	Cohort Study	To evaluate a mobile health app for COPD self-management (including oximetry).	The app was associated with an improvement in quality of life (CAT) and increased patient confidence in self-management.
Ho et al. 2016[5]	Randomized Controlled Trial (RCT)	To determine the effectiveness of telemonitoring (including SpO_2) in COPD patients in Taiwan.	Telemonitoring significantly reduced emergency room visits and improved quality of life, with high satisfaction (90%).
McDowell et al. 2015[6]	Randomized Controlled Trial (RCT)	To evaluate the effectiveness of telemonitoring home care (SpO_2) in patients with COPD.	It found a 25% reduction in hospitalizations (RR: 0.75) in the telemonitoring group compared to usual care.
Pinnock & McKinstry 2016[7]	Paradigm/Opinion Article	Discuss the promise and challenges of digital technology in respiratory diseases.	Digital technology (including oximeters) has potential, but it requires a paradigm shift for effective integration.
Sanchez-Morillo et al. 2016[8]	Systematic Review	To review the use of predictive algorithms in home monitoring of COPD and asthma.	Algorithms that use data from monitors (such as oximeters) can effectively predict exacerbations.
Segrelles-Calvo et al. 2015[9]	Observational Study (PROMETE)	To evaluate a home telecare program (with oximetry) for severe COPD.	The program significantly reduced hospital readmissions at 12 months (30% fewer readmissions
Shah et al. 2017[10]	Observational Study	Identify and predict COPD exacerbations using a digital health system (including SpO_2).	Continuous digital monitoring of vital signs, including SpO_2, can identify physiological changes days before an exacerbation.

Frequency of acute exacerbations

Two studies focused specifically on the ability of digital systems to predict exacerbations. A systematic review on predictive algorithms concluded that models using household monitoring data (including oximetry) are effective in predicting these events.[8] Shah et al.[10] demonstrated that a digital health system monitoring SpO_2 was able to identify predictive physiological changes days before the onset of a patient-reported exacerbation.

Rate of hospitalizations and emergency room visits

Three primary studies and 1 systematic review reported reductions in hospitalisations or emergency room visits. McDowell et al.[6] in RCTs, found a 25% reduction in hospitalizations in the telemonitoring group (RR: 0.75). Segrelles-Calvo et al.[9] reported 30% fewer hospital readmissions at 12 months in patients with severe COPD using telecare. Ho et al.[5] also observed a significant reduction in emergency room visits. The review by Aranburu-Imatz et al.[2] corroborated that telemonitoring interventions are associated with lower hospitalization rates.

Health-related quality of life

Three studies assessed quality of life. Ho et al.[5] reported significant improvement in quality of life in the intervention group. Hardinge et al.[4] evaluating mobile health app with oximetry, also noticed improvements in the COPD Assessment Test (CAT) score. This was supported by the systematic review by Aranburu-Imatz et al.[2] that associated telecare with improvements in quality of life.

Treatment adherence and patient satisfaction

Satisfaction and adherence were high in studies that measured these outcomes. Ho et al.[5] reported 90% satisfaction with the telemonitoring system. Hardinge et al.[4] observed that patients felt more confident in self-management of the disease using mobile technology. A statement from the European Respiratory Society also highlighted that telemonitoring improves adherence.[1]

Challenges and barriers

Despite the benefits, barriers were identified. Pinnock & McKinstry argue that digital technology, while promising, requires a paradigm shift and better integration into health systems to avoid being just a "panacea."

DISCUSSION

The results of this systematic review indicate that smart oximeters significantly improve the management of COPD.

The ability to detect early decreases in SpO_2 and predict exacerbations was a central finding, with digital systems demonstrating the ability to identify physiological changes days before the event, allowing for rapid interventions.[8,10] The decrease in hospitalizations was a robust outcome, with studies reporting reductions of 25% to 30% in hospitalization rates or readmissions,[6,9] relieving pressure on health systems and reducing costs.[2,5] Improvement in quality of life (assessed by instruments such as the CAT) was also observed,[2,4,5] suggesting greater control and well-being for patients.

Early detection of exacerbations is critical, as these events increase morbidity and mortality. Remote monitoring promotes proactive care, in line with guidelines such as those in GOLD (2024).[3] The reduction in hospitalizations optimizes resources, while the improvement in quality of life and high satisfaction (reaching 90% in 1 study) reflect good acceptance of the devices by patients.

The implications of these findings suggest that the adoption of smart oximeters can transform COPD care, leading to more proactive management, reduction of healthcare costs associated with exacerbations and hospitalizations, and substantial improvement in patient well-being and autonomy.

However, limitations include technological barriers, such as internet access and digital proficiency, especially in the elderly. The integration of data in electronic medical records and data security require attention, as pointed out by studies on the implementation of new

digital technologies.[7]

Future studies should include larger RCTs, with prolonged follow-up, and cost-effectiveness analyses.

CONCLUSION

Smart oximeters have demonstrated significant potential to optimize COPD management by reducing exacerbations, hospitalizations, and improving quality of life. Overcoming technological barriers and standardizing protocols are essential for its large-scale adoption. Future research should focus on robust clinical trials and implementation strategies to maximize the clinical and economic benefits of this technology, aiming to better integrate these devices into clinical practice and health policies.

Authors' contributions

Gabriel Mathias Vitoreti: Conceptualization
Homero Grein Neto: Methodology
Mariana Tiboni Nacamura: Writing (original draft)
Luiz Eduardo Latorre Guimarães: Writing (proofreading and editing):

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Artificial intelligence in SUS radiology: current landscape, barriers, and integration strategies

Inteligência artificial na radiologia do SUS: panorama atual, barreiras e estratégias de integração

Luis Gustavo Machado Farias[1], Alan Cristian Cordeiro Siqueira[2], Fernanda Marcondes Ribas[2], Kammilly Fernanda Alves dos Santos[3]

ABSTRACT

Introduction: Artificial intelligence (AI) is emerging as a strategic tool for modernizing diagnostic radiology in the Brazilian Unified Health System (SUS), with the potential to improve efficiency, reduce diagnostic delays, and mitigate regional inequalities.

Objective: To critically analyze the available evidence on the use of AI in radiology in Brazil, identifying advances, limitations, and directions for its sustainable implementation.

Method: A narrative review of the literature published between 2018 and 2024 was conducted, including clinical guidelines, systematic reviews, and institutional reports on the direct use of AI, as well as secondary data from DATASUS.

Result: Significant growth in demand for imaging exams in the Unified Health System (SUS) was observed, contrasting with low levels of digitization and connectivity in public facilities. National reports point to gains in efficiency and diagnostic accuracy with the use of AI, although structural barriers, gaps in professional training, and regulatory challenges persist.

Conclusion: The progressive and evidence-driven incorporation of AI into radiology within the Unified Health System (SUS) can promote a structural reconfiguration of diagnostic care, providing that safety, equity, and ethical governance criteria are ensured.

KEYWORDS: Artificial intelligence. Radiology. Health systems. Technological innovation. Brazil.

RESUMO

Introdução: A inteligência artificial (IA) emerge como ferramenta estratégica para modernizar a radiologia diagnóstica no Sistema Único de Saúde, com potencial de aprimorar a eficiência, reduzir atrasos diagnósticos e mitigar desigualdades regionais.

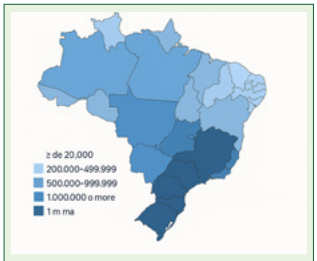
Objetivo: Analisar criticamente as evidências disponíveis sobre o uso da IA na radiologia brasileira, identificando avanços, limitações e direções para sua implementação sustentável.

Método: Realizou-se revisão narrativa da literatura publicada entre 2018 e 2024, incluindo diretrizes clínicas, revisões sistemáticas e relatos institucionais de uso direto de inteligência artificial, além de dados secundários provenientes do DATASUS.

Resultado: Observou-se crescimento expressivo na demanda por exames de imagem no Sistema Único de Saúde, contrastando com baixos níveis de digitalização e conectividade nas unidades públicas. Relatos nacionais apontam ganhos em eficiência e precisão diagnóstica com o uso de inteligência artificial, embora persistam barreiras estruturais, lacunas na formação profissional e desafios regulatórios.

Conclusão: A incorporação progressiva e orientada por evidências da IA na radiologia do Sistema Único de Saúde pode promover reconfiguração estrutural do cuidado diagnóstico, desde que assegurados critérios de segurança, equidade e governança ética.

PALAVRAS-CHAVE: Inteligência artificial. Radiologia. Sistemas de saúde. Inovação tecnológica. Brasil.



SUS imaging exams in 2023

Central Message

Artificial intelligence (AI) has been consolidated as an emerging technology of high complexity in Brazilian radiology, with applications associated with the reduction of morbidity and mortality, optimization of diagnostic flows, and mitigation of operational overload. Its clinical potential stands out especially in populations that are highly dependent on the public imaging network, such as cancer patients, patients with respiratory diseases, and trauma victims. Thus, AI should be seen and understood as a strong collaborator in medical care.

Perspective

In international comparison, although high-income countries have greater technological maturity, the implementation of AI in public health systems in middle-income countries, such as Brazil, still faces structural, regulatory, and formative barriers. In this context, the precise characterization of demand and installed infrastructure is essential to guide public policies, prioritize technological investments, and structure research agendas focused on the national reality.

[1]Faculdade Evangélica Mackenzie do Paraná, Curitiba, Paraná, Brazil;
[2]Mackenzie Evangelical University Hospital of Curitiba, Curitiba, Paraná, Brazil;
[3]Faculdades Pequeno Príncipe, Curitiba, Paraná, Brazil.

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INTRODUCTION

Artificial intelligence (AI) has been consolidated as an emerging technology of high complexity in Brazilian radiology, with applications associated with the reduction of morbidity and mortality, optimization of diagnostic flows, and mitigation of operational overload in the Unified Health System (SUS). Its clinical potential stands out especially in populations that are highly dependent on the public imaging network, such as cancer patients, patients with respiratory diseases, and trauma victims.[1]

The continuous growth in the demand for tests, combined with the pressure for care efficiency, favored the adoption of automated approaches for screening, early detection, and risk stratification, with algorithmic support.[1,2] In recent decades, technical advances have consolidated the feasibility of machine learning applied to medical imaging, highlighting the role of standardized structured data and operational gains in various stages of the diagnostic chain. These elements have supported recommendations from scientific societies and regulatory bodies, such as the Ministry of Health, the Federal Council of Medicine, the World Health Organization, and initiatives of the Brazilian AI Strategy (EBIA).[3]

Despite conceptual and technological advances, important barriers to the practical implementation of AI in the SUS persist — including insufficient infrastructure, absence of specific regulations, and lack of continuous technical training.[4] The low digitization and connectivity of public imaging services, evidenced by official data2, limits the integration of algorithms and compromises the clinical applicability of the available solutions.

This article presents a critical review of the literature on the use of AI in Brazilian radiology, focusing on regional inequalities, installed technological capacity, care impact, and the construction of regulatory frameworks. The analysis seeks to contextualize the current state of scientific evidence, identify areas of uncertainty, and discuss implications for clinical practice, elaboration of guidelines, and definition of priorities in applied research.[5]

METHOD

This review was conducted based on a structured literature search in the PubMed, Crossref (used as an alternative to Embase), Cochrane Library, and LILACS databases, covering publications indexed between 2018 and 2024. The search strategy combined the descriptors "Artificial Intelligence", "Radiology" and "Brazil", selected from the controlled vocabularies MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors), associated by Boolean operators (AND/OR), with the objective of maximizing sensitivity and specificity. Specific strategies were adapted according to the syntax of each database.

Randomized clinical trials, meta-analyses, systematic reviews, clinical guidelines issued by recognized scientific societies, as well as observational studies with robust design and clinical applicability, including institutional experiences documented in the context of the SUS, were included. The inclusion criteria included studies published in English or Portuguese, with access to the full text and direct relevance to the application and integration of AI in Brazilian radiology.

Isolated case reports, editorials, duplicate publications, non-systematic narrative reviews, and articles without direct clinical or structural focus were excluded. Study selection was performed independently by 2 reviewers with medical training, with disagreements resolved by consensus. The analysis prioritized evidence of high methodological quality classified according to the GRADE system, whenever available.

The objective was to gather and synthesize recent and relevant recommendations and findings on the adoption of AI in Brazilian radiology, offering critical subsidies to clinical practice, formulation of public policies and strengthening of evidence-based diagnostic infrastructure. This study did not involve experimentation on human beings, nor primary data collection. As this is a literature review with exclusive use of secondary data in the public domain, it is exempt from consideration by the Research Ethics Committee, according to CNS Resolution No. 510/2016.

DISCUSSION

Distribution and demand for imaging tests

The demand for imaging exams in the SUS varies significantly according to the region, socioeconomic profile, and level of urbanization, reflecting inequalities in access, asymmetric distribution of equipment, and digital connectivity, in addition to the availability of qualified professionals and diagnostic support technologies.[6]

In 2023, according to DATASUS data, more than 28 million outpatient imaging exams were performed in Brazil, with a predominance of ultrasounds (19.[3] million), CT scans (3.[1] million) and magnetic resonances (957 thousand).[7] Production is concentrated in states such as São Paulo, Minas Gerais and Rio de Janeiro, while the North and Northeast regions have lower per capita coverage (Figure 1).

Population studies point to a growing trend in the request for highly complex tests, especially among the elderly, cancer patients, and trauma victims, driven by factors such as population aging, expansion of screening programs, and appreciation of early diagnosis.[8] This regional disparity is also evidenced in the absolute volume of tests performed in the SUS (Figure 2).

According to the National Registry of Health Establishments (CNES), only 32.5% of public units with imaging services have computed tomography or magnetic resonance imaging, and less than 24% have integration with archiving and communication systems (PACS/RIS).[2] This technological limitation compromises the feasibility of applying artificial intelligence-based solutions, which require digitized, standardized, and interoperable data.

In international comparison, although high-income countries have greater technological maturity, the implementation of AI in public health systems in middle-

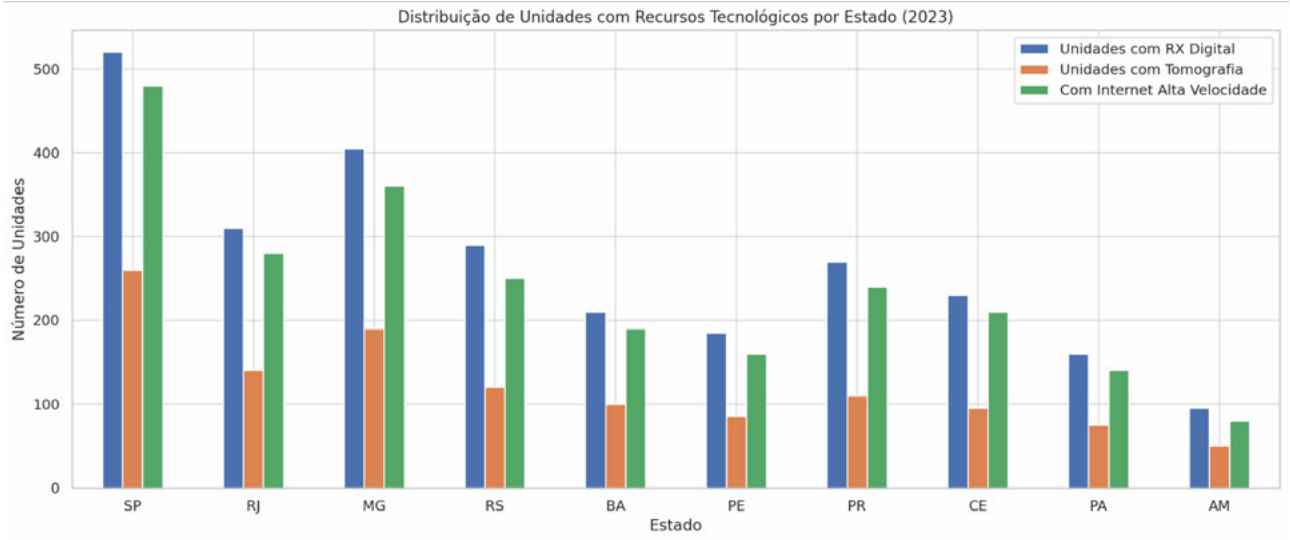

FIGURE 1— Distribution of units with technological resources by Brazilian state (2023). Data from CNES/DATASUS.

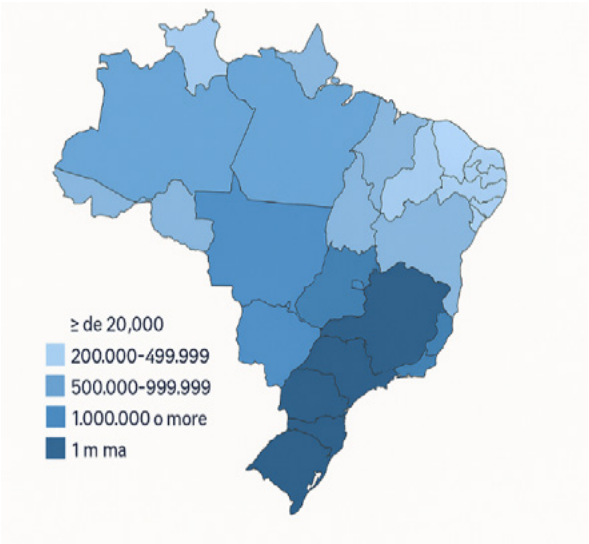

FIGURE 2 — Volume of imaging exams performed in the SUS by Brazilian state in 2023. Data from SIA/SUS.

income countries, such as Brazil, still faces structural, regulatory, and formative barriers. In this context, the precise characterization of demand and installed infrastructure is essential to guide public policies, prioritize technological investments, and structure research agendas focused on the national reality.

Architecture and operation of AI systems in radiology

The application of AI in radiology involves the interaction between supervised algorithms, convolutional neural networks, and large volumes of labeled medical data, with the aim of automating tasks such as detection, segmentation, screening, and diagnostic classification of images.[5] Systems operate through organized pipelines that connect image acquisition, digital preprocessing, and diagnostic inference based on previously trained models.

The effectiveness of these algorithms depends on elements such as the standardization of images (e.[9,] in DICOM format), the curation of balanced datasets, and the integration with archiving and communication systems (PACS/RIS). This set allows a structured processing chain, with extraction of characteristics, visual normalization and association with previous clinical findings. Convolutional neural networks stand out in this process for their ability to identify complex patterns, with cross-validation based on image banks annotated by experts.[5]

Recent evidence highlights the role of approaches such as transferred learning, supervised fitting, and hybrid models (ensembles) in performing specific tasks, such as screening for pulmonary nodules, osteoarticular fractures, and mammographic lesions.[3] These advances have allowed the development of systems with performance comparable to that of experienced radiologists, especially in the prioritization of critical examinations.

In addition to diagnosis, these algorithms contribute to the monitoring of operational indicators — such as average time to issue reports, error rate, and rework — and enable clinical decision support tools with the potential to personalize care flows.[9] By intervening in critical stages of the diagnostic process, AI acts as a complementary instrument to medical practice, whose safety and applicability depend on factors such as algorithmic transparency, data traceability, and continuous validation in real clinical contexts.

Evolution of AI-mediated diagnostic imaging criteria, methods and systems in the Brazilian and international context

Diagnostic imaging in Brazil is based on the integration of clinical findings, laboratory tests, and methods such as radiography, computed tomography, magnetic resonance imaging, and digital mammography. These procedures follow care protocols defined by institutions such as the Brazilian College of Radiology, the American College of Radiology, and the World Health Organization.[10] Diagnostic criteria recommend the identification of radiological patterns associated with the clinical context, often complemented by confirmatory tests or repeat examinations.

The request and prioritization of tests consider clinical-epidemiological factors, such as age, cancer

history, chronic diseases, and risk exposures. In groups of greater vulnerability, structured algorithms — such as BI-RADS, Lung-RADS, and probability scales — have been progressively incorporated into clinical practice, with good results in stratification and automated imaging screening.

In recent years, visual biomarkers and computational algorithms have been integrated into the diagnostic routine with the support of AI. This has allowed automated triage, reduction of interobserver variability, and prioritization of emergency reports.[9] Tools based on convolutional neural networks have been applied in the detection of pulmonary nodules, occult fractures, intracranial hemorrhages, and changes in bone density, with performance similar to that of experienced radiologists.

These resources have been progressively incorporated into automated clinical flows, both in the public and private sectors. In Brazil, multicenter studies conducted in university hospitals have shown that the use of diagnostic algorithms reduced response time by up to 32% and increased accuracy in priority cases.[5]

The current integration of AI in clinical-radiological flows in Brazil, its practical applications, adopted conducts, emerging protocols, and clinical decision support

The integration of AI into clinical-radiological flows in Brazil requires a multimodal and progressive approach, which combines diagnostic technology, integrated care protocols, and continuous professional training. These strategies aim to improve operational efficiency, reduce the time to issue reports, minimize rework, and expand access to exams in areas with limited coverage.[11]

Emerging guidelines from the Brazilian College of Radiology and pilot projects conducted by the Ministry of Health recommend that the adoption of AI systems occur in a staggered manner, based on the degree of digitalization of the unit, local epidemiological profile, and type of examination.[12] University hospitals and public referral services have been using validated algorithms for automated screening in chest exams, mammography, and cranial CT scans in emergency contexts as a front line.

These tools have been supported by evidence from cohort studies and experiences with robust technical validation, especially in institutions with academic-technological partnerships. In the absence of adequate infrastructure or internal technical support, viable alternatives include remotely assisted reports, cloud-based systems, or partnerships with regional support centers.[13]

Structuring interventions — such as continuous training of radiologists[4], standardization of care protocols, and modernization of the technology park with a focus on connectivity and image curation — are essential for the effective application of AI. These actions are especially relevant in overloaded outpatient units, places without specialists, and regions with poor digital infrastructure.

New trends and technologies

Recent advances in applied research, multicenter simulations, and clinical validations have been transforming the integration of AI into radiological practice, with a special impact in the context of the SUS. The incorporation of deep learning algorithms, automated segmentation, and preclassification by neural networks has enabled the development of emerging diagnostic platforms, predictive models, and high-sensitivity screening strategies — especially in outpatient settings with high demand and shortage of specialists.[14]

Controlled clinical trials conducted in Brazilian university hospitals have demonstrated the effectiveness of algorithms to detect pulmonary nodules and fractures in tomography and radiography scans, with satisfactory performance in at-risk populations, such as the elderly, cancer patients, and victims of traumatic brain injury.[5]

Among the innovations with the greatest potential impact, the following stand out: automated screening platforms integrated with PACS, already implemented in experimental clinical settings; risk prediction models with continuous learning capacity; and validated operational protocols for application in mammography and cranial tomography, with gains in response time and reduction of pending reports.

These solutions, validated in different outpatient settings, have already demonstrated a measurable impact on diagnostic efficiency and clinical prioritization (Table 1).

Recent updates from the Brazilian College of Radiology, in line with guidelines from the American College of Radiology and the Food and Drug Administration (FDA), recommend the assisted use of AI in screenings, with a requirement for mandatory local validation and human supervision in final reports.[15]

Structural barriers, methodological uncertainties and controversies about validation, regulation and applicability of AI in diagnostic imaging in the Brazilian public sector

Despite recent advances in the integration of AI into diagnostic imaging, critical gaps persist that hinder its consolidation in the Brazilian public sector. Among the main obstacles are the scarcity of randomized controlled trials with multicenter validation, the absence of long-term data on real clinical impact, and the lack of external validations in small units, which limits the extrapolation of the available evidence (Table 2).[16]

In the regulatory field, there is still no consensus regarding the degree of acceptable autonomy for diagnostic algorithms, nor on the obligation of review by human radiologists in all cases. International guidelines, such as those of the FDA and the American College of Radiology, contrast with the Brazilian scenario, which lacks clear regulations by the Federal Council of Medicine and the National Health Surveillance Agency, reflecting different interpretations of safety, legal liability, and auditability criteria.[17]

In addition, public units in the North and Northeast regions remain underrepresented in AI validation

TABLE 1 — Recent innovations in radiological diagnosis with AI – Brazil

Innovation / Technology	Clinical Application	Current Status
AI for Fracture Detection	Orthopedic X-ray in the emergency department	Validated pilot study5
AI-Automated Triage	Digital mammography	University Hospital Experience
Prioritization platform	Urgent CT scans (stroke, trauma)	Workflow data in SUS hospitals
Automated image curation	Urgent CT scans (stroke, trauma)	Cohort studies and local validation

TABLE 2 — Key recommendations for diagnostic AI - Context and limitations

Technical Axis	Recommended Intervention	Conduct in Doubtful Cases	Recomendação Atual
AI Diagnostics	Autonatized screening with local validation	Expert review before the final report	Pilot studies in university hospitals1
PACS Integration	Partial integration with human supervision	Internal protocols	Isolated institutional experiences17
Regulation and standardization	Lack of regulatory consensus in Brazil	Divergences between CFM, ANVISA and FDA	Need for clear regulation
Population inclusion	Representation of vulnerable populations	Low generalization to the North/Northeast	Evaluations concentrated in the Southeast region18
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studies, compromising the applicability of technological solutions in contexts with limited infrastructure, low connectivity, and scarcity of qualified professionals. Populations such as indigenous people, riverside dwellers, pregnant women, and patients with multiple comorbidities are also rarely included in the datasets used to train the algorithms currently available.[18]

From an operational point of view, the dependence on high-cost technologies, the heterogeneity in the structuring of images (DICOM, PACS) and inequalities in access to servers and networks widen the distance between the technical production of centers of excellence and their implementation in the daily life of the SUS. Recognizing these gaps is essential to guide public policies based on real-world evidence and foster more inclusive clinical and technological research, aligned with the structural demands of the Brazilian health system.

The analysis of the available evidence on the adoption of AI in diagnostic imaging in the SUS points to significant advances in different domains, with emphasis on automated screening, increased efficiency in diagnostic flows, and clinical decision support in complex exams, such as tomography and mammography.[19]

There is consensus among national and international guidelines — such as those of the Brazilian College of Radiology and the American College of Radiology — regarding the assisted and supervised use of AI. This position is supported by multicenter studies, workflow analyses and institutional validations.[3]

However, uncertainties persist regarding the applicability of these technologies in contexts with limited infrastructure, reduced interoperability, and lack of validation in small units. The literature lacks methodologically robust studies that evaluate clinical impact in environments with low technological density and in the long term.

Although the effectiveness of AI is well demonstrated in hospitals with advanced digital integration, its adoption in peripheral units of the SUS, especially in primary care and in regions with low connectivity or lack of specialists, has not yet been sufficiently proven.[20]

In addition, there are divergences between international regulatory frameworks — such as the FDA and EMA — and the lack of clear regulations in Brazil, which generates uncertainties about minimum safety criteria, technical responsibility, and validation requirements.

These factors reinforce the urgency of fostering multicenter research with regional diversity, studies based on real-world evidence, cost-effectiveness analyses, and continuing education programs. Such measures are essential to ensure that technological advances translate into concrete, equitable and sustainable improvements in diagnostic imaging in the public health system.

CONCLUSION

The critical analysis of the evidence on the adoption of AI in Brazilian radiology highlights the importance of a structured care approach, guided by evidence and supported by carefully incorporated technological innovations. The consolidation of AI as a diagnostic support tool represents a relevant functional advance, with the potential to reduce regional inequalities, improve triage, and increase the effectiveness of imaging care in the SUS.[21] However, the diversity of care models, inequalities in infrastructure, and the complexity of local contexts require a continuous process of monitoring implementation, reviewing algorithmic robustness, and periodically updating clinical protocols. The effective adoption of these technologies requires constant professional qualification, investments in interoperability, data curation, and ethical validation. In this context, revisions such as this are strategic tools to guide public policies, update clinical guidelines, and support institutional decisions. They contribute to safer, more equitable, and evidence-based medical practice — one that balances technological innovation with operational feasibility and patient care centricity.

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Authors' contributions

Luis Gustavo Machado Farias - Conceptualization, Writing (original draft)
Alan Cristian Cordeiro Siqueira - Formal Analysis, Supervision
Fernanda Marcondes Ribas – Research, Writing (proofreading and editing)
Kammilly Fernanda Alves dos Santos - Supervision, Methodology

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Endoscopic gastrostomies: what can be their complications and possible correlations?

Gastrostomias endoscópicas: quais podem ser suas complicações e possíveis correlações?

Isabelle Terumi Tanioka Corrêa[1], Roberto Oliveira Basso[2], Leonardo Moreira Dias[2], Carlos Roberto Naufel Junior[1], Guilherme Andrade Coelho[1]

ABSTRACT

Introduction: Percutaneous endoscopic gastrostomy is currently the method of choice for medium- to long-term enteral nutrition for patients with insufficient oral nutrition.

Objective: To individualize its indication, to determine when it is indicated and contraindicated, and to understand and avoid predictable complications.

Method: A retrospective, observational, analytical, case-control study using data from the electronic medical records of those who underwent the procedure from September 2022 to September 2024, with an emphasis on postoperative complications and possible correlated factors.

Result: Seventeen patients were included, who progressed well without complications related to the method, and none developed surgical wound infection until the time of removal, including those who continued with the gastrostomy, regardless of the use of antibiotic prophylaxis.

Conclusion: This study allowed us to outline the epidemiological profile of patients undergoing percutaneous endoscopic gastrostomy in a recognized endoscopy service, contributing data to this topic, a topic that is still very little discussed in clinical studies.

KEYWORDS: Endoscopic gastrostomy. Postoperative complication. Wound infection.

RESUMO

Introdução: A gastrostomia endoscópica percutânea é atualmente o método de escolha para nutrição enteral de média a longa permanência para pacientes com alimentação por via oral insuficiente.

Objetivo: Individualizar sua indicação, para saber quando ser indicada, contraindicada, e entender e evitar complicações previsíveis.

Método: Estudo observacional analítico retrospectivo do tipo caso-controle utilizando dados de prontuário eletrônico dos que realizaram o procedimento de setembro de 2022 a setembro de 2024, com ênfase nas complicações pós-operatórias e possíveis fatores correlacionados a ela.

Resultado: Foram incluídos 17 pacientes que evoluíram bem sem complicações referidas ao método e nenhum evoluiu com infecção de ferida operatória até o momento da retirada, incluindo aqueles que ainda permaneceram com a gastrostomia, independente do uso ou não de antibioticoprofilaxia.

Conclusão: Este estudo permitiu traçar o perfil epidemiológico dos pacientes submetidos à gastrostomia endoscópica percutânea em um serviço reconhecido de endoscopia, colaborando com dados ao tema, tema este que ainda é muito pouco referido em estudos clínicos.

PALAVRAS-CHAVE: Gastrostomia endoscópica. Complicação pós-operatória. Infecção de ferida.

Central Message

Percutaneous endoscopic gastrostomy was developed in the 1980s and revolutionized the mode of enteral feeding for patients who rely on this route for nutrition. Because it is an endoscopic and minimally invasive procedure, it allows comfort and lower risks compared to the prolonged use of nasogastric or nasoenteral tubes.

Perspective

Percutaneous endoscopic gastroscopy should not be used routinely, but its use should be individualized according to strict criteria for each service. This saves inappropriate indication by placing it preferentially for patients with higher morbidity. Its use, in a judicious way, promotes comfort and ease of handling in those with greater clinical complexity, and prevents health systems from being unnecessarily burdened.

[1] Mackenzie Evangelical University Hospital of Paraná, Curitiba, PR, Brazil;
[2] Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

Percutaneous endoscopic gastrostomy was developed by specialists in the 1980s. The main pioneers of this procedure were Drs. James P. Gauderer and Jeffrey L. Ponsky, who developed the technique and contributed significantly to its popularization.[1] It has revolutionized the way enteral feeding is provided to patients who depend on this route for nutrition, since in addition to being an endoscopic and minimally invasive procedure, it allows comfort and lower risks of irritation, ulceration, bleeding, gastroesophageal reflux and pneumonia, compared to the prolonged use of nasogastric or nasoenteral tubes.[2,3]

It is possible for the patient to tolerate approximately 10 days without diet, with hydroelectrolyte replacement alone, before severe protein catabolism occurs, depending on their baseline health status.[2] However, in order to maintain adequate nutrition, even before catabolism occurs, it is considered good medical practice to establish a nutritional route, preferably enteral route, if the oral route is not possible. Enteral nutrition avoids the risk of bacterial translocation, bloodstream infection, and is economically more advantageous compared to parenteral nutrition for those with viable gastrointestinal tracts.[2,3]

Due to the minimally invasive technique used in its performance, the procedure offers greater comfort and quality of life to those who need enteral nutrition for medium to long time, as it replaces nasoenteral and nasogastric tubes, which cause too much discomfort3, in addition to not producing large incisions and scars, as in the case of surgical gastrostomies.[2]

Defining the need for the enteral feeding route in advance and performing the procedure after the indication is well done can prevent weight loss and malnutrition and, consequently, lead to a shorter hospital stay and recovery time.

There are some techniques described for percutaneous endoscopic gastrostomy. The main ones are: pull (the most common), push, and Russell or introduce.[2,4]

In the pull technique, basically the gastrostomy tube is pulled inside the stomach, through the endoscope, into the lumen of the gastrointestinal tract. It is the most commonly used method and was developed by James Gauderer et al.[1] In the push, the gastrostomy tube is pushed into the lumen of the organ through the abdominal wall, without pulling inside the cavity, which is the second most used method. The Russell or introduction technique is defined by the insertion of the gastrostomy tube through a trocar, with a dilator and guidewire.

There is controversy regarding the use of antibiotic prophylaxis 30-60 minutes before the procedure. There are some meta-analyses on the subject in which it is argued that the use of antibiotics, such as penicillins and cephalosporins, reduce systemic infections and surgical wounds, and justify their use due to the vulnerability of patients.[3,5,6] At the same time, there are studies in the literature showing that antibiotic prophylaxis has not obtained positive results in terms of reducing the number of wound infections.[7]

Percutaneous endoscopic gastrostomy can be removed as soon as enteral feeding is no longer necessary or when complications related to the procedure arise, in which only its removal can solve the problem. It is usually removed endoscopically and the wound heals in the first few days, depending on the conditions and comorbidities of the patients.[2]

The indications are basically for those who need enteral access for nutrition, both absolute and complementary, of medium to long duration, or for those who need gastric decompression (less frequent)[2-5,7] some examples being neurological and psychomotor diseases (such as sequelae of cerebrovascular disease, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and dementias), reduced level of consciousness (ICU patients in coma), head and neck neoplasms, esophageal neoplasms or lesions, victims of severe facial trauma or polytraumatized, congenital abnormalities such as tracheoesophageal fistula.

The main contraindications of the procedure are divided into absolute (some examples: coagulation disorder, sepsis, bulky ascites, peritoneal carcinomatosis, and obstruction to the passage of the endoscopy) and relative (some examples: hepatosplenomegaly, peritoneal dialysis, portal hypertension, obesity, and pregnancy).[2,4,6]

The main complications related to the procedure are characterized by endoscopic technical difficulties related to the procedure and the patient, late complications associated with difficulty in maintaining and managing the gastrostomy, and in wound care.[2,3,4]

The objective of this study was to promote data on the indication and contraindication of percutaneous endoscopic gastrostomy and to understand/avoid the foreseeable complications.

METHOD

This research was conducted between September 2022 and September 2024 at the Digestive Endoscopy Service of the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil. It was approved by the Research Ethics Committee of the Evangelical Beneficent Society of Curitiba, under opinion CAAE 84194524.9.0000.0103, in accordance with the precepts of Resolution 466/12 of the National Health Council/Ministry of Health.

This is a retrospective case-control study. Data collection was carried out through an active search in the MVPEP electronic medical record system of 17 cases that underwent the procedure, regardless of the technique used. The selection was made by searching for the ICD-Z931 code and/or the 0309010039 procedure code (percutaneous endoscopic gastrostomy). Patients of all age groups and genders

were included. Only those in which it was possible to obtain complete access to postoperative clinical follow-up, either by hospitalization or outpatient return, were considered. Those whose procedure was incomplete, unsuccessful, or with post-procedure follow-up outside the institution were excluded.

For data collection, a standardized protocol was created with which clinical information was searched for (Tables 1, 2 and 3).

Follow-up time was defined as the interval between the dates of gastrostomy and the last one recorded in the clinical evaluation or death. During the follow-up period analyzed, no deaths were recorded.

Statistical analysis

It was descriptive conducted to understand the distribution of the variables of the data set, using contingency tables for categorical data and measures of central tendency and dispersion for numerical data. The chi-square test of independence was used to verify the association between the sociodemographic and clinical characteristics of the patients. The test analyzes the existence of a significant association between categorical variables, under the null hypothesis that the variables are independent and the alternative hypothesis that the variables are dependent. A significance level $\alpha = 0.05$ was adopted for all tests. Thus, for p-value ≥ 5%, the null hypothesis was not rejected. The analyses were performed with the R software version 4.4.2 (R Core Team, 2024).

RESULT

Table 1 shows the sociodemographic profile of the patients. The mean age was 54.4+/-19.8 years and most were aged between 41 and 80 years (70.6%). Regarding gender, the majority were men (58.8%).

TABLE 1 — Characterization of the sociodemographic profile of the patients (n = 17)

Variable	Group	Total
Age, mean (SD)		54,4 (19,8)
Age group, n (%)	0-20	1 (5,9)
	21-40	2 (11,8)
	41-60	7 (41,2)
	61-80	5 (29,4)
	>80	2 (11,8)
Gender, n (%)	Female	7 (41,2)
	Male	10 (58,8)

Table 2 details the comorbidities and reasons for the placement of gastric gastrostomy by tube (GGT). Overall, 52.9% had no comorbidities, Among those who did (47.1%), the most frequent were categorized as diabetes mellitus and neurological (37.5% each), followed by ulcerative and vascular colitis (12.5% each), The main reason for placing GGT was neurological (70.6%), with stroke being the most common cause (41.7% of neurological reasons), followed by COVID-19 (16.7%) and cerebral palsy (25%). Other reasons were dysphagia (11.8%) and trauma (11.8%). The majority (76.5%) were not using antibiotics and none had infectious complications.

TABLE 2 — Characterization of the sample according to comorbidities and reasons for placing GGT

Has comorbidities, n (%)	No	9 (52,9)
	Yes	8 (47,1)
Comorbidities, n (%)	Diabetes mellitus	3 (37,5)
	Neurological	3 (37,5)
	Ulcerative colitis	1 (12,5)
	Vascular	1 (12,5)
Reason for placing the GGT, n (%)	Malnutrition	1 (5,9)
	Dysphagia	2 (11,8)
	Neurological	12 (70,6)
	Trauma	2 (11,8)
Neurological reasons, n (%)	Stroke	5 (41,7)
	COVID	2 (16,7)
	Status epilepticus	1 (8,3)
	Guillain-Barré	1 (8,3)
	Cerebral palsy	3 (25,0)
Antibiotic in use, n (%)	No	13 (76,5)
	Yes	4 (23,5)
Infectious complications, n (%)	Hassle-free	17 (100,0)
	There were complications	0 (0,0)

Table 3 shows the description of the placement of GGT in the sample. The majority (88.2%) did not need to be transferred. The time until GGT placement varied greatly, with the majority (58.8%) having been placed less than 1 month earlier (time 0). Other frequent times were 1 month (17.6%) and 2 months (11.8%) after admission, only 1 had GGT placed after 3 months and another after 29 months; the majority (64.7%) had already withdrawn the GGT at the time of the analysis, and most withdrawals occurred between 0 and 1 year after placement (72.7%).

TABLE 3 — Characterization of the sample according to the GGT placement

Variable	Category	Total
There was a pass-through, n (%)	No	15 (88,2)
	Yes	2 (11,8)
Time to GGT placement (months), n (%)	0	10 (58,8)
	1	3 (17,6)
	2	2 (11,8)
	3	1 (5,9)
	29	1 (5,9)
Removed GGT, n (%)	Not yet withdrawn	6 (35,3)
	Yes	11 (64,7)
Time to withdrawal of GGT (years), n (%)	0-1	8 (72,7)
	1-2	2 (18,2)
	2-3	1 (9,1)

Association Analysis

Table 4 presents the analysis of the association between the time until GGT withdrawal and the age group, considering 3 categories of time in years: 0-1, 1-2 and 2-3. The p-value was calculated using the chi-square test. Among those who had GGT removed at 0-1 years (n

= 8), the highest proportion belonged to the 61-80 year age group (50%, n = 4), followed by 41-60 years (25%, n = 2). The 0-20 and >80 age groups contributed 11% (n = 1) and 13% (n = 1), respectively. In the group with a withdrawal time of 1-2 years (n = 2), 50% (n = 1) were between 41-60 years, and the other 50% (n = 1) were older than 80 years. The group with withdrawal at 2-3 years (n = 1) was in the 41-60 age group. There was no statistically significant association between the time until GGT withdrawal and the age group (p = 0.[6]).

TABLE 4 — Analysis of the association between time to removal of GGT and age group

	Time until withdrawal (years)			
Variable	0-1 n= 8	1-2 n = 2	2-3 n = 1	p-value [1]
Age group, n (%)				0.6
0-20	1 (11%)	0 (0%)	0 (0%)	
21-40	0 (0%)	0 (0%)	0 (0%)	
41-60	2 (25%)	1 (50%)	1 (100%)	
61-80	4 (50%)	0 (0%)	0 (0%)	
>80	1 (13%)	1 (50%)	0 (0%)	

[1] Chi-square test

Table 5 presents the reasons for the placement of GGT and the sociodemographic and clinical factors that led to its application.

TABLE 5 — Analysis of the association between the reasons for placing the GGT and the patients' sociodemographic and clinical factors

Variable	Malnutrition n = 1	Dysphagia n = 2	Neurological n = 12	Trauma n = 2	p-value [1]
Age group, n (%)					0,040
0-20	0 (0%)	0 (0%)	0 (0%)	1 (50%)	
21-40	0 (0%)	0 (0%)	2 (17%)	0 (0%)	
41-60	0 (0%)	1 (50%)	6 (50%)	0 (0%)	
61-80	0 (0%)	0 (0%)	4 (33%)	1 (50%)	
>80	1 (100%)	1 (50%)	0 (0%)	0 (0%)	
Time to withdrawal (years), n (%)					0,066
0-1	0 (0%)	2 (100%)	4 (67%)	2 (100%)	
1-2	1 (100%)	0 (0%)	1 (17%)	0 (0%)	
2-3	0 (0%)	0 (0%)	1 (17%)	0 (0%)	
Time to placement (months), n (%)					>0.9
0	1 (100%)	1 (50%)	6 (50%)	2 (100%)	
1	0 (0%)	1 (50%)	2 (17%)	0 (0%)	
2	0 (0%)	0 (0%)	2 (17%)	0 (0%)	
3	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	
29	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	
Comorbidities, n (%)					0,067
DM	0 (0%)	1 (50%)	2 (50%)	0 (0%)	
Neurological	0 (0%)	1 (50%)	2 (50%)	0 (0%)	
RCU	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
Vascular	1 (100%)	0 (0%)	0 (0%)	0 (0%)	
There was a pass-through, n (%)					0,8
Not	1 (100%)	2 (100%)	10 (83%)	2 (100%)	
Yes	0 (0%)	0 (0%)	2 (17%)	0 (0%)	

[1] Chi-square test

Table 6 presents the analysis of the association between infectious complications and antibiotic use. Since none of the patients had infectious complications, it was not possible to establish statistical associations between the variables analyzed. These data suggest a low occurrence of infectious complications in the group evaluated.

TABLE 6 — Analysis of the association between infectious complications, antibiotic use, and comorbidities

	Infectious complications	
Variable	Complications-free n = 17	There were complications n = 0
Antibiotic in use, n (%)		
No	13 (76%)	0 (0%)
Yes	4 (24%)	0 (0%)
Comorbidities, n (%)		
Diabetes mellitus	3 (38%)	0 (0%)
Neurological	3 (38%)	0 (0%)
Ulcerative colitis	1 (13%)	0 (0%)
Vascular	1 (13%)	0 (0%)

DISCUSSION

After analyzing the epidemiological results obtained in this data collection, the fact that it is not possible to correlate the patient's age with his early rehabilitation and return to oral feeding goes against the results previously described in the literature, which in turn point to younger patients as having a greater tendency to remove GGT by recovery. In addition, despite the small volume of scientific substrate found in the databases regarding the removal of GGT, another factor that predisposes to its removal also stands out, that is, the procedure due to head and neck neoplasms, a factor that was not present in the sample studied.[8] During the period in which the data were collected, 3 cases of attempted endoscope progression were recorded in patients with head and neck neoplasms; however, due to the advanced stage of the lesions, it was not possible to perform the procedure and the patients, therefore, did not meet the inclusion criteria. In these cases, early oncological diagnosis could have avoided failure, and consequently positively influenced the final prognosis.

This sample indicated, with statistical significance, that age influenced the reason for the placement of GGT, allowing a better understanding of the epidemiological profile. Taking into account that many elderly people have an indication for the passage of GGT due to malnutrition, it is possible to draw a parallel with the literature, which in turn indicates nutritional scores to determine the best time, ensuring greater survival.[9] Understanding the epidemiological patterns of the services is, therefore, fundamental to know what type of evaluation to carry out, aiming at better medical care,

In addition, it was observed that neurological causes for GGT predominated among those who removed the tube in less than 1 year, which corroborates findings already described in other articles, which demonstrated a mean time of 5 months in neurological involvement, either due to rehabilitation that allowed the return to oral diet, or due to lack of improvement in the status in force of use of GGT.[10]

In addition, in the present sample, it was possible to observe that the time required for GGT placement to be indicated predominated at 10 months (58%), a result that was in line with that obtained and published by another national reference service, where approximately 58% of the sample was also submitted to GGT in 10 month.[11] Despite the early indication in more than half of the cases, it proved to be accurate, considering that about 64% remained with GGT for more than 1 year.

Finally, the results obtained showed the absence of infectious complications, despite the low number of cases in which antibiotics were prescribed. This result may serve to question the current protocols of medical conduct postulated in the international literature on the subject. Currently, antibiotic therapy is recommended, preceding the procedure, mainly penicillins, for the prophylaxis of surgical wound infection. Depending on the method used for the procedure, there was no statistical significance in the causal relationship between antibiotic prophylaxis and lower rates of surgical wound infection.[12,13] Thus, the present study suggests that this conduct should not be applied routinely, so that the indication or not should actually be individualized according to the infection rates of each service. Thus, patients are spared from higher morbidity associated with the inadvertent prescription of antimicrobial agents, and health systems are avoided from being unnecessarily burdened during the management of complex patients, such as those with gastrostomies.

CONCLUSION

GGT is the current method of choice for enteral feeding in many patients who need it to maintain adequate nutritional status, with varying comorbidities. However, there is a lack of national studies related to the subject, in regard to the profile of patients undergoing the procedure, possible complications and how they can be avoided. It is possible to establish a standard of characteristics for each patient in whom the procedure was indicated and individualize it in terms of care, technique used, prophylaxis, and even define contraindications for those at higher risk.

Authors' contributions

Isabelle Terumi Tanioka Corrêa - Formal Analysis, Investigation, Writing (original draft)
Roberto Oliveira Basso - Formal Analysis, Methodology
Leonardo Moreira Dias - Writing (proofreading and editing)
Carlos Roberto Naufel Junior - Conceptualization
Guilherme Andrade Coelho - Conceptualization

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Atypical obstructive Meckel's diverticulum in a young patient

Divertículo de Meckel obstrutivo atípico em paciente jovem

Ana Júlia Ribas Sigwalt[1], Cecília Schneider[2], Gabriella Micheten Dias[2], Isabelle Tomelin Rothenburg[2], Marjorie Secatto Batista[2], Marcos Fabiano Sigwalt[3]

KEYWORDS: Meckel diverticulum. Emergency. General surgery.
PALAVRAS-CHAVE: Divertículo de Meckel. Emergência. Cirurgia Geral.

INTRODUCTION

Meckel's diverticulum (DM) is the most common congenital anomaly of the gastrointestinal tract, with an incidence of approximately 2-4% in the population. Its pathophysiological process consists of incomplete closure or failure in the absorption of the omphalomesenteric duct (yolk), between the 7th and 8th weeks of gestation. Generally, more than half of the cases manifest in childhood or up to 20 years of age, being rare in individuals over 40 years of age.[1-3]

In many situations, DM has no symptoms and is commonly detected incidentally during interventions such as laparotomies, laparoscopies, or necropsies. When any type of complication arises, it can present with a wide variety of clinical manifestations, which should be considered in the differential diagnosis of patients with acute obstructive or inflammatory abdomen. Common symptoms are fever, vomiting, abdominal pain, and blood in the stool — not unique to Meckel's disease.[1,3-5]

The treatment of choice for symptomatic diverticulum is surgical resection. The most common forms are wedge diverticulectomy, or segmental bowel resection, and anastomosis, especially when there is bowel ischemia or obstruction. However, the management of asymptomatic forms requires individualized evaluation, considering the patient's clinical history, the size of the diverticulum, and the risks and benefits of the surgical procedure.[1,4-6]

This report aims to describe an atypical case of a young patient with obstructive DM, relating the discussion to current studies on the same topic. It was approved by the Human Research Ethics Committee of Universidade Positivo, Curitiba, PR, Brazil – CAAE no. 76173623.8.0000.0093

CASE REPORT

A 26-year-old female born in Curitiba, PR, Brazil reported abdominal pain for 8 days, focusing on the epigastric region, of mild intensity, radiating to the back, lasting 1 h and spontaneous improvement. She presented nausea, weakness and inappetence concomitantly, absence of fever and urinary alterations. He had sought another emergency medical care 2 days earlier, where an abdominal computed tomography (CT) scan without contrast was performed, which did not indicate changes in the abdominal region, suggesting normality. The patient began to increase the frequency and worsen the intensity of the pain, and he went to the hospital emergency department 24 h later. On admission, she was in good general condition, lucid, oriented in time and space, afebrile, acyanotic, anicteric, hydrated and normocolored. Regarding vital data, the patient had a BP of 100 x 60 mmHg, a pulse rate of 105 bpm, and a saturation rate of 98%. Abdominal physical examination showed decreased bowel sounds, almost absent, and a slightly distended abdomen, with diffuse pain on palpation, especially in the lower region, with no signs of peritoneal irritation. In addition, a small amount of feces was found in the rectal ampulla when performing the digital rectal examination.

Laboratory tests revealed elevated CRP, rod-shaped cells, and leukocytosis. Abdominal X-rays on admission revealed air-fluid levels in the rectal ampulla, without pneumoperitoneum. Abdominal CT with intravenous contrast revealed small bowel obstruction, with possible adhesions.

[1]Pontifical Catholic University of Paraná, Curitiba, PR, Brazil;
[2]Positivo University, Curitiba, PR, Brazil;
[3]Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil.

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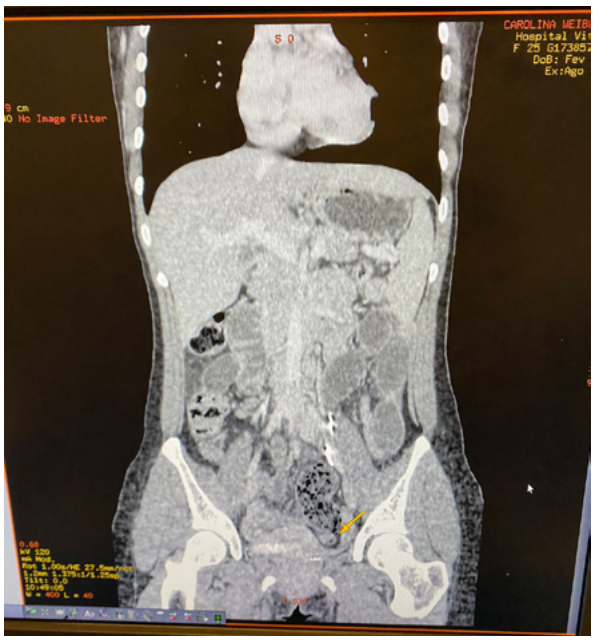

FIGURE 1 — Contrast-enhanced CT scan of the abdomen demonstrating the presence of intestinal obstruction at the level of the small intestine, suggesting possible bridles.

The patient was then submitted to laparoscopy on the same day. During the procedure, distension in small bowel loops was observed upstream of the DM with a wide and engorged base (70 cm from the ileocecal valve) and thinning downstream. The hardened luminal content, which caused the obstruction, was within the diverticulum and expanded into the ileum lumen in the topography of the diverticulum. Therefore, we opted for suprapubic transverse incision laparotomy and segmental enterectomy with removal of the diverticulum area and enteroanastomosis.

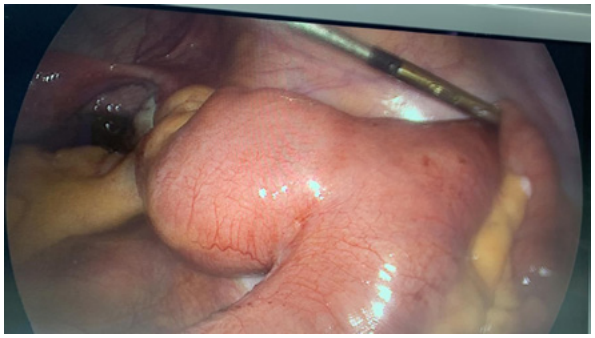

FIGURE 2 — Meckel's diverticulum with contents completely obstructing the ileum

FIGURE 3 — Meckel's diverticulum exposed for segmental enterectomy.

The patient was discharged, in good condition, the day after the operation. He returned on outpatient basis on the 14th day, with good evolution, without manifesting any complications.

DISCUSSION

DM is a condition that predominantly affects pediatric patients and is one of the most common causes of bleeding in this phase, due to the persistence of the proximal portion of the congenital vitile-intestinal duct. It is presented in the form of a pouch and contains the 3 layers of the intestinal wall - which is why it is considered a true diverticulum - located at the antimesenteric border. This congenital anomaly is present in 2% of the population, located 61 cm from the ileocecal junction and is 5 cm long, although there are variations.[5]

DM presents as an asymptomatic condition until any of its complications manifest themselves, usually in diverticula larger than 2 cm, a situation in which the patient usually presents symptoms of obstruction, hemorrhage, or gastrointestinal inflammation.[3] According to the literature, the chance of this anomaly becoming symptomatic throughout life is only 4-6%.[6]

Obstruction occurs in about 36% of symptomatic adults, either due to ileoileal intussusception, invagination, volvulus, stenosis secondary to chronic diverticulitis, internal hernia, Littre's hernia (extension of the hernial sac), inflammatory bridles, or phytobezoar.[6] Internal hernias occur due to the persistence of the fibrotic portion that connects the diverticulum to the umbilicus. Other types of hernia that can eventually become a complication of DM are inguinal, femoral, and umbilical due to intestinal loop entrapment.[2]

Hemorrhage is the most common complication in children under 2 years of age and occurs in the rectum. It is caused by inflammation of the ectopic gastric mucosa, caused by the evolution of the disease to intestinal hemorrhagic ulcer. Inflammation can occur due to DM or perforation of the walls of the diverticula, causing peritonitis.[3] For this reason, the most common symptoms are vomiting, abdominal pain and distension, fever, and blood in the stool.[1,3] Other rarer complications are diverticular fistulization in the bladder and the development of tumors.[4]

The clinical picture of the complications requires tests for investigation, since it is a differential diagnosis of acute inflammatory or obstructive abdomen, such as acute appendicitis.[3,6] Also, when symptomatic, the disease can manifest itself with different intensities, ranging from almost painless and benign conditions to potentially fatal situations, which often require emergency care.[2] For this reason, the identification of the diverticulum is usually incidental during laparotomies and laparoscopies (0.14-4.5 %) or necropsies (0.3-4%).[6] Retrospective studies indicate that this condition is most frequently observed in the right abdomen, accounting for 67% of cases, with the majority located at the level of the umbilicus (37.5%), followed by the upper and lower right quadrants (17-12.5%).[2]

Despite advances in imaging and technology, the

clinical diagnosis of symptomatic or complicated DM is still challenging, often confirmed only during laparotomic or laparoscopic exploratory surgical procedures.[6]

Diagnosis is usually based on the association of clinical suspicion with imaging tests. However, these tests may not have adequate sensitivity and specificity, making a surgical approach necessary for confirmation.[4]

Several methods of complementary tests are cited in the literature, such as abdominal radiography, contrast-enhanced examination of the small intestine, computed tomography, ultrasonography, arteriography, technetium 99 pertechnetate scintigraphy and capsule endoscopy. However, most of these tests tend to reveal only alterations resulting from complications and have limited sensitivity and specificity.[3,6]

Direct observation of the diverticulum is essential for accurate diagnosis. It can be performed through operations or through endoscopy of the small intestine, such as double balloon endoscopy, which allows the endoscope to advance deeper into the ileum until the diverticulum is identified.[3]

Early recognition when complicated is crucial, as a delay in the surgical approach, especially after 36 h in cases of strangulation, can lead to significant morbidity and mortality rates of up to 25%.[1] The definitive symptomatic treatment is surgical resection, which can be performed by laparotomy — still the most common access route — or by laparoscopy. These procedures allow the resection of the diverticulum using 1-3 trocars, either by intraperitoneal resection or exteriorization of the intestinal segment containing the diverticulum.[3]

The choice of surgical procedure, such as diverticulectomy, wedge resection, or segmental resection, depends on the height-to-diameter ratio of the diverticulum (considered long when this ratio is greater than 2) and the type of complication presented.[1] Diverticulectomy is indicated for incidental, long diverticula, or in cases of diverticulitis at the tip of the diverticulum, while segmental resection is recommended when the base of the diverticulum is inflamed, in short diverticula, or in situations of melena, intestinal ischemia, or perforation.[5] The extent of resection should be guided by the type of complication and intraoperative findings, such as bleeding, presence of ectopic tissue, necrosis, perforation, peridiverticular abscess, or suspected neoplasia.[6]

As a final message, DM may present not only inflammatory but also obstructive complications, resulting in partial or total occlusion of the ileum. This clinical picture makes diagnosis difficult, due to the wide spectrum of diseases that must be considered in these circumstances and the atypical age for the development of this anomaly. Therefore, surgeons who treat patients with acute abdominal pain should be aware of this possibility since it may be a medical emergency.

Authors' Contributions

Ana Júlia Ribas Sigwalt: Formal Analysis, Research, Writing (original draft)
Cecília Schneider: Formal Analysis, Methodology
Gabriella Micheten Dias: Formal Analysis, Methodology
Isabelle Tomelin Rothenburg: Writing (revision and editing)
Marjorie Secatto Batista: Conceptualization
Marcos Fabiano Sigwalt: Conceptualization

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Schwannoma de nervo glossofaríngeo em adolescente

Glossopharyngeal nerve schwannoma in an adolescent

José Fernando Polanski[1,2], Louise Ferreira Iunklaus[1], Arthur Ricardo Carminatti Ortinã[1], Erika Yumi Nakagawa[2], Carolina Rodrigues Laranjeira Vilar[2], Felipe Lopes de Moraes Pironatto[1], Marja Cristiane Reksidler[3]

KEYWORDS: Neurilemmoma, Glossopharyngeal Nerve, Parapharyngeal Space, Parapharyngeal Space
PALAVRAS-CHAVE: Neurilemoma, Espaço Parafaríngeo, IX Nervo Craniano, IX Nervo Craniano

INTRODUCTION

Schwannnoma is a benign neoplasm that originates in the myelin sheath of peripheral nerves, spinal nerves, and cranial nerves in Schwann cells. Those of cranial nerves can be seen along the path of the nerves in the intracranial region or in the location of the head and neck. The olfactory and optic nerves are the only cranial nerves that are not affected, as they lack these cells. The most common origin is the eighth cranial nerve, the vestibulocochlear. It has an unknown etiology, and rarely occurs in the oral and maxillofacial region (approximately 1% of cases), requiring surgical treatment of the lesion. In this region, the most common sites are the tongue and oral floor, followed by the oral mucosa, lips, gums, palate and mandible. They are solitary, slow-growing, smooth-surfaced, encapsulated tumors, usually asymptomatic. In more advanced cases, paresthesia and pain due to compression of nerves and adjacent structures may occur.[1,2]

Imaging tests such as computed tomography (CT), magnetic resonance imaging, and ultrasound are useful in diagnosis to estimate tumor margins, structural components, and determine if there is infiltration into surrounding structures. On CT scans, a well-defined mass capable of capturing contrast is observed. Magnetic resonance imaging presents as hypointense or isointense lesions on T1-weighted sequences. On T2-weighted sequences, they are generally homogeneous in moderate signal intensity, although cysts or degenerative changes may be observed within them with higher intensity compared to other compartments, and they present variable enhancement with contrast administration. Histopathological examination allows the identification of possible characteristics compatible with schwannoma. The treatment of this neoplasm consists of surgical excision with a safety margin to ensure a reduction in recurrence rates and favor a good prognosis.

The objective of this report was to describe the case of a young patient with glossopharyngeal nerve schwannoma in the oral cavity who underwent surgical treatment.

CASE REPORT

This report was approved by the Research Ethics Committee of the Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil – under opinion number 6.224.417.

A young 16-year-old Caucasian woman was admitted to a tertiary hospital after referral to the Emergency Care Unit with a history of a mass in the oral cavity with 2 months of evolution, associated with dysphagia and dysphonia. She denied dyspnea, fever, or recent weight loss. At the initial evaluation, the patient had a protuberance in the posterior region of the oropharynx on the left, with a smooth texture and fibroelastic on palpation. An incisional biopsy of the expansive lesion was performed under general anesthesia, removing whitish fragments that were sent for anatomopathological analysis by immunohistochemistry, which showed low-grade mesenchymal neoplasia with neural phenotype. Magnetic resonance imaging of the skull and neck was requested to evaluate the extent of the lesion and therapeutic planning, which demonstrated a well-defined expansive formation in the parapharyngeal space on the left, posterolaterally displacing the internal and external carotid arteries, and the jugular vein, with radiological characteristics compatible with a low-aggressive primary neoplasm of probable neural origin. Contrast-enhanced CT scan of the neck was also performed, which showed an expansive formation with heterogeneous

[1] Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brasil;
[2] Serviço de Otorrinolaringologia, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brasil;
[3] Hospital Erasto Gaertner, Curitiba, PR, Brasil.

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enhancement centered in the parapharyngeal space, measuring 5.8 x 3.0 x 4.2 cm in the largest diameters - longitudinal, anteroposterior and transverse - respectively.

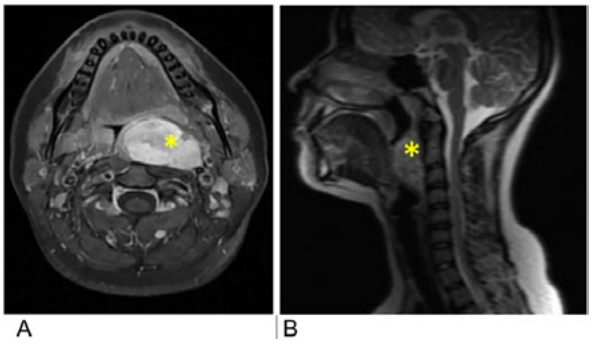

FIGURE 1 — Preoperative T1-weighted magnetic resonance imaging: A) axial section showing the lesion (*); B) sagittal section showing the lesion (*)

Surgical resection was performed with osteotomy of the left lateral mandible, resection of a parapharyngeal tumor, and reconstruction with a microsurgical flap. The patient recovered well after the procedure, complaining of acute pain in the left preauricular region after the first bites of each meal, symptoms compatible with the first bite syndrome, with no other sequelae in the follow-up.

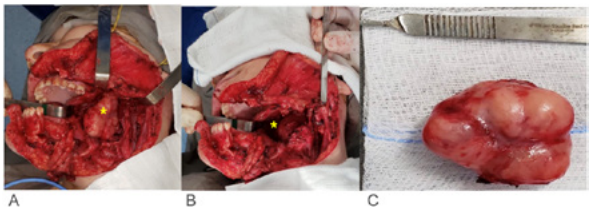

FIGURE 2 — Operative access via mandibulotomy: A) well-defined mass with regular contours visualized in the left parapharyngeal region (*); B) visualization of the operative region after resection of the mass (*); C) appearance of the lesion after resection

DISCUSSION

Schwannoma's is a benign, solitary, slow-growing tumor with rare occurrence in the bucco-maxillofacial region, especially in the oral cavity, as in the case reported.[1,3] In the mouth it is most often seen during the second and third decade of life, with no clear preference for sexes. It mainly affects the soft tissues, with a higher incidence on the tongue.[3] The size of the tumor varies between millimeters and centimeters, rarely exceeding 5 cm.[1] The main symptom reported is painless bulging, and in glossopharyngeal nerve schwannomas the clinical presentation varies from dysphonia, dysphagia and dysarthria to taste changes in the posterior region of the tongue.[2,3] The preoperative diagnosis of schwannoma is difficult, with the differential diagnosis including several benign and malignant causes considering the absence of specific symptoms in the initial phase of the disease.[2] The (CT) images reveal well-circumscribed homogeneous masses that enhance with contrast. However, CT is not very useful in diagnosis due to the limitation of soft tissue differentiation, particularly in small lesions.[1,2] Magnetic resonance imaging is the imaging modality of choice due to the higher tissue contrast and spatial resolution.[1] Histopathological features are used for diagnostic confirmation. Identifying the source nerve can be tricky, as it can be difficult to distinguish between tumors of the lingual, hypoglossal, and glossopharyngeal nerves.[2]

First-bite syndrome should be suspected when the patient describes pain in parotid topography that occurs with the first bite of each meal and improves with subsequent bites. The pathophysiology has been attributed to the unbalanced sympathetic and parasympathetic innervation of the parotid gland and is typically related to the operations of the parotid or parapharyngeal region.[4]

Surgical excision of benign schwannoma with a safety margin is the treatment of choice and favors a good prognosis for the patient, as well as a lower chance of recurrence and malignant transformation of the lesion. Radiotherapy is not indicated. Early diagnosis and the work of multidisciplinary teams are essential for a positive outcome of the condition.

Authors' contributions:
Conceptualization: José Fernando Polanski
Formal analysis: Carolina Rodrigues Laranjeira Vilar
Research: Marja Cristiane Reksidler, Erika Yumi Nakagawa
Methodology: Arthur Ricardo Carminatti Ortinã
Supervision: José Fernando Polanski
Written by: Louise Ferreira Iunklaus, Felipe Lopes de Moraes Pironatto
Writing (proofreading and editing): José Fernando Polanski

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Surgical treatment of Gradenigo's syndrome

Tratamento cirúrgico da síndrome de Gradenigo

José Fernando Polanski[1,2], Erika Yumi Nakagawa[1], Louise Ferreira Iunklaus[1], Arthur Ricardo Carminatti Ortinã[1], Carolina Rodrigues Laranjeira Vilar[1], Enzo Zanelato[2], Eduardo de Barros Sarolli[1,3]

KEYWORDS: Gradenigo's syndrome. Abducens nerve palsy. Media acute otitis. Petrous apicitis. Petrositis.
PALAVRAS-CHAVE: Síndrome de Gradenigo. Paralisia do nervo abducente. Otite média aguda. Apicite petrosa. Petrosite.

INTRODUCTION

Gradenigo syndrome (GS) was first described by Guiseppe Gradenigo in 1907, and is characterized by the triad: otitis media complicated with otorrhea, facial pain in the trigeminal nerve region, and abducens nerve palsy.[1] This condition can be explained by the dissemination, by contiguity, of the middle ear infection to the apex of the petrous part of the temporal bone through aerated bone cells. In areas close to the petrous apex, passages of the abducens and trigeminal nerves are located, which can lead to paralysis and pain in the area of innervation of these.[2]

Diagnosis includes detailed history, thorough physical examination, and neurological evaluation. Imaging exams such as computed tomography and magnetic resonance imaging are essential for the differential diagnosis as well as to aid in therapeutic decision and surgical planning.

The treatment is still controversial. Most authors are in favor of early surgical intervention, while new reports have described satisfactory results with conservative treatment alone.

With the advent of potent antibiotics, complications of ear infections have become increasingly rare, and the incidence of GS has been decreasing. It is currently considered a rare but potentially fatal disease.

The objective of this article is to report a clinical case of GS as a complication of acute otitis media.

CASE REPORT

This report was approved by the Ethics Committee of the Hospital de Clínicas of the Federal University of Paraná - Curitiba, PR, Brazil - under opinion number 6.553.230.

A young 13-year-old boy presented with an initial clinical picture of severe frontal headache for about 1 month, evolving 2 weeks later with worsening of the headache associated with right otalgia, high fever and diplopia. He sought emergency medical attention and was referred to a tertiary service. On physical examination, the patient was in regular general condition, feverish, and presented paralysis of the 6th cranial nerve on the right. Other aspects of preserved extrinsic ocular mobility. Left otoscopy was within normal ranges, and the right showed an intact tympanic membrane, but bulging and hyperemic. He did not present phlogistic signs in mastoids or signs of peripheral facial paralysis. Computed tomography of the ears and mastoids and skull showed signs of acute otomastoidopathy on the right, complicated by collection involving the petrous apex and promoting regional osteolysis. There was also an association with asymmetric enhancement involving Meckel's cavum, Dorello's canal, and cavernous sinus on the right, which is probably reactional in nature. Based on the clinical and radiological findings, the diagnosis of Gradenigo syndrome was confirmed (Figures 1 and 2).

During hospitalization, ceftriaxone and metronidazole were initiated. The patient developed intolerance to metronidazole, which was replaced by clindamycin. On the 3rd day, with no improvement in the condition with clinical measurements, he underwent mastoidectomy and tympanotomy with placement of a ventilation tube on the right, a procedure performed without complications.

On the first postoperative day, he reported improvement in headache, and he still had diplopia and paralysis of the abducens nerve. After 14 days of hospitalization, he was discharged from the hospital with complete improvement of symptoms. There

[1] Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil;
[2] Otorhinolaryngology Service, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil;
[3] FAG University Center, Cascavel, PR, Brazil

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was total involution of the paralysis of the 6th cranial nerve on the right.

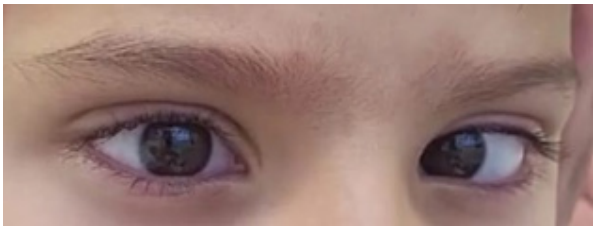

FIGURE 1 — Image of abducens nerve palsy on the right.

FIGURE 2 — Axial computed tomography scan demonstrating the involvement of the right temporal bone, including the petrous apex region (*).

DISCUSSION

The patient presented classic signs and symptoms of GS. However, studies show that only 13-42% of patients with petrous apicitis have the complete triad.[1,2]

Most cases result from acute otitis media and can be explained by the anatomy of the petrous portion of the temporal bone. The spread of the infection from the middle ear to the petrous apex occurs through aerated cells, which are found in 80% of people in the mastoid and in only 30% in the apex of the petrous part.[3] The apex is separated only by the dura mater of the ganglion of the trigeminal nerve and the canal of Dorello, through which the abducens nerve passes, making them more vulnerable to extradural inflammation in petrous apicitis. Retroorbital/facial pain is a result of trigeminal nerve involvement, and diplopia occurs due to involvement of the abducens nerve, which innervates the lateral rectus muscle. Cranial nerve involvement may take time to appear, occurring from 1 week to 3 months from the onset of otitis.[4]

Imaging studies are essential for the diagnosis of petrosal apex lesions, differential diagnoses, therapeutic decision, surgical planning, as well as confirmation or exclusion of intracranial complications. CT scan may show bone erosions and aerated cell opacification. MRI is useful for evaluating soft tissue injuries, and can provide more details, including the cause of the injury, nerve and meningeal involvement, possible underlying osteomyelitis, and neoplastic lesions.[5]

Possible intracranial complications include meningitis, intracranial abscess, or cavernous sinus thrombosis. In addition, it can affect other cranial nerves such as facial, trochlear, vestibulocochlear, vagus, oculomotor, glossopharyngeal, or accessory. Ophthalmologic complications such as papilledema, proptosis, and spread through the sympathetic plexus around the carotid artery leading to Horner's syndrome have also been described.[4]

There is no consensus in the literature regarding the treatment of GS. Because it is potentially fatal, most authors recommend early surgical intervention with tympanotomy with ventilation tube associated or not with surgical drainage of the mastoid. However, some recent studies have demonstrated success in conservative treatment with the use of broad-spectrum antibiotics, reserving surgical treatment for conditions refractory to conservative therapy or those with signs of a chronic process.[1]

Thus, it is believed that cases should be evaluated individually taking into account the clinical evolution and associated surgical risks. In this case, we opted for a combination of surgical intervention and antibiotic therapy, with significant improvement of all signs and symptoms.

Authors' contributions

José Fernando Polanski – Conceptualization, Writing (original draft)
Erika Yumi Nakagawa – Research, Methodology
Louise Ferreira Iunklaus – Methodology, Research
Arthur Ricardo Carminatti Ortinã – Investigation, Writing (original draft)
Carolina Rodrigues Laranjeira Vilar – Conceptualization, Methodology
Enzo Zanelato – Research, Conceptualization
Eduardo de Barros Sarolli – Supervision, Writing (original draft)

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Chondroid syringoma in the external auditory canal

Siringoma condroide em meato acústico externo

José Fernando Polanski[1,2], Carolina Rodrigues Laranjeira Vilar[2], Louise Ferreira Iunklaus[2], Arthur Ricardo Carminatti Ortinã[2], Erika Yumi Nakagawa[2], Ana Carolina Machado Maciel[1], Gabriel Felipe Moreira de Souza[2]

KEYWORDS: Ear canal. Conductive hearing loss. Chondroid syringoma.
PALAVRAS-CHAVE: Meato acústico externo. Perda auditiva condutiva. Siringoma condroide

Lesion (*) at the entrance of the right external auditory canal

INTRODUCTION

Chondroid syringoma, also called mixed skin tumor, is a rare benign neoplasm originating from eccrine or apocrine sweat glands. Clinically, it is characterized by a single, well-defined, slow-growing, usually painless and asymptomatic nodular lesion. The head and neck region is the most frequently affected, especially the scalp, face, and nose. Its size varies from 0.[5] to 3 cm with an approximate incidence of 1% of skin tumors.[1,2] The diagnosis is challenging due to clinical nonspecificity, and histopathological confirmation is essential, often associated with immunohistochemical study. The treatment of choice is complete surgical excision, usually with a low recurrence rate.[2]

CASE REPORT

The research was approved by the Research Ethics Committee of the Hospital de Clínicas of the Federal University of Paraná, Curitiba, PR, Brazil – under no. 6.553.235.

A 69-year-old woman was referred to the otorhinolaryngology service complaining of hypoacusis, otalgia and foreign body sensation in the right external acoustic meatus, which began about 6 months ago. Otoscopy revealed a pearlaceous mass with vessels in the posteroinferior region of the right external auditory canal, obstructing approximately 90% of the circumference, resulting in ipsilateral conductive hearing loss. Contrast-enhanced computed tomography of the ear and mastoid showed a rounded formation, with lobulated contours and polypoid aspect, with diffuse but heterogeneous contrast enhancement. The lesion originated in the posterior portion of the right external auditory canal, measuring 2.2 x 2.0 x 2.0 cm, with no signs of erosion of adjacent bone structures. She underwent surgical excision of the lesion under general anesthesia, with complete removal and flap preparation for better aesthetic results. Anatomopathological examination, associated with immunohistochemistry, confirmed the diagnosis of chondroid syringoma. In the outpatient follow-up, the patient remained without recurrence, with complete improvement of symptoms.

DISCUSSION

Chondroid syringoma is a rare tumor, described by Billroth in 1859 as a neoplasm similar to mixed salivary gland tumors. Hirsch and Helwig consolidated the term in 1961, describing its origin in sweat glands.[1] Reports in this topography are scarce in the literature.[3] When present in this location, it can cause otological symptoms, such as hypoacusis and ear fullness. Differential diagnosis includes epidermal cysts, inflammatory polyps, osteomas, pleomorphic adenomas, schwannomas, and squamous cell carcinoma. Complementary investigation with imaging studies helps in defining the extent of the lesion and in surgical planning, but a definitive diagnosis is only possible with histopathological analysis. Histologically, chondroid syringoma is composed of epithelial elements (ductal and tubular structures, with eccrine/apocrine differentiation) and mesenchymal stroma (with chondroid, fibrous, adipose or myxoid areas).[1] Immunohistochemistry helps to differentiate it from other neoplasms with a similar appearance, such as pleomorphic adenoma of the salivary glands. Although malignant

[1]Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil;
[2]Otorhinolaryngology Service, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil.

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transformation is rare, aggressive cases have been reported, justifying the need for long-term clinical follow-up.[4] The treatment of choice is complete surgical excision with safety margins, aiming to reduce the risk of recurrence. Other therapeutic approaches, such as electrodesiccation, dermabrasion, and vaporization with CO2 laser, have been described, but have presented less satisfactory results.[2]

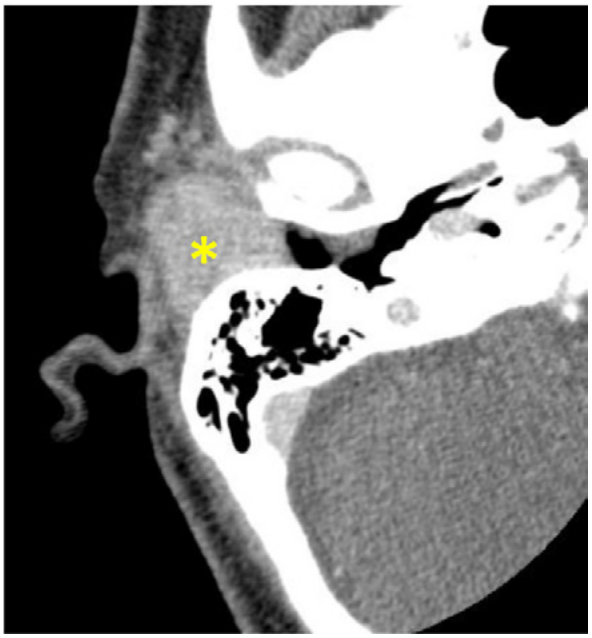

FIGURE 1 — Axial CT scan showing lesion (*) at the entrance of the external auditory canal

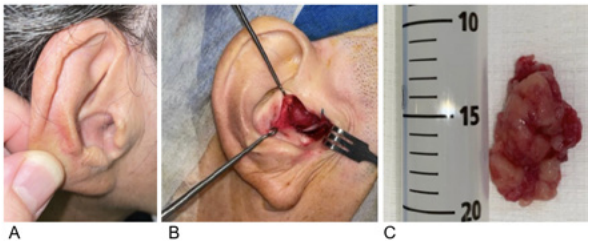

FIGURE 2 — Right external acoustic meatus: A) mass obstructing 90% of the meatus circumference; B) Lempert type 3 surgical access to remove the tumor; C) Extension of excised mass (cm)

As a final message, chondroid syringoma is a rare benign neoplasm that is difficult to diagnose clinically due to the non-specificity of the symptoms. The case presented here highlights the importance of histopathological evaluation and a complete surgical approach and long-term follow-up due to the possibility, albeit remote, of recurrence or malignant transformation.

Authors' contributions

Conceptualization: José Fernando Polanski
Formal analysis: Louise Ferreira Iunklaus
Investigation: Erika Yumi Nakagawa, Gabriel Felipe Moreira de Souza
Methodology: Arthur Ricardo Carminatti Ortinã
Supervision: José Fernando Polanski
Writing: Carolina Rodrigues Laranjeira Vilar, Ana Carolina Machado Maciel
Writing (proofreading and editing): José Fernando Polanski

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PSA and Gleason: keys to understanding prostate cancer staging

PSA e Gleason: chaves para compreender o estadiamento do câncer de próstata

João Arthur Motta dos Santos[1], Pedro Henrique Duarte Carvalho[1], Paulo Eduardo Dietrich Jaworski[2], Samya Hamad Mehanna[1]

ABSTRACT

Introduction: Prostate cancer is the most common neoplasm in men in Brazil, except for non-melanoma skin cancer. Prostate-specific antigen (PSA), although useful, can be elevated in benign conditions. Therefore, biopsy and Gleason score (GS) are essential for diagnosis, risk stratification, and understanding the relationship with factors such as body mass index.

Objective: To evaluate the correlation between PSA and GS, and to compare the GS obtained by biopsy with that of the surgical specimen (SC).

Method: This is an epidemiological, cross-sectional, retrospective study carried out by collecting data from the medical records of patients diagnosed with prostate cancer treated at a tertiary hospital, cataloging clinical data, laboratory tests, and anatomopathological findings. The sample consisted of 109 men.

Result: The mean age was 67 years. The most common stage of PSA was 7 (70.64%), with 40.36% corresponding to the sum of 3 + 4 and 30.27% to 4 + 3. When comparing age variables with PSA, there was no significant difference between the groups by age group. When comparing the PSA results from the biopsy with that from the surgical specimen, it was found that 13.76% were understaged and 30.27% were overstaged. There was no statistical significance in the comparison between PSA values and PSA results from the surgical specimen.

Conclusion: Discrepancies were observed between the PSA results from the biopsy and the PSA results from the surgical specimen, demonstrating difficulties in staging patients, which may impact treatment choice and prognosis in prostate cancer.

KEYWORDS: Prostate specific antigen. Neoplasm grading. Prostatic neoplasms.

Central Message

Prostate cancer is the most common neoplasm in men in Brazil. Prostate-specific antigen (PSA), while useful, can be elevated in benign conditions as well. Thus, biopsy and Gleason score are fundamental for diagnosis, risk stratification, and understanding of the relationship with various factors such as body mass index

Perspective

The discrepancies between the results of the Gleason score of the biopsy and those of the surgical specimen demonstrate difficulties in the staging of patients, which can impact the choice of treatment and prognosis in prostate cancer.

RESUMO

Introdução: O câncer de próstata é a neoplasia mais comum em homens no Brasil, exceto pele não melanoma. O antígeno prostático específico (PSA), embora útil, pode elevar-se em condições benignas. Assim, a biópsia e o escore de Gleason (EG) são fundamentais para diagnóstico, estratificação de risco e compreensão da relação com fatores como índice de massa corpórea.

Objetivo: Avaliar a correlação entre o PSA e o EG, e comparar o EG obtido pela biópsia e o da peça cirúrgica.

Método: Trata-se de estudo epidemiológico, transversal e retrospectivo realizado a partir da coleta dos dados de prontuários de pacientes diagnosticados com câncer de próstata atendidos em hospital terciário, catalogando dados clínicos, exames laboratoriais e anatomopatológicos. A amostra foi composta por 109 homens.

Resultado: A média de idade foi de 67 anos. EG mais observado foi o 7 (70,64%), sendo 40,36% correspondente à soma 3 + 4 e 30,27% a 4 + 3. Ao cruzar as variáveis de idade com o EG, não houve diferença significativa entre os grupos por faixa etária. Ao comparar o EG da biópsia com o da peça cirúrgica, constatou-se que 13,76% foram subestadiados e 30,27% super. Não houve significância estatística na comparação entre os valores de PSA e o EG da peça cirúrgica.

Conclusão: Foi possível observar discrepâncias entre o resultado do EG da biópsia e da peça cirúrgica, demonstrando dificuldade no estadiamento dos pacientes, o que pode impactar na escolha do tratamento e no prognóstico no câncer de próstata.

PALAVRAS-CHAVE: Antígeno prostático específico. Gradação de tumores. Adenocarcinoma prostático.

[1] Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil;
[2] Hospital Universitário Evangélico Mackenzie, Curitiba, PR, Brazil

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INTRODUCTION

Prostate cancer (PC) represents an important public health problem on a global scale, with a higher incidence in developed countries. It is characterized by the uncontrolled growth of prostate cells, significantly affecting the health of individuals. According to estimates by the National Cancer Institute (INCA), for the 2023–2025 triennium, about 72 thousand new cases are expected per year in Brazil, corresponding to 10.2% of the total number of neoplasms diagnosed in the period. When non-melanoma skin cancer is excluded, PC is the most common malignant neoplasm among Brazilian men.[1]

Predominant in individuals with advanced age, PC is rare in patients younger than 50 years, with a mean age at diagnosis of 68 years.[2] The introduction of prostate-specific antigen (PSA) as a biomarker helped in the early detection of the disease, contributing to the reduction of advanced cases and the increase in diagnoses of localized tumors.[2,3] However, it has important limitations, such as low specificity and sensitivity. High levels can be associated with benign conditions, such as benign prostatic hyperplasia, chronic prostatitis, and even factors such as prostatic manipulation and recent ejaculation.[4,5] The positive predictive value of PSA is estimated at only 25%, which results in a significant number of unnecessary biopsies.[6]

The Gleason score (EG) is the main histopathological tool used for the classification and prognosis of PC. This system evaluates the degree of cell differentiation and is represented by the sum of 2 predominant histological patterns, ranging from 2 to 10, with higher scores indicating more aggressive neoplasms.[7] In order to improve its clinical applicability, the International Society of Urologic Pathology (ISUP) proposed alternative gradation, aiming at standardization and better prognostic stratification.[8,9]

Although widely used, ultrasound-guided transrectal prostate biopsy — the gold standard for initial diagnosis — has limitations, with false-negative rates ranging from 21-28%, in addition to histological underestimation in up to 17% of cases.[10] Studies have shown a significant discrepancy between the EG obtained in the biopsy and that determined in the surgical specimen after radical prostatectomy, with underestimation rates of up to 74.6% and overestimation in about 11% of the cases.[11-13]

In view of these diagnostic limitations, it is relevant to investigate the accuracy of the histopathological staging of PC by comparing the Gleason scores obtained by biopsy and surgery, as well as to explore the correlation between PSA levels and tumor aggressiveness. Such analyses can contribute to a more accurate staging, helping to define the prognosis and the most appropriate therapeutic choice.

METHOD

This study was approved by the Human Research Ethics Committee of the Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil – CAAE:71607223.9.0000.0103

This is a retrospective, cross-sectional, observational, and quantitative study. The population was restricted to patients classified by the International Classification of Diseases (ICD-10) as malignant neoplasm of the prostate (C61) between November 1, 2019 and April 17, 2023 who entered the Urology Service and Mackenzie Evangelical Hospital in Paraná, totaling an initial number of 269 (n=269). In addition, demographic data were collected on age considering the number of completed years at the time of the operation, pre- and postoperative PSA levels, and pre- and postoperative EG.

Of these, those who had already undergone previous radiotherapy, hormone therapy, any previous manipulation of the prostate, and had other tumors of the male genitourinary tract were excluded. Risk stratification was performed according to the criteria of the European Association of Urology using PSA and ISUP values; however, due to the lack of detailed data, digital prostate examination was not used as a criterion. In addition, patients with incomplete and duplicate medical records were excluded, resulting in 109 patients (n=109).

Statistical analysis

The collected data were compiled on the Excel platform. For the statistical analysis, the chi-square test, the Kruskal-Wallis test and Pearson's correlation test were used, and values of $p<0.05$ were considered statistically significant.

RESULT

After selection according to the eligibility criteria, 109 patient records were included for analysis during the stipulated period. The mean and median ages were 67 years, with 95.41% between 50 and 79 years. The standard deviation was 7.14.

The most observed EG was 7, totaling 70.64%. In the distribution by ISUP prognostic group, there was a higher frequency of ISUP 2 (40.36%) compared to ISUP 3 (30.27%). When comparing the EG of the biopsy with the EG of the surgical specimen, the ISUP biopsy with the ISUP specimen, and the risk stratification using the chi-square test, a statistically significant difference was found between the values obtained in the biopsy and in the surgical specimen ($p<0.01$). When analyzing these data, it was found that, of the 109 patients, 13.76% were overclassified and 30.27% were underclassified (Table 1).

TABLE 1 — Overall and subgroup agreement rate

	Total	6	7	8	9	10
n patients	109	26	60	13	8	2
Overclassification	15(13.7%)	0	3(5%)	6(46.2%)	4(50%)	2(100%)
Concordant classification	61 (56%)	5 (19.2%)	80.00%	4(30.7%)	4(50%)	0
Subclassing	33(30.3%)	21(80.8%)	9(15%)	3(23.1%)	0	0

The correlation between the EG of the biopsy and that of the surgical specimen was performed, and a moderate and statistically significant correlation was identified

(R=0.43; p<0.01). When comparing age with EG and with the ISUP, there was no significant difference between the groups, but there was a trend towards statistical significance when comparing age with risk stratification (Table 2).

TABLE 2 — Comparison of age (y-axis) with the patient's risk stratification (x-axis, n=109, p=0.077191)

	Low	Medium	High	Total
40-49	0	2	0	2
50-59	2	10	4	16
60-69	2	33	15	50
70-79	0	20	18	38
80+	1	1	1	3
Grand total	5	66	38	109

When performing specific analysis by age groups, comparing the EG of the biopsy with the EG of the surgical specimen, the ISUP biopsy with the ISUP specimen, and the risk stratification (RE) before the operation with the postoperative one, only the 70-79 year group showed a statistically significant difference in the comparisons between the pre- and postoperative findings (p<0.05, Table 3). Data on patients under 40 years of age were excluded from this comparison due to the low sample representation.

TABLE 3 — Disagreement of biopsy and preoperative RE findings with PC and post-RE findings by age group

	EG biopsy vs EG PO	ISUP biopsy vs ISUP PO	ER pre x ER PO
50-59	0.8732	0.9469	0.49874
60-69	0.0692	0.1444	0.00388
70-79	0.0111	0.0097	0.00349
80+	1	1	1

EG = Gleason score; PO=post-surgery; ER=Risk stratification; ISUP=International Society of Urological Pathology

It is noteworthy that we chose to use preoperative PSA values, as they better reflect the disease status at the time of the operation, and there was a need to eliminate outlier values, resulting in n=104 for the statistical analysis. Using the Kruskal-Wallis test, p=0.46856 was obtained, indicating that there is no statistical significance in the comparison between groups. The preoperative PSA value was also compared with the ISUP as well as with the risk stratification of the surgical specimen, resulting in p=0.36345 and p=0.23414, respectively, without statistical significance.

When relating PSA values as suggested by the guidelines of the European Association of Urology with EG, ISUP and risk stratification, no significant difference was found between the groups.

DISCUSSION

Gleason, age, and risk stratification

The high incidence of PC in Brazil requires special public health attention.[1] It is crucial to understand in depth the epidemiological profile of affected men, including histopathology, and risk stratification. With this knowledge, authorities can promote early diagnosis, develop effective treatment strategies targeted at specific groups, and increase patient survival.

Thus, the comparison of the data collected and analyzed with the national and international literature makes it possible to identify relevant characteristics. Regarding epidemiology, 83.49% of the patients were 60 years of age or older, and there were no patients under 40 years of age, which is in accordance with the international literature, which reports a significant increase in risk with age.[14-16]

In the sample, it was observed that 7.33% patients had EG 6, 70.64% had EG 7 and 21% had the sum of EG 8 and 9, which conflicts with the data available in the international literature, which indicate a more balanced distribution, with around 41% EG 6, 36% EG 7 and 15.2% EG 8-10.[17] This can be explained by the exclusion of data from patients who did not undergo RP, leading to an increase in the mean EG.

In the data collected in this study, no significant correlation was identified between older ages with EG and UPSI, but there was a trend towards significance in the correlation between higher age and risk stratification, which is in line with the international literature, which indicates this relationship.[18-20] This result indicates the need for further studies, with larger samples, so that the data presented are more reliable for the Brazilian population.

Gleason super and subclassification

In the sample analyzed, a significant number of underclassifications (13.76%) and overclassifications (30.27%) were observed, with a significant difference according to the statistical analysis. In the literature, discrepancy rates of up to 51% between the EG of the biopsy and the surgical specimen are also being observed, and this leads to questions about the accuracy of the chosen treatment and the need for further evaluation of patients, reinforcing that treatments for PC should not be based exclusively on EG.[21-23]

King in 2000[24] suggested that, given the clinical implications of EG, staging of organ-confined PC should include the likelihood of histological update when EG are used in the following settings: stratification of patients for clinical trials; comparison of outcomes for specific therapies based on biopsy classification; the use of tables or formulas to predict update risks; and for the recommendation of radical therapy.

It is worth noting that in the 70-79 age group, there were significant disagreements between the pre- and post-surgical data. The target population of PC is an older population and is characterized by tumor heterogeneity. This leads to increased discordance between biopsy and PC, especially at older ages.[25] In addition, PC upgrading is also more likely to occur in older patients,26 which may be due to physicians tending to offer less aggressive treatments to elderly patients.[27]

Because the tumor volume of older patients is larger, and because the biopsy targets small samples, the result may not reproduce reality. The true staging is established only with the PC, which will have the total volume of the tumor for analysis.

PSA and histological grade

The data found did not demonstrate a significant

correlation between higher PSA values with higher EG, and there was also no statistical significance when comparing it with the risk stratification of PSA, according to the EAU, disagreeing with data in the international literature.[19] However, it is not possible to affirm this in this study, and further research is needed to establish a larger sample of the Brazilian population.

In the literature, there are studies that emphasize that the extremes of PSA are not linearity in relation to the degree of the neoplasm; levels below 3.5 ng/ml tend to cause tumors in a more advanced stage in relation to those with PSA between 3.5 and 10 ng/ml.[28] In PSA above 70 ng/ml, the prognosis worsens, but ends up plateauing.[29] Such facts may affect an attempt at direct correlation even with the removal of outlier values.

The analysis revealed important limitations, such as the absence or incompleteness of data on the Gleason score of the surgical specimen in part of the sample, which impacted the statistical consistency of the results. Despite this, the study was conducted with methodological rigor and offers relevant contributions on PC in the population treated by a university hospital, serving as a basis for future more comprehensive investigations.

CONCLUSION

The study identified the importance of screening in higher-risk groups. The significant rate of over- and underestimation of EG in biopsies indicates that this parameter should not be used in isolation for therapeutic decisions. The absence of correlation between high PSA and high EG reinforces the limitations of PSA as a predictor of aggressiveness. Thus, the need for a multiparametric approach for the staging and appropriate management of prostate cancer is highlighted.

Authors' contributions
João Arthur Motta dos Santos – Conceptualization, Formal Analysis
Pedro Henrique Duarte Carvalho – Methodology, Research
Paulo Eduardo Dietrich Jaworski – Supervision, Writing (proofreading and editing)
Samya Hamad Mehanna - Project Management

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BioSCIENCE Case Report
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When the body turns against itself: a significant case of antisynthase syndrome with positive anti-Jo-1

Quando o corpo se volta contra si: um caso marcante de síndrome antissintetase com anti-Jo-1 positivo

Rafaely Cristine dos Santos[1], Fernanda Nicoly Jobins Jarentchuk[1], Giovanna Jorge Sabino[1], Tailine Fontanella Galvani[1], Thelma Larocca Skare[1]

KEYWORDS: Dermatomyositis. Myositis. Arthritis. Glucocorticoids.
PALAVRAS-CHAVE: Dermatomiosite. Miosite. Artrite. Glucocorticoides.

INTRODUCTION

Idiopathic inflammatory myopathies are a group of autoimmune diseases that, although they primarily affect the muscles, often involve other organ systems.[1] There are several subtypes of myositis that course with their own clinical profile. One of the most significant extramuscular manifestations with a prognostic impact is interstitial lung disease (ILD), which is the main pulmonary manifestation in patients with IIM.[1]

Within the spectrum of connective tissue diseases that are associated with ILD, antisynthetase syndrome (ASA) is considered one of the most common variants.[1] ASA is characterized by a constellation of clinical findings, including myositis, fever, Raynaud's phenomenon, "mechanic's hands," arthritis, and, crucially, ILD.[1,2] This syndrome is strongly associated with the presence of antibodies directed against aminoacyl-tRNA synthetases, with the anti-Jo-1 antibody — directed against histidyl-tRNA synthetase — being the most frequently detected.[2]

Myositis is the most classic manifestation of antisynthetasis and is central to the diagnosis.[3,4] The anti-Jo-1 antibody may be present and related to important clinical and prognostic manifestations, especially in pulmonary involvement.[4] The presence of characteristic skin changes (mechanic's hands) is a classic finding whose examination is easily accessible, guiding the physician to search for and treat possible pulmonary involvement early.

The objective of this report was to describe and analyze the clinical case of a patient with antisynthetase syndrome, confirmed by the positivity of the anti-Jo-1 antibody. The report will detail the clinical manifestations presented by the patient, with attention to myositis and skin changes, and discuss the relevance of the anti-Jo-1 antibody as a marker in the antisynthetase syndrome.

CASE REPORT

This report was approved by the Research Ethics Committee of Faculdade Evangélica Mackenzie - CEP/FEMPAR, Curitiba, PR, Brazil under protocol 7.787.404 and the patient agreed with the description by signing a free and informed consent form.

A 50-year-old man, an auto mechanic, started the condition in November 2024 with inflammatory joint pain in his hands and knees, accompanied by morning stiffness of approximately 30 min. In December 2024, he developed interstitial pneumonia, when he was diagnosed with pulmonary fibrosis. In January 2025, the condition worsened, with the appearance of daily fever, loss of 8 kg and progressive muscle weakness. In May 2025, complaints of erythematous skin lesions on the left arm and abdomen persisted, as well as pain and asymmetric muscle weakness in the lower limbs, which were more pronounced on the right.

The examinations performed revealed the following: 1) standard chest tomography of pulmonary fibrosis with ground-glass opacities and bronchiectasis; 2) spirometry with severe restrictive disorder (FVC 49%, DLCO 44%); 3) elevated inflammatory markers (ESR 38 mm/h, CRP 5.9 mg/dL) with increased CPK (791 U/L) indicating myositis activity; 4) anti-Jo1 antibody with significantly high titer (>200); 5) abdominal ultrasonography with left renal lithiasis and grade II hydronephrosis; 6) Ultrasonography of the wrists revealed bilateral compressive neuropathy.

The patient had serological and clinical markers compatible with antisynthetase syndrome, especially the high-titre anti-Jo1 (>200), which confirms the diagnosis. Cutaneous manifestations included "mechanic's hands", with thickening and fissures in the fingers, as well as erythematous lesions on the arm, left forearm, and abdomen and are considered characteristic of

[1]Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brasil.

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this syndrome. Pulmonary involvement was evidenced by interstitial fibrosis on imaging studies (chest CT with ground-glass opacities), whereas muscle weakness (quadriceps 5/5, glutes 4/5) and elevation of CK (791 U/L) and aldolase (5.91) reinforced myopathic involvement.

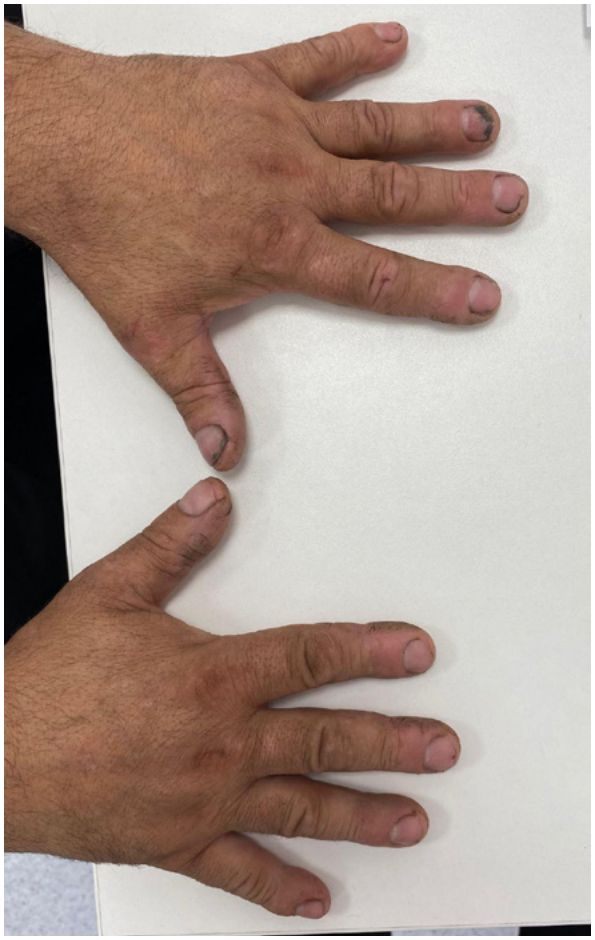

FIGURE — Characteristic cutaneous manifestation of dermatomyositis, showing the "mechanic's hands" sign, with hyperkeratosis and fissures in the digital pulps.

The therapeutic approach was based on immunosuppression with mycophenolate mofetil (500 mg 3x/day) and prednisone at high doses (30 mg/day) followed by gradual reduction. In addition, supplements (calcium and vitamin D) were prescribed for the prevention of osteoporosis and physical therapy for muscle rehabilitation. Planning included laboratory monitoring (CK, pulmonary function) and follow-up at the rheumatology outpatient clinic for reassessment.

At the last return visit (05/12/2025), the patient reported subjective improvement; however, he persisted with weakness in the lower limbs and active skin lesions. There was no respiratory worsening, but he remained sedentary due to physical limitations. The reduction in prednisone was tolerated without intercurrences, and mycophenolate was maintained at the dose. Laboratory tests showed inflammatory stability (CRP 3.7 mg/L), with no additional elevation of muscle enzymes. Continuous follow-up was reinforced for therapeutic adjustment according to clinical response.

DISCUSSION

The strong interrelationship between amyositis and antisynthetase antibodies (ASA) such as the anti-Jo-1 antibody configures a pathogenic axis of great clinical relevance, since this entity can manifest as a subtype of idiopathic inflammatory myopathies within the ASA spectrum.[1] In this context, the detection of the anti-Jo-1 antibody, the most common antisynthetase antibody in patients with dermatomyositis, acquires significant prognostic importance, since it is closely related to specific clinical manifestations and a higher risk of pulmonary involvement.[2,4]

In this scenario, the identification of classic cutaneous signs, such as "mechanic's hands", becomes a crucial element in the physical examination, functioning as an easily accessible marker that can direct the clinician to the investigation and early management of ILD, an extramuscular complication with the greatest impact on the morbidity and mortality of these patients.[1,3]

The differential diagnosis of autoimmune myositis is broad and should consider its association with malignant neoplasms, which occurs in up to 30% of cases, especially in the first years after diagnosis.[1] The most frequently related tumors include ovarian, lung, breast, colorectal cancer, and non-Hodgkin's lymphomas, with elderly patients and those with severe skin manifestations at higher risk.[1]

In addition to oncological investigation, it is essential to differentiate autoimmune myositis from other conditions that course with muscle weakness and dermatological changes.[1] Among the differential diagnoses, muscular dystrophies stand out, which generally have a slower evolution and a positive family history, as well as metabolic and endocrine myopathies.[1]

Autoimmune necrotizing myopathy, associated with the use of statins and the presence of anti-HMG-CoA reductase antibodies, is another important diagnosis, as it can mimic antisynthetase syndrome in clinical and histopathological aspects, although it typically does not present the characteristic cutaneous manifestations of that of this entity.[1]

For the definitive diagnosis, a combination of clinical criteria, laboratory tests (CK and aldolase elevation), electromyographic and histopathological findings is recommended, and muscle biopsy is essential to demonstrate the typical perivascular and perifascicular inflammatory infiltrate.[5] The search for specific autoantibodies (anti-Mi-2, anti-TIF1γ, anti-NXP2) helps not only in diagnostic confirmation, but also in risk stratification for neoplasms and systemic complications.[5]

The anti-Jo-1 antibody is the most frequent anti-synthetase antibody, being present in 60-70% of cases.[6] This antibody is associated with clinical manifestations such as ILD, myositis, arthritis, and cutaneous involvement, playing a relevant role in the activity and progression of the disease.[7-9]

Studies investigated the relationship between serum anti-Jo-1 levels and ASA activity in 115 antibody-positive patients.[10] The results showed that baseline levels of anti-Jo-1 were lower in patients with ILD at the time of

diagnosis compared to those without ILD (122 vs. 158 U/ml, p=0.012), suggesting possible variation in the immune response according to the affected organ.[11,12] On the other hand, higher levels were observed in patients with muscle weakness (168 vs. 122 U/ml, p=0.018), skin involvement (153 vs. 122 U/ml, p=0.009), and arthritis (164 vs. 120 U/ml, p=0.006), indicating a correlation with extrathoracic manifestations.[10]

In longitudinal analyses, variations in anti-Jo-1 levels were shown to be more relevant than absolute values, with significant positive correlations with changes in global disease activity, muscle and lung scores ($p<0.05$). In addition, there was a negative association with pulmonary function parameters (%FVC and %FEV1, $p<0.0001$), reinforcing the potential of anti-Jo-1 as a dynamic marker of organic activity.[6,10] However, baseline levels did not correlate with prognosis, with advanced age and high levels of C-reactive protein being the main risk factors for mortality.

These findings highlight that anti-Jo-1 is more associated with changes in disease activity over time than with initial organic involvement.[10] Therefore, continuous monitoring of the levels of this antibody can offer valuable support for the clinical evaluation and therapeutic management of ASA, especially in patients with pulmonary or muscular involvement.

The prognosis of antisynthetase syndrome is influenced by several factors, including the serologic profile (especially the presence and levels of anti-Jo-1), the severity of pulmonary and muscle involvement, and the response to immunosuppressive therapy. Studies have shown that patients with anti-Jo-1 have a higher risk of progression of ILD, the main determinant of morbidity and mortality in this population.[1,2]

Although anti-Jo-1 is not an independent predictor of mortality, its elevated serum levels (>200 U/mL) are associated with greater overall disease activity and the need for combination therapies.[4] ILD is the leading cause of death, especially in patients with rapid decline in lung function (FVC < 50%).[5]

The prognosis of the patient in question was poor due to the presence of established pulmonary fibrosis and partial response to treatment, but recent clinical stability suggests possible control of the disease with close monitoring. The multidisciplinary approach, including rheumatology, pulmonology, and physiotherapy, is essential to mitigate complications and improve quality of life.

As a final message, the case is highly clinically relevant because it is a patient with antisynthetase syndrome, a rare condition with a potentially severe course. The early identification of specific clinical signs—such as mechanic's hands, proximal myositis, Raynaud's phenomenon, arthritis, and interstitial lung disease—added to positivity for the anti-Jo-1 antibody, allow for timely diagnosis and immediate initiation of immunosuppressive therapy, which was essential for controlling the evolution of the disease and patient survival. In addition, this case reinforces the importance of an interdisciplinary approach and continuous surveillance in the face of possible systemic complications. Interstitial lung disease, which is often associated with antisynthetase syndrome, is one of the leading causes of morbidity and mortality in these patients, which requires regular respiratory function assessment and follow-up with pulmonology.[2,4]

Authors' contributions

Fernanda Nicoly Jobins Jarentchuk – Conceptualization, Formal Analysis
Giovanna Jorge Sabino – Methodology, Writing (original draft)
Rafaely Cristine Dos Santos - Formal Analysis, Conceptualization
Tailine Fontanella Galvani - Formal Analysis, Methodology
Thelma Larocca Skare - Project Administration

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Unraveling vascular inflammation in diabetes mellitus: experimental evidence to guide clinical care

Desvendando a inflamação vascular no diabete melito: evidências experimentais para guiar o cuidado clínico

Luciane Bittencourt Carias de Oliveira[1], Osvaldo Malafaia[1], Fernando Issamu Tabushi[1], Stephanie Rubianne Silva Carvalhal[2], Sérgio Ossamu Ioshii[2], Rodrigo Schuh[2], Laís Soares Rodrigues[2], Thomas Horlem[3], Nicolau Gregori Czeczko[1]

ABSTRACT

Introduction: Endothelial dysfunction, a precursor of vascular diseases, is modulated by systemic inflammation, intensified in type 2 diabetes mellitus (T2DM). Streptozotocin (STZ)-induced models allow investigating the relationship between systemic inflammation and early vascular changes, especially in the aorta.

Objective: To evaluate systemic and vascular inflammation in STZ-induced diabetic Wistar rats by measuring plasma IL-6 and TNF-α and histological/immunohistochemical analysis (CD68) in different aortic segments.

Method: Experimental study with 20 male rats distributed as control (n = 10) and diabetic (n = 10). Plasma samples were analyzed for IL-6 and TNF-α, and aortic segments were subjected to histology and immunohistochemistry.

Result: Diabetic rats showed a significant increase in TNF-α ($p < 0.05$), confirming systemic inflammation. IL-6 remained unchanged. There was no detectable vascular inflammation in any of the aortic segments studied (histology and CD68).

Conclusion: The model demonstrated systemic inflammation associated with T2DM. There was no evidence of detectable vascular inflammation in any of the aortic segments studied. These findings reinforce the usefulness of systemic markers, such as TNF-α, in the early detection of cardiovascular risk in diabetics.

KEYWORDS: Inflammation. Diabetes mellitus. Endothelium. TNF-α, CD68.

RESUMO

Introdução: A disfunção endotelial, precursora de doenças vasculares, é modulada pela inflamação sistêmica, intensificada no diabete melito tipo 2 (DM2). Modelos induzidos por estreptozotocina (STZ) permitem investigar a relação entre inflamação sistêmica e alterações vasculares precoces, especialmente na aorta.

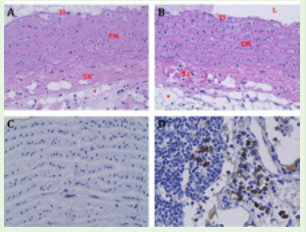
Objetivo: Avaliar inflamação sistêmica e vascular em ratos Wistar diabéticos induzidos por STZ, por meio da dosagem plasmática de IL-6 e TNF-α e da análise histológica/imuno-histoquímica (CD68) em diferentes segmentos da aorta.

Método: Estudo experimental com 20 ratos machos distribuídos em controle (n = 10) e diabético (n = 10). Amostras plasmáticas foram analisadas para IL-6 e TNF-α, e segmentos da aorta submetidos à histologia e imuno-histoquímica.

Resultado: Ratos diabéticos apresentaram aumento significativo de TNF-α ($p < 0,05$), confirmando inflamação sistêmica. IL-6 permaneceu inalterada. Não houve inflamação vascular detectável em nenhum dos segmentos aórticos estudados (histologia e CD68).

Conclusão: O modelo demonstrou inflamação sistêmica associada ao DM2. Não houve evidência de inflamação vascular detectável em nenhum dos segmentos da aorta estudados. Os achados reforçam a utilidade de marcadores sistêmicos, como TNF-α, na detecção precoce do risco cardiovascular em diabéticos.

PALAVRAS-CHAVE: Inflamação. Diabete melito. Endotélio. TNF-α, CD68.



Immunohistochemistry for CD68 in the abdominal aorta showing sparse lymph node macrophages (anti-CD68, 400×)

Central Message

In an experimental model of type 2 diabetes mellitus, increased systemic inflammation (elevated TNF-α levels), but no signs of detectable vascular inflammation, is observed in different segments of the aortic wall. These findings indicate that vascular aggression in diabetes may begin silently, before the onset of visible atherosclerosis, reinforcing the importance of early diagnosis and intervention.

Perspective

The results of this study suggest that systemic inflammation in diabetes precedes any detectable vascular inflammation, analyzing several segments of the aorta. Thus, it opens the opportunity for therapies that aim to modulate the inflammatory response before the development of atherosclerosis. The experimental model of type 2 diabetes, with the use of streptozotocin (STZ), can contribute to the identification of early markers and guide strategies for the prevention of cardiovascular complications in diabetic patients.

[1]Graduate Program in Principles of Surgery, 1Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil;
[2]Federal University of Paraná, Curitiba, PR, Brazil;
[3]Department of Physiology, Federal University of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

Chronic low-grade inflammation is recognized as one of the main pathophysiological mechanisms associated with diabetes mellitus (DM), particularly in regard to increased cardiovascular risk. Patients are more likely to develop atherosclerosis, a phenomenon that results from the complex interaction between metabolic, immunological, and hemodynamic factors. In this scenario, pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), play a central role by modulating processes of insulin resistance, endothelial dysfunction, and vascular remodeling.[1-3]

At the same time, the activation of macrophages in the vascular wall is a critical event in the progression of local inflammation. The CD68 marker, classically used as an indicator of the presence of tissue macrophages, allows the evaluation of the intensity and regional distribution of the inflammatory response in different segments of the arterial tree. The heterogeneity of the aorta, with structural and hemodynamic variations among its segments, can influence cellular infiltration and inflammatory response, configuring potential regional patterns of vulnerability to vascular damage.[4-6]

The simultaneous investigation of systemic inflammatory mediators and cellular markers of vascular inflammation in an experimental model of diabetes provides important subsidies for understanding the interface between systemic inflammation and local inflammation. In addition, the study of these variables in different regions of the aorta can contribute to clarify the initial mechanisms of atherogenesis in diabetic individuals, offering perspectives for the identification of therapeutic targets and strategies for the prevention of cardiovascular complications.[7-9]

Thus, the present study aimed to evaluate the presence of systemic inflammation by means of plasma IL-6 and TNF-α assay, as well as to investigate the expression of CD68 in different segments of the aorta of diabetic rats, seeking to identify possible regional patterns of vascular inflammation associated with diabetes.

METHOD

This is an experimental study, approved by the Ethics Committee on the Use of Animals of the Biological Sciences Sector (CEUA-UFPR), protocol No. 23075.065293/2022-16, in accordance with Law No. 11,794/2008 and current animal experimentation standards (Figure 1).

Twenty male Wistar rats (Rattus norvegicus, Var. Albinus), from previous mating, and kept in standard plastic cages, under a 12-h light/dark cycle, temperature of 23 ± 1°C, with free access to water and commercial feed (Nuvital Nutrients Ltda, Curitiba, PR). The animals were randomly distributed into 2 groups: control (CG, n = 10) and diabetic (GD, n = 10).

Induction occurred on the 5th postnatal day, by single intraperitoneal injection of streptozotocin (STZ, 100 mg/kg), dissolved in 10 mM citrate buffer (pH 4.5). The animals in the control group received only the citrate buffer. Confirmation of diabetes was performed at 80 days of life, by glucose tolerance test (GTT).

During the experiment, the animals were weighed weekly and their growth was evaluated monthly by the Lee index. At 90 days, they were euthanized by decapitation, with blood collected in heparinized tubes, centrifuged at 4528 g for 7 min. The plasma obtained was stored at -80°C. The aorta artery was removed and segmented (arch and abdominal), fixed in formalin and subsequently stored in 70% alcohol for histological and immunohistochemical analyses.

Plasma concentrations of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were determined by enzyme-linked immunosorbent assay (ELISA), as instructed by the manufacturers (Biomatik, Ontario, Canada). Histological analysis (hematoxylin-eosin and Gomori's trichrome) and immunohistochemistry for CD68 were performed at the Ioshii Pathology Diagnostics and Consulting LTDA Laboratory, Curitiba-PR.

Statistical analysis

The data were evaluated for normality using the Shapiro-Wilk test. Comparisons between groups were made using Student's t-test or the Mann-Whitney test, considering $p<0.05$ as significant.

RESULT

Body mass gain was monitored weekly from 4 to 13 weeks of age. No significant differences were observed between the groups in body mass gain or in the area under the curve (AUC) of the Lee index.

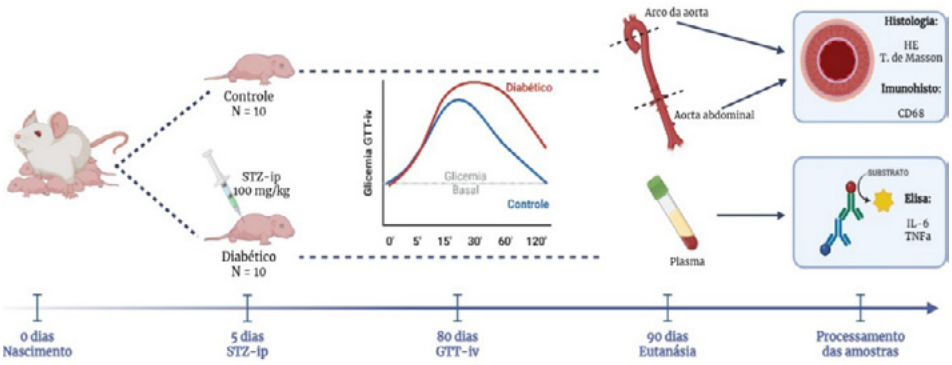
In the intravenous glucose tolerance test (ivGTT), performed at 80 days, the diabetic animals showed marked glucose intolerance compared to controls ($p < 0.0001$, Figure 2).

ELISA analysis revealed significantly higher plasma levels of TNF-α in the diabetic group ($p < 0.0001$), with no differences in IL-6 concentrations between the groups (Figure 3).

The histopathological evaluation of the aortic segments showed exuberant endothelial cells, myxoid deposits and vacuolar degeneration ranging from mild to severe in diabetic animals. No macrophages were detected in histology or immunohistochemistry for CD68, except for a few macrophages in the lymph node of 1 sample (Table and Figure 4). The control group showed no alterations. There was no statistical difference between the segments of the aortic arch and the abdominal aorta.

DISCUSSION

Experimental models of streptozotocin (STZ)-induced diabetes are essential tools to understand the inflammatory and atherosclerotic mechanisms associated with chronic hyperglycemia. Intraperitoneal administration of STZ on the 5th postnatal day, as used in this study, reproduces relevant characteristics of type 2 diabetes mellitus (DM2) and allows early evaluation of vascular alterations. This route of administration presents



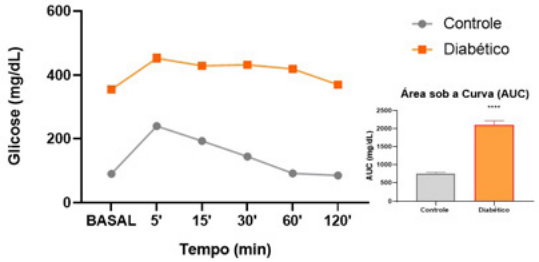
Legend: STZ-ip: Intraperitoneal Streptozotocin; GTT-iv: Intravenous glucose tolerance test.

FIGURE 1 — Scheme of the experimental design

TABLE — Histopathological and immunohistochemical findings in the aortic segments of diabetic rats

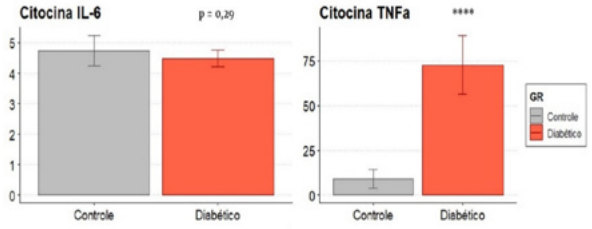
DIABETIC GROUP	Thickness	Cells Endothelial Lush	Deposits Myxoids	Degeneration Vacuolar	Cells CD68
Animal 11					
Sample 1 AA	0,3531	N	S	2	
Sample 2 AA	0,2568	S	S	2	
Sample 3 AAB	0,1947	N	N	1	
Sample 4 AAB	0,1605	N	N	0	
Animal 12					
Sample 1 AA	0,321	S	S	3	
Sample 2 AA	0,2889	N	S	2	
Sample 3 AAB	0,1798	N	N	1	
Sample 4 AAB	0,1605	S	S	2	
Animal 13					
Sample 1 AA	0,2054	N	N	1	
Sample 2 AA	0,1926	S	S	2	
Sample 3 AAB	0,1477	N	N	1	
Sample 4 AAB	0,1412	N	N	1	
Animal 14					
Sample 1 AA	0,2568	S	S	3	
Sample 2 AA	0,1926	N	S	2	
Sample 3 AAB	0,1605	N	N	1	
Sample 4 AAB	0,1605	N	S	2	
Animal 15					
Sample 1. AA	0,3852	S	S	3	
Sample 2 AA	0,2568	S	S	3	
Sample 3 AAB	0,1733	N	N	1	
Sample 4 AAB	0,1605	N	N	1	
Animal 16					
Sample 1. AA	0,2247	N	N	1	
Sample 2 AA	0,1926	N	S	2	
Sample 3 AAB	0,1605	N	N	1	
Sample 4 AAB	0,1541	S	S	2	
Animal 17					
Sample 1 AA	0,2568	S	S	3	
Sample 2. AA	0,2375	N	N	1	
Sample 3 AAB	0,1605	N	N	1	
Sample 4 AAB	0,1605	N	S	2	
Animal 18					
Sample 1 AA	0,3338	S	S	3	
Sample 2 AA	0,2531	S	S	3	
Sample 3 AAB	0,1669	N	N	1	
Sample 4 AAB	0,1412	N	N	1	
Animal 19					
Sample 1 AA	0,2375	S	S	2	
Sample 2 AA	0,2054	N	S	3	
Sample 3. AAB	0,1605	N	N	1	
Sample 4 AAB	0,1541	N	N	1	
Animal 20					
Sample 1 AA	0,244	S	S	3	
Sample 2 AA	0,1798	S	S	2	
Sample 3 AAB	0,1605	N	N	1	
Sample 4 AAB	0,1605	N	N	1	

Legend: 4 samples from each animal were analyzed (2 from the aortic arch and 2 from the abdominal aorta). Endothelial cell hyperplasia, myxoid deposits, vacuolar degeneration (grades 1 to 3) and presence of CD68-positive macrophages were evaluated. Abbreviations: AA, aortic arch; AAB, abdominal aorta; N, no; S, yes; grade 1, mild; grade 2, moderate; grade 3, intense.



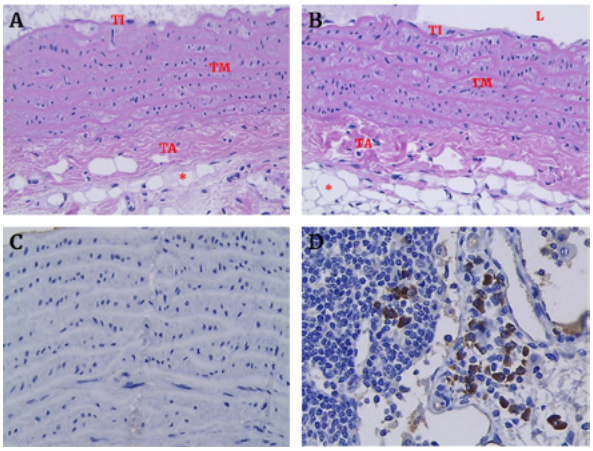
Caption: Blood glucose was measured at 5, 15, 30, 60 and 120 min after glucose injection. AUC values were calculated for each group. Normality was verified using the Shapiro–Wilk test and statistical comparison was performed using Student's t-test (**** $p < 0.0001$).

FIGURE 2 — Intravenous glucose tolerance test (ivGTT) in control and diabetic rats at 80 days of age.



Legend: Normality was confirmed by the Shapiro–Wilk test and the comparison between the groups was performed by the Student's t-test (**** $p < 0.0001$).

FIGURE 3 — Statistical analysis of plasma levels of TNF-α and IL-6 in control and diabetic rats.



Legend: A) Hematoxylin-eosin (HE) staining of the abdominal aorta; B) HE of the aortic arch; C) immunohistochemistry for CD68 in the aortic arch showing absence of macrophages; D) immunohistochemistry for CD68 in the abdominal aorta showing sparse macrophages in the lymph node (anti-CD68, 400×).

FIGURE 4 — Histological and immunohistochemical images representative of aortic segments of diabetic rats.

safety, efficacy, and applicability in experimental protocols.[10-12]

In the present study, diabetic induction resulted in persistent hyperglycemia at 80 days, confirming the effectiveness of the model. Despite the glycemic alteration, there was no significant weight loss, suggesting that, at this stage, the systemic metabolism of the animals was not yet severely impaired, a finding compatible with studies that describe the gradual progression of metabolic alterations in young models of STZ-induced DM.[13,14]

Serological analysis showed a significant increase in TNF-α in the diabetic group, while IL-6 levels remained unchanged. This inflammatory profile suggests immune imbalance: TNF-α, recognized as a central mediator of vascular inflammation, stimulates the expression of endothelial adhesion molecules, promotes leukocyte recruitment, and intensifies oxidative stress. The absence of IL-6 elevation may reflect immunologic exhaustion from chronic inflammation or early stage of disease. Studies indicate that IL-6 and TNF-α often act synergistically in atherogenesis, and the mismatch in this interaction can influence the chronology of vascular injury.[15-17]

From the morphological point of view, the presence of exuberant endothelial cells, myxoid deposits, and vacuolar degeneration, without detection of macrophages or foamy cells, suggests an initial structural alteration, prior to the inflammatory infiltrate typical of atherosclerosis. Negative immunostaining for CD68 reinforces the absence of significant macrophage infiltration. These findings are in line with studies that describe endothelial dysfunction as an early, potentially reversible event, in the sequence that culminates in inflammation and atherosclerotic plaque formation.[18,19]

The absence of detectable vascular inflammation at this stage does not invalidate the hypothesis of future progression to advanced atherosclerotic lesions. On the contrary, the isolated increase in TNF-α suggests systemic inflammatory activation capable of impacting the vascular wall over time. This moment may represent a critical window for therapeutic interventions aimed at the early modulation of the inflammatory response.[20,21]

Thus, this study contributes to the characterization of an experimental model of T2DM with potential for future investigations on the interaction between systemic inflammation and vascular remodeling. The integration of temporal analyses, including additional markers such as IL-1β, CRP, and VCAM-1, combined with the functional assessment of vascular reactivity, may deepen the understanding of the sequence of events that link hyperglycemia to inflammation and arterial damage. These data can support the development of earlier and more effective diagnostic and therapeutic strategies in the context of cardiovascular complications of diabetes mellitus.

CONCLUSION

The induction of type 2 diabetes mellitus with STZ on the 5th postnatal day proved to be effective, resulting in persistent hyperglycemia and a significant increase in TNF-α, with no change in IL-6 levels and no loss of body mass. No tissue inflammation was detected in the aortic segments evaluated, suggesting that the model represents an initial stage of endothelial dysfunction. These results reinforce the potential of the model for studies on early mechanisms of vascular injury in diabetes mellitus type 2.

Authors' contributions

Luciane Bittencourt Carias de Oliveira – Conceptualization, methodology, validation, writing, revision and editing.
Osvaldo Malafaia – Supervision.
Fernando Issamu Tabushi – Project management, writing – proofreading and editing.
Stephanie Rubianne Silva Carvalhal – Methodology.
Sérgio Ossamu Ioshii – Methodology, validation.
Rodrigo Schuh – Methodology, validation.
Laís Soares Rodrigues – Methodology, validation.
Thomas Horlem – Validation.
Nicolau Gregori Czeczko – Project Management.

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BioSCIENCE Review Article
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Analysis of cytokines and CD68 in the aorta: new parameters for studying inflammation in type 2 diabetes mellitus

Análise de citocinas e CD68 na aorta: novos parâmetros para estudo da inflamação no diabete melito tipo 2

Luciane Bittencourt Carias de Oliveira[1], Osvaldo Malafaia[1], Fernando Issamu Tabushi[1], Stephanie Rubianne Silva Carvalhal[2], Sérgio Ossamu Ioshii[2], Rodrigo Schuh[2], Laís Soares Rodrigues[2], Thomas Horlem[3], Nicolau Gregori Czeczko[1]

ABSTRACT

Introduction: Atherosclerosis is a central element in the pathogenesis of contemporary cardiovascular diseases. Atherosclerosis can be defined as a slowly progressive inflammatory process associated with several causal factors. The pathophysiological process is characterized by a complex inflammatory cascade, initiated by vascular endothelial injury, leading to vascular narrowing and hardening.

Objective: To review the presence of a systemic inflammatory process through the analysis of interleukin-6 and tumor necrosis factor alpha (TNF-a) markers in the inflammatory tissue manifestations in different segments of the aorta.

Method: An integrative review was carried out in the PubMed and Scielo databases. The search used the following keywords: "inflammation, atherosclerosis, type 2 diabetes mellitus, CD68, IL-6, THFa, endothelium" and their English versions. Inclusion criteria included review articles, experimental studies, and preclinical and clinical research, written in Portuguese and English and available in full text. The selected articles were analyzed based on the technologies discussed, future prospects and challenges mentioned, and diseases related to the article's central idea.

Result: 63 articles were evaluated.

Conclusion: Pro-inflammatory cytokines are examples of inflammatory markers with serological expression. Tissue inflammatory markers, such as CD68, the macrophage activation glycoprotein, identified through immunohistochemical analysis, can allow the assessment of the vascular inflammatory process, especially in the context of atherosclerosis.

KEYWORDS: Inflammation. Atherosclerosis. Type 2 diabetes mellitus. CD68. IL-6, THFa. Endothelium.

Central Message

Among the most important risk factors for vascular inflammation, type 2 diabetes mellitus plays a crucial role. This inflammation, through oxidative stress, dyslipidemia, and insulin resistance, is strongly linked to the development and progression of atherosclerosis and, consequently, a significant increase in the risk of associated cardiovascular events

Perspective

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression. Tissue inflammatory markers, such as CD68, macrophage activation glycoprotein - identified through immunohistochemical study - may allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

RESUMO

Introdução: A patogênese das doenças cardiovasculares contemporâneas tem, na aterosclerose representação central. Elas podem ser definida como processo inflamatório de progressão lenta e associado a vários fatores causais. O processo fisiopatológico é caracterizado por complexa cascata inflamatória, iniciada por lesão do endotélio vascular, levando ao estreitamento e endurecimento vascular.

Objetivo: Revisar a presença de processo inflamatório sistêmico através da análise dos marcadores interleucina-6 e fator de necrose tumoral alfa (TNF-a) na manifestação inflamatória tecidual em diferentes segmentos da artéria aorta.

Método: Revisão integrativa realizada nas bases de dados PubMed e Scielo. A busca utilizou as seguintes palavras-chave: "inflamação. aterosclerose. diabete melito tipo 2, CD68, IL-6,THFa, endotélio" e suas versões ao inglês Os critérios de inclusão compreenderam artigos de revisão, estudos experimentais, pesquisas pré-clínicas e clínicas, escritos em português e inglês e disponíveis em texto completo. Os artigos selecionados foram analisados com base nas tecnologias abordadas, perspectivas futuras e desafios mencionados, doenças referidas relacionados à ideia central do artigo.

Resultado: Foram avaliados 63 artigos.

Conclusão: As citocinas pró-inflamatórias, são exemplos de marcadores inflamatórios com expressão sorológica. Marcadores inflamatórios teciduais, como por exemplo o CD68, glicoproteína de ativação de macrófagos, identificada através de estudo imuno-histoquímico, podem permitir a avaliação do processo inflamatório vascular, especialmente no contexto da aterosclerose.

PALAVRAS-CHAVE: Inflamação. Aterosclerose. Diabete melito tipo 2. CD68. IL-6,THFa. Endotélio.

[1]Graduate Program in Principles of Surgery, Evangelic Mackenzie Faculty of Paraná, Curitiba, PR, Brazil;
[2]Federal University of Paraná, Curitiba, PR, Brazil;
[3]Department of Physiology, Federal University of Paraná, Curitiba, PR, Brazil.

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INTRODUCTION

The pathogenesis of contemporary cardiovascular diseases has a central representation in atherosclerosis. This disease can be defined as an inflammatory process of slow progression and associated with several causal factors.[1] The pathophysiological process of atherosclerosis is characterized by a complex inflammatory cascade, initiated by injury to the vascular endothelium, leading to vascular narrowing and hardening.[2]

The involvement of the inflammatory and atherosclerotic process occurs predominantly in large and medium-sized arteries, such as the aorta, coronary, carotid and iliac arteries. These arteries are more susceptible to injury due to the turbulent flow and hemodynamic stress that occurs at arterial bifurcations and curvatures.[3] Experimental studies with emphasis on the distribution of atherosclerosis along the aorta artery are still small, and have demonstrated heterogeneous activation of inflammatory pathways in its axis. Small-caliber arteries (resistance arteries) can also be affected, contributing to microvascular complications.[4]

Among the most important risk factors for vascular inflammation, type 2 diabetes mellitus (DM2) plays a crucial role. This inflammation, through oxidative stress, dyslipidemia, and insulin resistance, is strongly linked to the development and progression of atherosclerosis, and consequently a significant increase in the risk of cardiovascular events associated with it. Chronic hyperglycemia, characteristic of DM2, plays an important role in triggering and perpetuating the systemic inflammatory state.[5,6]

Experimental studies in rats, through the use of DM2 models with the use of streptozotocin (STZ), the most widely used substance for this purpose, have been fundamental to understand how chronic hyperglycemia leads to endothelial dysfunction, and subsequent inflammation, accelerating atherosclerosis in diabetics.[7,8] These models have served as substrates for the study of inflammatory, atherosclerotic, and DM2-related processes, aiming at glycemic control, inflammation reduction, and prevention of cardiovascular complications.

The analysis of inflammation, through inflammatory markers, is fundamental for scientific research. These markers allow molecular plasma analyses, and tissue analyses, in specific organs or segments, such as segments of the aortic artery.[9,10] While serological inflammatory markers may indicate a systemic manifestation of inflammation, tissue markers have the function of analyzing the occurrence of localized tissue inflammation.

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression, with interleukin-6, tumor necrosis factor alpha (TNF-a) and interleukin-1 being some of the most relevant for the study of inflammation and atherosclerosis.[11,12]

Tissue inflammatory markers, such as CD68, a macrophage-activating glycoprotein, identified through immunohistochemical study, can allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

Thus, the objective of this integrative review was to evaluate the presence of systemic inflammatory process through the analysis of interleukin-6 and tumor necrosis factor-alpha (TNF-a) markers in the tissue inflammatory manifestation in different segments of the aortic artery.

METHOD

This is an integrative literature review conducted in the PubMed and Scielo databases. The search used the following keywords: "inflammation. atherosclerosis. type 2 diabetes mellitus, CD68, IL-6, THFa, endothelium" and their Portuguese versions The inclusion criteria included review articles, experimental studies, preclinical and clinical research, written in Portuguese and English and available in full text. The selected articles were analyzed based on the technologies addressed, future perspectives and challenges mentioned, diseases referred to related to the central idea of the article, resulting in 63 articles

DISCUSSION

Cardiovascular diseases

The study called Framingham Score popularized the idea of cardiovascular risk factors, conditions or behaviors that increase the chances of acute myocardial infarction or stroke. The data obtained through this study generated more than 3,700 publications in indexed medical journals, and addressed several risk factors for cardiovascular diseases, such as hypertension, sedentary lifestyle and obesity. Studies have refined the idea of "good" and "bad" cholesterol and, as early as 1960, pointed to smoking as an important risk factor. This work continues to branch out from the heart to the brain, and even to the molecular level, adapting to the demands of science and being a valuable source of information on cardiovascular health.[13-16]

In order to analyze more recent data related to these diseases, the Cardiovascular Statistics – Brazil[17] which included chapters addressing 5 specific conditions: cerebrovascular disease, coronary artery disease, cardiomyopathy and heart failure, and atrial fibrillation. The publication follows the methodology used by the American Heart Association in the annual production of Heart Disease & Stroke Statistics Update[18], which also emphasizes epidemiological and public health data. The Cardiovascular Statistics – Brazil 2023[17] update, included more data on those diseases and brought new chapters on behaviors and risk factors for women.

Through the data mentioned above, it was found that 2 main cardiovascular diseases stand out from the others: 1) coronary artery disease in the first place in the ranking of the most fatal in Brazil, registering in the last 10 years an increase of more than 50% in hospitalizations for acute myocardial infarction, reaching an average of 90 thousand cases per year; and 2) in second place the stroke.[1] WHO data[19] on CVDs describe the repercussions on population morbidity and mortality, reduced life expectancy, and also on the individual's work disability.

The editorial board of The Lancet Neurology, in its 2024 publication, and in partnership with the World

Stroke Organization, emphasized the importance of behavioral attitudes in the prevention of stroke, which could cause up to 10 million deaths by 2050, recommending urgent actions to reverse this scenario.[20]

Inflammation and atherosclerosis

Some pioneering studies on the chronic inflammation of atherosclerosis have defined it as an accumulation of lipids, inflammatory cells, and connective tissue in the arteries. Through several publications, they have described the complex pathophysiological process of atherosclerosis, addressing the mechanisms of atheromatous plaque formation and the progressive narrowing and hardening of arterial walls, through the intricate interaction between the pathogenic components of the disease.[2,4,10,21-23]

The relationship between immunity and atherosclerosis was also addressed by several other authors, who praised the role of innate and adaptive immunity, and the participation of macrophages and lymphocytes in the formation of the atherosclerotic process, in addition to defining atherosclerosis as a response of immunocompetent cells against lesions that produce pro-inflammatory cytokines.[8,21,22]

Studies have described that the onset of the inflammatory process is characterized by endothelial dysfunction, which favors the infiltration and subendothelial retention of low-density lipoproteins (LDL) in the arterial intima layer.[24] These studies also highlight that the chronic inflammatory process begins soon after birth and persists throughout life. During this period, as didactically described by some studies,[8,25] this process is modulated by the spectrum of modifiable and non-modifiable risk factors. The modifiable ones are mainly represented by dyslipidemia, systemic arterial hypertension, smoking, DM2, sedentary lifestyle and obesity, and the non-modifiable ones by advanced age, male gender and genetic predisposition. The presence of these factors influences the establishment and also the evolution of inflammation.

Some authors have described that LDL, when retained in the subendothelial space, undergoes oxidative modifications, through a reduction in the bioavailability of nitric oxide, and significantly stimulates the evolution of the local inflammatory response through the recruitment of circulating monocytes to the arterial intima layer. Other authors have detailed the process in which circulating monocytes migrate to the subendothelial space, differentiate into macrophages and phagocytize the oxidized LDL, transforming them into so-called foamy cells, full of lipids. These authors also addressed that these cells are fundamental components in early atherosclerotic lesions, and detailed that this recruitment of circulating monocytes is facilitated through the expression of cell adhesion molecules in the endothelium, such as VCAM-1 (vascular cell adhesion molecule -1) and ICAM-1 (intercellular adhesion molecule-1).[26-30]

Several studies have reviewed the steps described by other authors in the formation of atherosclerotic plaques, citing the recruitment of monocytes, the differentiation into macrophages that phagocytize the oxidized LDL, and their transformation into foamy cells, key components of the initial atherosclerotic lesions. The participation of pro-inflammatory cytokines, such as TNFa, IL-1B and IL-6, which are released by immune and vascular cells and influence the proliferation of smooth muscle cells, perpetuating the evolution of the inflammatory state, was also highlighted.[26,31]

Researchers have described the progression of atherosclerotic plaque, with the formation of a necrotic nucleus, composed of apoptotic cells, cellular debris, and cholesterol crystals. The development of this plaque may favor neovascularization from the vasa vasorum, which may contribute to the instability of the lesion due to the fragility of these new vessels. The instability of this plaque can progress to rupture, which occurs more frequently in regions of greater vulnerability, such as the edges of the fibrous layer, leading to the exposure of thrombogenic material to the blood flow and triggering the formation of thrombi. These thrombi can partially or totally obstruct the arteries, and trigger acute thrombotic events, such as myocardial infarction or stroke. In addition to plaque rupture, calcification or ulceration may occur, which can also progress to acute thrombotic complications.[31-34]

Studies that evaluated the presence of topographic predisposition to the formation of atheromatous plaques observed a preference for sites of greater turbulence and shear of blood flow, determining a greater probability of vascular lumen obstruction and consequent cardiovascular complications in these sites. They emphasized the involvement of the coronary arteries, with repercussions on coronary artery diseases, and described the importance of the atherosclerotic process in the carotid arteries, responsible for the decrease in cerebral blood supply and increasing the risk of ischemic strokes. The inflammatory and atherosclerotic involvement of the arteries of the lower limbs - responsible for peripheral arterial diseases - is also well detailed in the literature.[31,35-37]

The aorta is described as a vessel frequently affected by atherosclerosis, particularly in its abdominal portion. The importance that chronic inflammation in the aortic wall determines for the occurrence of greater fragility and local dilation, and consequent formation of aortic aneurysms, potentially responsible for fatal hemorrhagic events, is emphasized.[38-40]

Studies have also demonstrated the presence of atherosclerosis without clinical manifestation, that is, without the occurrence of cardiovascular events, known as subclinical atheroclerosis. This phase can be characterized by a wide range of lesions, from early plaques to thin layers of high-risk fibroatheromas, with calcified plaques. In these studies, the gaps that still remain in the identification and treatment of those with subclinical atherosclerosis are emphasized, who, despite being apparently healthy, are at risk of developing atherosclerotic cardiovascular events.[12,41,42]

Inflammation and aortic artery

Recent studies have elucidated the molecular mechanisms by which systemic inflammation affects

the structural and functional integrity of the aorta. They demonstrated that chronic exposure to pro-inflammatory cytokines, such as TNF-a and IL-6, promotes the degradation of the extracellular matrix in the aortic wall, compromising its elasticity and resistance.[43,44]

Understanding the interaction between systemic inflammation and aortic health has important implications for prevention strategies. Recent research has proposed a risk stratification model for aortic diseases based on systemic inflammatory biomarkers, offering a potentially valuable tool for the early identification of individuals at high risk. In the context of therapeutics, anti-inflammatory approaches have been promising in the treatment of aortic diseases. A clinical trial revealed that the use of selective IL-1β inhibitors significantly reduced the progression of abdominal aortic aneurysms in patients with elevated markers of systemic inflammation.[45.46]

Inflammation and diabetes mellitus

T2DM is one of the most prevalent metabolic diseases in the world. It progressively evolves and is characterized by pancreatic β cell dysfunction and peripheral insulin resistance, leading to defects in glucose metabolism and chronic low-grade inflammation. The relationship between inflammation and T2DM involves multiple molecular and cellular mechanisms that contribute to the development and progression of the disease. Chronic inflammation can contribute to the development of T2DM and this, in a bidirectional way, can exacerbate inflammatory processes. The complexity and interconnectedness of these pathophysiological processes has gained increasing interest in the scientific community. There is an interrelationship between DM2 and inflammation, demonstrating molecular mechanisms that connect the altered state of glucose to the activation of inflammatory pathways. Chronic hyperglycemia induces the formation of advanced glycation end products (AGEs), which interact with their receptors (RAGEs), triggering signaling pathways that culminate in the activation of pro-inflammatory transcription factors, such as nuclear factor kappa B (NF-κB). These mechanisms perpetuate the presence of inflammation and promote a vicious cycle of metabolic dysregulation.[5,43,47]

Studies emphasize that in the process in which chronic hyperglycemia, with inadequate previous glycemic controls, induces an inflammatory state, it can lead to the perpetuation of diabetic complications - even after normalization of glycemic levels - due to the persistence of inflammation. This phenomenon, called "metabolic memory", was initially described by "The Diabetes Control and Complications Trial", in addition to describing chronic low-grade inflammation - also called "metainflammation" - as a subclinical state characterized by the persistent production of pro-inflammatory mediators, such as the cytokines interleukin-1β (IL-1β), necrosis factortumor-a (TNF-a) and interleukin-6 (IL-6). The activation of these inflammatory pathways in metabolic tissues, such as the pancreas and adipose tissue, contributes significantly to the dysfunction of pancreatic β cells and insulin resistance, central elements in the pathophysiology of DM2. This subclinical inflammatory state has been implicated in both the pathogenesis and progression of diabetes. In visceral adipose tissue, adipocyte hypertrophy and macrophage infiltration occur, leading to a chronic inflammatory state. This inflammatory microenvironment results in the increased secretion of adipokines and pro-inflammatory cytokines, exacerbating systemic insulin resistance.[48-50]

The role of the immune system in the pathogenesis of insulin resistance and DM2, as well as in atherosclerosis, is well highlighted in the literature. The discovery of the influence of a multiprotein complex called "inflammasome" (NLRP3) on the pathogenesis of these diseases has brought new perspectives to the study of the relationship between innate immunity and metabolism. Inflammasome activation is accomplished by several metabolic "danger signals," such as: free fatty acids, amyloid, advanced glycation products, urate crystals, including saturated fatty acids, and cholesterol crystals. After this activation, the production of potent pro-inflammatory cytokines, such as IL-1β and IL-18, is orchestrated. Chronic inflammasome activation not only contributes to insulin resistance, but is also implicated in pancreatic beta cell dysfunction and death.[51,52]

The role of the gut microbiota in modulating inflammation in metabolic diseases, especially T2DM, and changes in the composition of this microbiota (dysbiosis) have been associated with increased intestinal permeability, allowing the translocation of bacterial endotoxins, such as lipopolysaccharide, into the systemic circulation. This process, called "metabolic endotoxemia" activates Toll-type receptors, crucial components of the innate immune system for the initial detection of microbial invaders, in various tissues, amplifying the inflammatory response and insulin resistance. These studies bring new therapeutic possibilities in the treatment of DM2 and its complications, remodeling the intestinal microbiota through interventions such as medications, probiotics, prebiotics, fecal microbiota transplantation and diets.[53,54]

Experimental model of diabetes

Studies have reported important aspects regarding the induction of diabetes in animal models, which are important substrates for the study of several metabolic alterations, including inflammation. They described the use of toxic chemicals for induction, targeting pancreatic β cells. Aloxan was described as the first substance to be used, whose action occurred through the generation of free radicals, leading to the fragmentation of β cells. However, due to its low stability, short half-life, acidic nature of the solution (precluding intraperitoneal use), and increased renal toxicity, it has become the drug of second choice. Streptozotocin (STZ), an antibiotic derived from Streptomyces achromogene, and considered essentially analogous to nitrosourea, then became the most widely used substance. These authors detailed that the nitrosourea portion of the STZ is responsible for damage to β cells, while its deoxyglucose portion is responsible for the transport of

the native molecule across cell membranes. Since STZ uses glucose transporter 2 to access pancreatic β cells, other organs, which also express this transporter such as kidney, liver, and intestine, are also affected.[55,56]

Other authors have described that STZ can be used to induce type 1 diabetes and DM2. High doses of STZ severely impair insulin secretion, which can lead to the formation of ketone bodies and polyuria, a characteristic condition of uncontrolled type 1 diabetes. On the other hand, low doses of STZ cause slight impairment in insulin secretion, being more similar to the later stages of DM2. This same author addressed that there are no standardized protocols for the preparation and administration of the STZ. It is usually dissolved in saline solution or citrate buffer, adjusting the pH to 4.5, the most suitable for injection.[57]

Recent research has addressed the routes of administration of STZ, which can be subcutaneous, intracardiac or intramuscular; however, it is more commonly administered intraperitoneally or intravenously. Although STZ doses can vary greatly between sex and strain, STZ dosages > 65 mg/kg are considered high, 40-55 mg/kg moderate, and < 35 mg/kg low.[55,56]

One study used a model of T2DM induced by intraperitoneal injection of STZ to evaluate the effect of fish oil supplementation on metabolic, cognitive, and behavioral disorders associated with the disease. In this model, newborn rats received a single intraperitoneal injection of STZ at a dose of 100 mg/kg, solubilized in 10 mM citrate buffer (pH 4.5).[58] The diabetization model, in the neonatal period used, proved to be valid to mimic time-dependent aspects of DM2, without significant changes in the increase in mass, food and water intake, and urine and fecal volume, over time.[59]

Inflammatory markers

Pro-inflammatory cytokines

Pro-inflammatory cytokines participate significantly in the modulation of the body's immune and inflammatory response. These molecular mediators are low molecular weight proteins, secreted by various cells of the immune system, such as macrophages, T lymphocytes, and dendritic cells, as well as by non-immune cells, such as fibroblasts and endothelial cells.[1]

Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-a) are examples of the most relevant pro-inflammatory cytokines in the study of inflammation. These molecules exert activation of the vascular endothelium, act on leukocyte adhesion and induce the expression of adhesion molecules, thus contributing to the progression of the atherosclerotic inflammatory process.

In addition, current research is exploring the therapeutic potential of modulating these cytokines in several diseases. Specific pro-inflammatory cytokine inhibitors, such as anti-TNF-a monoclonal antibodies, have shown efficacy in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis and Crohn's disease.[60]

The modulation of the inflammatory response, as a strategy to prevent and treat atherosclerosis, was emphasized through a study called CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study). In this research, the inhibition of interleukin-1β, Pro-inflammatory cytokine, through the use of the monoclonal antibody canakinumab, significantly reduced the occurrence of recurrent cardiovascular events in patients with previous coronary disease. This study was a milestone in understanding the role of inflammation in atherosclerosis, and provided new direction for future research and treatments in cardiology.

CD68

The history of immunohistochemistry begins in 1942, when researchers used the direct fluorescence method to identify pneumococci in infected tissue, and, since its initial use, the use of this technique has grown exponentially. Variations of the initial protocol were incorporated into the method, increasing the sophistication and sensitivity of the technique, with the development of kits in laboratories for research and pathological diagnosis.[61]

The principle of immunohistochemistry involves the use of a specific antibody to the peptide studied, whose interaction can be identified by binding to a marker, which can be a fluorescent molecule or enzyme (peroxidase or alkaline phosphatase), whose activity will be used to produce a colored complex in the presence of chromogen. Immunohistochemistry can be performed by direct and indirect methods. In the direct method, which is more commonly used for diagnostic purposes, the labeled antibody reacts directly with the antigen, and is therefore a much faster method. The indirect method involves the formation of a complex at the antigenic site consisting of antibodies labeled directly with the fluorescent molecule or with a chromogen revealed by means of a peroxidase reaction. This method is more sensitive.[62]

The main "target" of immunohistochemistry is membrane proteins, which are called markers, since they identify and distinguish various cell types. In order to define the molecules present on the cell surface, and thus demarcate the cell lineage and type, the technique of cluster of differentiation or CD is used.[63]

CONCLUSION

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression, with interleukin-6, tumor necrosis factor alpha (TNF-a) and interleukin-1 being some of the most relevant for the study of inflammation and atherosclerosis. Tissue inflammatory markers, such as CD68, a macrophage-activating glycoprotein, identified through immunohistochemical study, may also allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

Authors' contributions

Luciane Bittencourt Carias de Oliveira – Conceptualization, methodology, validation, writing, revision and editing.
Osvaldo Malafaia – Supervision.
Fernando Issamu Tabushi – Project management, writing – proofreading and editing.
Stephanie Rubianne Silva Carvalhal – Methodology.
Sérgio Ossamu Ioshii – Methodology, validation.
Rodrigo Schuh – Methodology, validation.
Laís Soares Rodrigues – Methodology, validation.
Thomas Horlem – Validation.
Nicolau Gregori Czeczko – Project Management.

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Quality of bowel preparation and adenoma detection: does fractionated dosing make a difference?

Qualidade do preparo intestinal e detecção de adenomas: a dose fracionada faz diferença?

Fabricio Grenteski[1], Laura Mendes Lopes[1,2], André Montes Luz[2], Jurandir Marcondes Ribas Filho[3]

ABSTRACT

Introduction: Colorectal cancer is responsible for at least 880,000 deaths annually worldwide. Colonoscopy is the gold standard in screening for this cancer, and adequate colonic preparation is essential.

Objective: To evaluate the quality of colonoscopic preparation using the Adenoma Detection Rate (ADR) and Boston Biopsy Score (BBPS), according to the preparation proposed to participants.

Method: Two groups were included. The first, with 32 participants, received a divided dose of sulfate solution with one dose the day before the examination. The second, composed of 19 participants, received the same solution in a single dose only the day before the examination.

Result: ADR was higher in the first group. Participants who received a purgative the day before the examination had greater sleep disturbance. Both the cecal intubation rate and the rate of adequate and excellent examinations (BBPS) were higher in the group receiving the divided dose. There was no significant difference when comparing the tolerability of the preparation between the 2 groups.

Conclusion: Splitting the purgative dose proved effective, improving the cecal intubation rate and ADR.

KEYWORDS: Colorectal neoplasms. Intestinal polyps. Gastrointestinal endoscopy. Colonoscopy. Screening programs.

RESUMO

Introdução: Câncer colorretal é responsável por pelo menos 880.000 mortes por ano no mundo. A colonoscopia é o padrão ouro no rastreio desse câncer, e o preparo colônico adequado é fundamental.

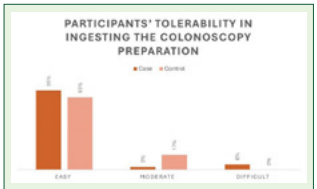
Objetivo: Avaliar a qualidade do preparo colonoscópico através da Taxa de Detecção de Adenoma (TDA) e Escala de Boston (BBPS) conforme o preparo proposto aos participantes.

Método: Foram incluídos 2 grupos. O primeiro, com 32 participantes, recebeu dose dividida de solução de sulfato com 1 dose da solução às vésperas do exame. O segundo, composto por 19 participantes, recebeu a mesma solução em dose única apenas no dia anterior ao exame.

Resultado: TDA foi maior no primeiro grupo comparativamente. Os participantes que receberam purgativo às vésperas do exame apresentaram maior distúrbio de sono. Tanto a taxa de intubação cecal quanto a de exames adequados e excelentes (BBPS) foram maiores no grupo que recebeu a dose dividida. Não houve diferença significativa quando se estudou a tolerabilidade em realizar o preparo comparando ambos os grupos.

Conclusão: dividir a dose do purgativo mostrou-se efetiva, melhorando a taxa de intubação cecal e a TDA.

PALAVRAS-CHAVE: Neoplasias colorretais. Pólipos intestinais. Endoscopia gastrointestinal. Colonoscopia. Programas de rastreamento.



Tolerance in ingesting bowel preparation

Central Message

Adenoma detection rate is a quality indicator in colorectal cancer screening. A task force by American Society for Gastrointestinal Endoscopy determined that a colonoscopy service should be capable of detecting polyps in at least 25% of patients undergoing colorectal cancer screening, with 30% for men and 20% for women. Achieving a high adenoma detection rate is strongly associated with favorable clinical outcomes.

Perspective

In the present study, the adenoma detection rate was higher among participants who received a split-dose regimen, with the second dose administered on the morning of the procedure, compared to those who received the purgative only on the day before

Supplementary Material - Instructions for split-dose colonoscopy preparation

[1] Evangelical Mackenzie Faculty of Paraná, Curitiba, PR, Brazil;
[2] General Surgery Department, Mackenzie Evangelical University Hospital, Curitiba, PR, Brasil;
[3] Mackenzie Presbyterian Institute, São Paulo, SP, Brazil.

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INTRODUCTION

In 2022, 20,245 people died from colorectal cancer (CRC) worldwide. There were approximately 45,000 new cases. It´s incidence varies depending on the region of the world, being more common in Australia, New Zealand, Europe, and North America, while the lowest are seen in Africa and Central and South Asia.[1]

Globally, according to one study conducted in 2018, approximately 880,000 people died from CRC.[2] It was observed that both incidence and mortality vary according to the Human Development Index (HDI) of the countries. Nations undergoing rapid economic transition, such as Brazil, have shown an increase in both incidence and mortality rates. Countries with a high HDI had increased incidence and decreased mortality, while those with very high HDI experienced a reduction in both rates.[3]

It is well known that most CRCs arise from the adenoma-carcinoma sequence. Vast majority of adenomas appear as intestinal polyps, which are detectable through endoscopic imaging examinations. Thus, colonoscopy becomes a powerful tool in the early diagnosis of CRC.

It´s screening current recommendation in the general population is to begin at age 50, starting 5 years earlier in the African descendent population, according to the American Society for Gastrointestinal Endoscopy (ASGE).[4] Nevertheless, organizations such as the American Cancer Society recommend screening starting at age 45 for individuals at average risk, with screening beginning 5 years earlier for high-risk populations or 10 years before the age at which a first-degree relative was diagnosed.[5]

Both the Brazilian Society of Coloproctology and the National Cancer Institute (INCA) maintain the recommendation to begin screening for intestinal polyps at age 50 for individuals at intermediate risk. The interval between colonoscopies remains every 10 years if the risk is low.

Adenoma detection rate (ADR) is a quality indicator in CRC screening. A task force by ASGE determined that a colonoscopy service should be capable of detecting polyps in at least 25% of patients undergoing CRC screening, with 30% for men and 20% for women. Achieving a high ADR is strongly associated with favorable clinical outcomes.[4]

It is known that adenoma removal through screening can prevent CRC development, and early diagnosis of localized cancer reduces mortality.[6] Among the various screening strategies and tests, colonoscopy has high sensitivity and specificity and provides the benefit of removing lesions during the procedure.

Colonoscopy allows for visualization of the rectum, colon, and the distal portion of the terminal ileum. It is both a diagnostic and therapeutic procedure, considered the gold standard for CRC screening and surveillance. A successful colonoscopy requires adequate bowel preparation. Excellent bowel preparation is extremely important as it allows proper visualization of the entire colonic mucosa and enhances the safety of therapeutic maneuvers.

Thus, adequate colonoscopic preparation is necessary for optimal colonic visualization. Split-dose preparation using purgatives, with one dose the day before and another on the day of the procedure, has proven superior to single dose preparation the day before the exam. According to the task force, the second dose should be taken 3-8 h before the procedure. This practice has shown to increase the ADR and improve patient acceptance of the preparation.[4]

Currently, the colonoscopy service at the hospital in this study conducts bowel preparation only on the day before the procedure. A recent study carried out at this facility found that approximately 25% of colonoscopies had inadequate or partially adequate preparation, which sometimes resulted in incomplete exams. Thus, an increase in ADR is expected with the addition of a purgative dose on the eve of the colonoscopy.

According to ASGE recommendations, an optimal screening exam requires adequate preparation and cecal intubation with photographic documentation. Incomplete examinations increase the risk of interval cancer and reduce ADR.

The primary objective of this study was to determine the ADR and cecal intubation rate according to the type of bowel preparation administered to patients at the CRC screening outpatient clinic to establish a quality indicator. The secondary objective was to evaluate correlations between the 2 types of bowel preparation in relation to age, sex, race, tolerability of each preparation through a standardized questionnaire, and characterize the epidemiological profile of the detected polyps according to histological type, size, and the presence or absence of high-grade dysplasia. The main objective of this study was the potential improvement in the quality of CRC screening and reduction of interval cancers.

METHOD

Research project was submitted to the Research Ethics Committee of Evangelical Mackenzie Faculty of Paraná, Curitiba, PR, Brazil and approved. The study required the signing of an Informed Consent Form by each patient invited to participate.

This is a longitudinal and individualized experimental study (clinical trial), in which a total of 84 candidates were selected. Among these, 52 composed the "case" group, in which participants received 1 dose of purgative the day before and another on the morning of the colonoscopy procedure. The "control" group included 32 participants who received a single-dose laxative preparation only on the day before the colonoscopy. Of the case group participants, 46 accepted the procedure after being invited, and 32 effectively underwent colonoscopy on the scheduled date.

In the control group, out of the 32 selected participants, 19 effectively completed the preparation and underwent the procedure on the scheduled date. The remaining 4 withdrew, while the others awaited

scheduling in the hospital's endoscopy service. Data were collected from patients indicated for CRC screening who were admitted to the outpatient clinic of the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil. Inclusion criteria included: age over 50, or 40 if there was a family history of CRC; asymptomatic status; no previous diagnosis of CRC; and no prior colonoscopy. Symptomatic individuals (e.g., gastrointestinal bleeding, recent bowel habit changes, weight loss, pencil-thin stools, prior CRC history) and those not meeting extended age criteria were excluded. Participant recruitment for the case group occurred between June and August 2024. Control group recruitment took place from November to December 2024. Participants in each group were consecutively enrolled until the required number was achieved. There was no randomization in this study. According to prior authorization, it was provided a split-dose colonoscopy preparation protocol using a sulfate solution (sodium picosulfate, magnesium oxide, anhydrous citric acid – Picoprep®) to the case group, and a single-dose protocol the day before the procedure to the control group. All participants were educated about the proposed dietary restrictions, fluid intake volumes, and timing of the doses. Each subject was monitored up to the date of their procedure. A database in Excel was used to track basic demographic data and examination dates. On the day of the colonoscopy, a structured questionnaire was administered to assess tolerance to the preparation, adverse events, and other relevant symptoms (see Supplementary Material at article´s end).

In the case group, patients received 2 doses of Picoprep® at different times: one at 6:00 PM the day before and one around 5:00 AM on the day of the exam, according to ASGE recommendations. For the control group, participants ingested the first sachet at 6:00 PM and the second at 10:00 PM the day prior to the procedure. Fasting began at 10:00 PM the night before the colonoscopy for both groups (solid and semi-solid foods). Clear liquids were allowed up to 2 h before the exam. The proposed diet included lowfiber processed or mashed foods such as potatoes, sweet potatoes, cassava, yams, rice, and lean poultry or fish. Foods high in fiber, carbonated beverages, colored juices, and others that could hinder visualization during the procedure, were prohibited. Each patient was instructed on the importance of intestinal preparation, fluid intake, physical activity on the day before the procedure, and the need for a companion on the examination day.

The questionnaire was based on validated studies to assess adverse effects and preparation tolerability, including nausea, vomiting, sleep disturbances, falls, fainting, abdominal pain, bloating, and anal irritation. Age, sex, and race were also collected. Patient understanding and adherence to preparation instructions were evaluated.

Colonoscopy reports were analyzed based on the Boston Bowel Preparation Scale (BBPS) and the following criteria: completeness of the exam, presence/absence and number of polyps, size, location, and presence of lesions suggestive of neoplasia. A complete exam was defined as one that identified anatomical landmarks such as the ileocecal valve or terminal ileum. BBPS scores above 7 were considered adequate. Examinations were also rated based on the endoscopist's subjective impression (adequate or inadequate). Exams interrupted due to poor preparation or anatomical limitations were labeled as incomplete.

Polyps were classified by histologic type, location, size, and presence of high-grade dysplasia. The categories used were hyperplastic polyps, tubular adenomas without high-grade dysplasia, and tubulovillous adenomas without high-grade dysplasia. No other histologic types were identified in this cohort.

Sedation was performed mostly by the endoscopist, with anesthesiologists involved only in selected cases. Sedatives used included benzodiazepines, fentanyl citrate, or propofol.

Risks associated with the procedure and preparation included dehydration, falls, nausea/vomiting, abdominal discomfort, rectal pain, diarrhea, syncope, hypersensitivity, renal impairment, intestinal perforation, gastric ulcers, and paralytic ileus. However, no urgent medical events were observed.

Statistical analysis

Results were summarized using descriptive statistics for quantitative variables and contingency tables for categorical variables. Group comparisons were conducted using the Chi-square or Fisher's exact test (for small samples) for categorical variables, and the Mann–Whitney U test for continuous variables. Data analysis was performed using Statistica software, version 7.

RESULT

Among the participants in the group submitted to the split-dose bowel preparation, 47% were male and 53% were female. In contrast, among those who received the single-dose preparation, 37% were male and 63% female. There was no statistically significant difference between the groups regarding participants' sex (p=0.48).

Regarding age, the mean age of participants in the split-dose group was 60 years, with a minimum age of 41 and a maximum of 83 years. The control group had a lower mean age of 57 years, ranging from 50-67 years There was no statistically significant difference between the groups in terms of age (p0.31).

Upon analyzing the self-reported race of participants based on the questionnaire applied after the examination, the majority identified as "white," with a higher proportion observed in the split-dose group, where 91% of participants self-identified as white. In the control group, although to a lesser extent, 72% of participants also identified as white. Individuals identifying as mixed-race ("pardo") or black comprised a minority in both groups (Figure 1). There was no statistically significant difference between the groups regarding participants' race.

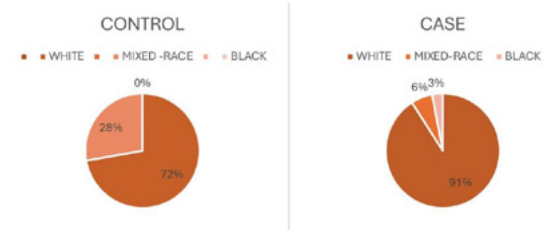

FIGURE 1 — Race of participants

When analyzing the quality of bowel preparation in the colonoscopies performed, the average BBPS score among patients was 6. A greater number of participants demonstrated inadequate preparation according to our criteria (BBPS <7). Among the participants who received a split-dose regimen, with 1 dose taken on the day of the examination, 20 participants (62.5%) presented with inadequate preparation (BBPS <7), while only 12 (37%) achieved a BBPS ≥7.

Among those who received a single dose of purgative the day before the examination, the results followed a similar trend observed in the case group: 61% presented with BBPS <7 and 39% met the criteria for adequate preparation. No statistically significant difference was found between the groups regarding BBPS scores (Figure 2, p=0.3).

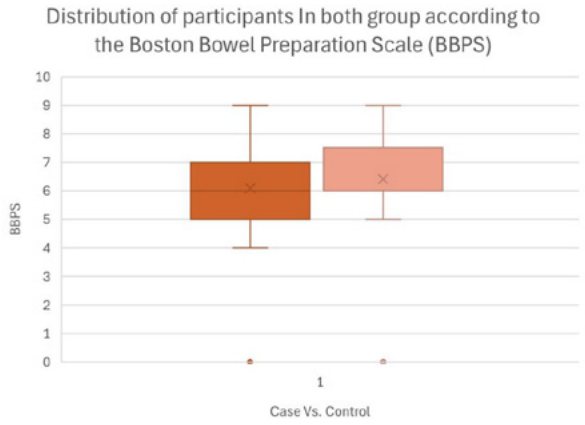

FIGURE 2 — Bowel preparation distribution in both groups according to BBPS scale

Regarding the cecal intubation rate (complete examinations with photographic documentation), both groups and demonstrated satisfactory results. Among participants who received a dose of purgative on the day of the examination, 94% underwent a complete examination. In the group that received the purgative only on the day prior to the procedure, 81% achieved a complete examination (Figure 3). There was no statistically significant difference between the groups in terms of cecal intubation rate (p=0.20).

Polyp detection rate was higher among participants who received a purgative dose on the day of the procedure: 31% of these individuals had polyps identified at the end of the examination, compared to 26% of participants who did not receive the split-dose regimen (p = 0.78). Regarding the size of the polyps found in both groups, it was observed that participants in the case group had a smaller mean polyp size compared to the control group, 5.88 mm vs. 8 mm, respectively (Figure 4, p=0.78).

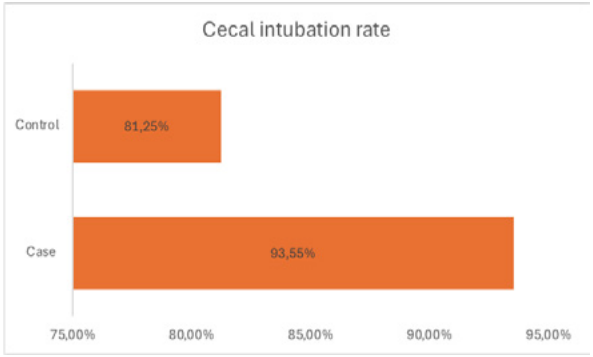

FIGURE 3 — Cecal intubation rate

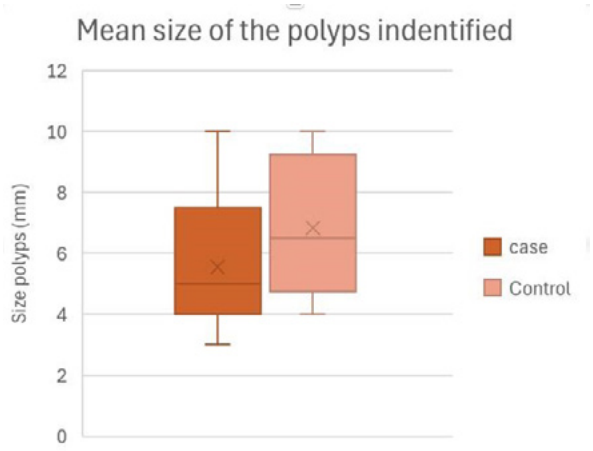

FIGURE 4 — Mean size of identified polyps

When analyzing the ADR, it was observed that participants who received a purgative dose on the day of the examination had a higher ADR compared to the control group: 22% of the polyps found in the case group were adenomas, vs. only 15.79% in the control group (Figure 5, p=0.36).

The histological types of adenomas identified after the examinations consisted of 3 types (Figures 5 and 6), none of which showed high-grade dysplasia, serrated histology, or adenoma size greater than 1 cm. Majority of participants in both the case and control groups had tubulovillous adenomas without dysplasia as the main histological finding. Other histological types identified were hyperplastic polyps and villous adenomas.

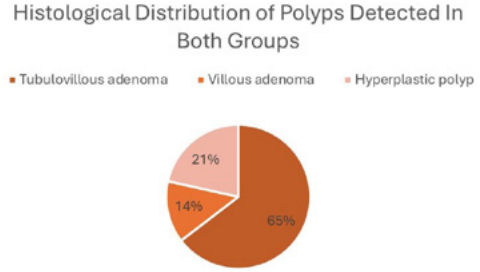

FIGURE 5 — Histological distribution of polyps

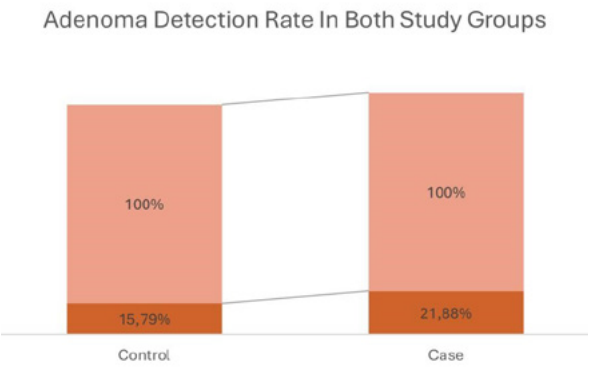

FIGURE 6 — Adenoma detection rate in both groups

The results of the questionnaires administered after the colonoscopy differed when comparing participants who received a purgative dose on the day of the examination vs. those who received it only on the previous day.

When participants were asked, "How difficult was it for you to ingest the studied medication?", 91% in the split-dose group reported ease of ingesting the laxative solution. The control group also reported ease of ingestion, with 83% indicating no difficulty. Only two participants in the case group found the ingestion of the solution difficult (Figure 7, p=0.65).

Among the analyzed symptoms, were considered nausea, abdominal pain, abdominal distension, anal irritation, sleep disturbance, falls and bruises, and syncope to assess the tolerability of the bowel preparation in each group. Sleep disturbance was reported by 47% of participants who received the purgative dose on the morning of the examination, with 26% reporting mild, 12% moderate, and 9% severe sleep disturbance. In contrast, when the same question was posed to the group that did not ingest the purgative during the night, 90% of the participants reported no sleep disturbance (Figure 7, p = 0.01).

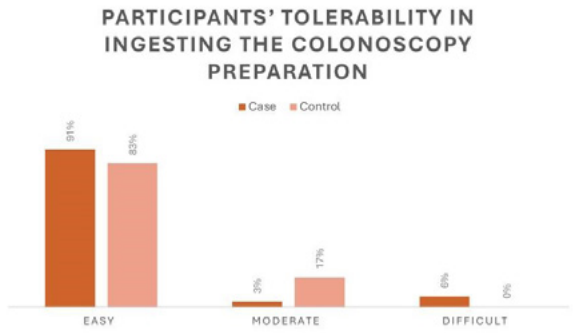

FIGURE 7 — Tolerance in ingesting bowel preparation

When investigating the prevalence of nausea and vomiting among participants, a higher incidence of these symptoms was observed in the splitdose group. Vast majority of participants either reported no symptoms or only mild symptoms. In the case group, approximately 20% experienced some degree of nausea. In the control group, about 17% reported mild nausea. Among all participants, only one individual in the split-dose group experienced syncope during preparation and required medical assistance. Abdominal pain, abdominal distension, and anal irritation were also evaluated through post-procedure questionnaires. Abdominal pain was reported by approximately 20% of participants who received the purgative on the morning of the exam, while about 15% of the control group reported some degree of abdominal pain (p=0.31). Regarding abdominal distension, both groups showed similar symptom rates (p=0.94). For anal irritation, a greater difference between the groups was noted (p=0.44); approximately 21% in the control group reported some degree of anal symptoms, compared to about 32% in the case group (Figure 8).

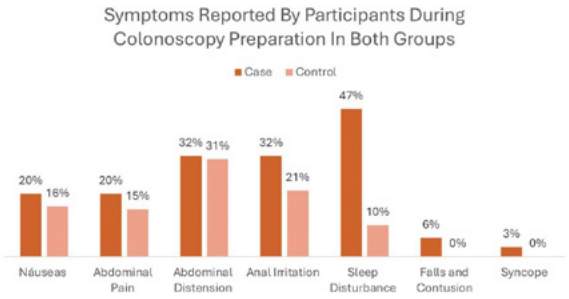

FIGURE 8 — Symptoms during bowel preparation for colonoscopy

DISCUSSION

Several studies have reinforced that split-dose bowel preparation regimens yield better outcomes in terms of both preparation quality and adenoma detection rate. A task force formed to standardize best practices in colonoscopy has reiterated that split-dose purgative regimens should routinely be implemented in services offering colonoscopy.[4]

The participants in the present study followed this same trend. Was observed that administering the purgative dose on the day of the exam improved the rate of adequate bowel preparation, according to the endoscopist's subjective assessment. However, the same improvement was not observed when using the BBPS as an isolated metric, where fewer participants in the split-dose group achieved a score ≥ 7 compared to the control group.

Sulfate-based solutions are osmotic purgatives widely used in bowel preparation for colonoscopy. In addition to being easy to use, they have minimal contraindications in patients with liver disease, congestive heart failure, or disorders related to electrolyte imbalance.

Another advantage of using split-dose sulfate-based purgative solutions is their greater tolerability, which has been consistently demonstrated in clinical practice. In a study evaluating colonoscopy preparation, polyethylene glycol was shown to be better tolerated than other methods, such as mannitol, with no significant difference in the final quality of bowel cleansing.[7]

In this study, only the purgative solution Picoprep® was used in 2 distinct groups, as previously described. Other types of bowel preparations, such as mannitol, were not evaluated. Both the purgative dose

administered on the day before the examination and the split-dose regimen were generally well tolerated. Vast majority of participants reported no symptoms when assessing nausea, vomiting, abdominal pain, bloating, and anal irritation. There was no statistically significant difference in tolerability between the two bowel preparation regimens, although participants in the split-dose group reported greater ease in following the instructions and a lower incidence of abdominal pain compared to those in the control group.

Another randomized clinical trial demonstrated the benefits of split-dose sulfate-based bowel preparation. There was a 15% increase in colonoscopies with excellent preparation quality compared to colonoscopies prepared with a single dose on the previous day.

Administering the purgative on the morning of the exam showed a trend toward a higher rate of colonoscopies with excellent preparation (BBPS score of 9). A total of 9 participants in the split-dose group achieved excellent bowel preparation, compared to 5 in the control group. The proportion of excellent preparations relative to the total was higher in the split-dose group— approximately 28%, compared to 26% in the control group.

It is recommended that the second dose of the purgative respects the necessary interval for the patient to undergo the examination, including travel time to the facility where the colonoscopy will be performed. According to Rex et al.[4,] the optimal timing for administering the second dose is between 3-8 h prior to the procedure.

However, a theoretical issue arises: The second dose may need to be taken very early, depending on the scheduled time of the examination. Nonetheless, clinical practice has shown that this early administration does not negatively impact the efficacy of bowel preparation, as evidenced by low rates of inadequate exams and high cecal intubation rates.

This observation was confirmed in this study. Was found that the cecal intubation rate (i.e., complete examinations with photographic documentation of the cecum) was higher among participants who received the split-dose regimen, despite a higher incidence of sleep disturbance: 94% in the intervention group vs. 81% in the control group. This is a relevant finding, as cecal intubation rate is considered a key quality indicator in colonoscopy. Complete examinations reduce the risk of interval colorectal cancer, particularly because incomplete exams fail to adequately evaluate the right colon.

Another important finding of this study relates to sleep quality. Sleep disturbances were significantly more frequent in the group that received the second dose of the purgative on the morning of the exam. In this group, participants took the second dose of Picoprep® between 5:00 and 7:00 AM, depending on the scheduled time of the procedure and ensuring a minimum interval of 3 h before the examination. This sleep interruption for laxative ingestion appears to be the main reason for the impaired sleep quality observed. There was a statistically significant difference between the groups regarding sleep disturbance during preparation (p=0.01): approximately 47% of participants in the intervention group reported some degree of sleep disturbance, compared to only 11% in the control group.

In the present study, the ADR was higher among participants who received a split-dose regimen, with the second dose administered on the morning of the procedure, compared to those who received the purgative only on the day before (p=0.36). Approximately 22% of participants in the intervention group had adenomas among the polyps detected, compared to around 16% in the control group. This study did not analyze ADR stratified by sex. The findings in the intervention group align with the recommendations of the most recent U.[5,] MultiSociety Task Force on Colorectal Cancer Screening, endorsed by the ACG.[4]

Despite the observed trend toward increased ADR with the addition of a second purgative dose on the day of the procedure, this difference did not reach statistical significance when compared to the control group. This may be partly explained by a higher dropout rate in the control group, which reduced its statistical power and representativeness.

Another important finding was the average size of polyps detected in both groups. Participants in the intervention group had smaller average polyp sizes than those in the control group. This may be attributed to the higher proportion of "excellent" bowel preparations (BBPS=9) in the intervention group. This observation is supported by findings from Repici et al.[8,] who demonstrated that colonoscopies with a BBPS score ≥ 8 enabled endoscopists to detect 100% of polyps larger than 5 mm. In contrast, in procedures with BBPS <7, only 88% of such polyps were detected. This finding has significant implications for patient outcomes and reinforces the clinical relevance of both the Boston scale and splitdose bowel preparation in routine CRC screening programs.

CONCLUSION

CRC has a high incidence and prevalence worldwide, and prevention remains the most effective strategy for reducing its impact. Therefore, assessing the quality of screening programs is essential. Bowel preparation using a split-dose purgative regimen administered on the day prior to the procedure is well supported by the literature and has proven to be effective. In this study, both the ADR and the cecal intubation rate showed a trend toward improvement in the group that received the split-dose regimen, compared to the control group. However, the high dropout rate in the control group may have affected the statistical significance of these findings. Tolerability was similar between the 2 regimens, although the split-dose preparation was associated with a higher frequency of sleep disturbances among participants.

Author´s contribution

Fabricio Grenteski – Conceptualization, Formal analysis
Laura Mendes Lopes – Investigation, Project administration
André Montes Luz – Supervision, Validation
Jurandir Marcondes Ribas Filho - Writing – review & editing, Methodology

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Evaluation of the applicability of the Tokyo criteria for patients with an indication for cholecystectomy

Avaliação da aplicabilidade dos critérios de Tóquio para pacientes com indicação de colecistectomia

Guilherme Andrade Coelho[1], Bernardo Huçulak Melo[1], Maria Eduarda Barcik Lucas de Oliveira[1], Bruna Corchak da Silva[1]

ABSTRACT

Introduction: Acute cholecystitis is characterized by acute inflammation of the gallbladder, usually resulting from biliary obstruction. The main symptoms include right upper quadrant abdominal pain, nausea, vomiting, and fever. Diagnosis is often based on the Tokyo Criteria, which consider clinical, laboratory, and imaging indicators.

Objective: To evaluate the sensitivity, specificity, and accuracy of the 2018 Tokyo Criteria for the diagnosis of acute cholecystitis.

Method: Retrospective analysis of 825 medical records of patients undergoing cholecystectomy. Signs and symptoms at admission, laboratory and imaging tests, and the pathological results of the surgical specimen were analyzed.

Result: The most common symptom was right upper quadrant pain. Leukocytosis was observed in 35.70% of cases, and elevated C-reactive protein in 69.70%. Ultrasonography was the most frequently requested imaging test, with cholelithiasis as the most frequent finding. Pathological analysis revealed 19.90% acute cases and 80.10% chronic cases. The 2018 Tokyo Criteria demonstrated a sensitivity of 77.40%, a specificity of 58.40%, and an accuracy of 66.10% for the diagnosis of acute cholecystitis.

Conclusion: The 2018 Tokyo Criteria demonstrated usefulness in the diagnosis of acute cholecystitis, with satisfactory sensitivity. However, the specificity indicates some inaccuracy in excluding cases other than acute cholecystitis. Overall accuracy is acceptable for classifying the presence or absence of the condition.

KEYWORDS: Acute cholecystitis. Cholelithiasis. Clinical practice guideline. Diagnosis. Sensitivity. Specificity.

Central Message

Acute cholecystitis is an inflammatory condition of the gallbladder and is a leading cause of acute abdomen and hospitalization. The distinction between chronic and acute conditions is fundamental, especially to guide appropriate clinical conduct. In this context, the Tokyo 2018 Criteria emerge as an auxiliary tool in the suspicion and diagnosis of acute cholecystitis, through the evaluation of 3 categories of signs: A (local inflammation), B (systemic signs of inflammation) and C (imaging findings).

Perspective

The diagnosis of acute cholecystitis, as well as its differentiation from chronic cholecystitis, can pose challenges. In this sense, the analysis of the efficacy of diagnostic criteria is essential to evaluate their applicability and reliability in medical practice. The use of the 2018 Tokyo Criteria suggests that there is an acceptable capacity to correctly classify the presence or absence of the disease, configuring it as a useful tool in clinical practice.

RESUMO

Introdução: Colecistite aguda caracteriza-se pela inflamação aguda da vesícula biliar, geralmente decorrente da obstrução das vias biliares. Os principais sintomas incluem dor abdominal no quadrante superior direito, náuseas, vômitos e febre. O diagnóstico é frequentemente baseado nos Critérios de Tóquio, que consideram indicadores clínicos, laboratoriais e de imagem.

Objetivo: Avaliar a sensibilidade, especificidade e acurácia dos Critérios de Tóquio de 2018 para o diagnóstico de colecistite aguda.

Método: Análise retrospectiva de 825 prontuários de pacientes submetidos à colecistectomia. Foram analisados sinais e sintomas na admissão, exames laboratoriais e de imagem, além do resultado anatomopatológico do espécime cirúrgico.

Resultado: O sintoma mais comum foi dor do quadrante superior direito. Leucocitose foi observada em 35,70% dos casos e elevação da proteína C reativa em 69,70%. Ultrassonografia foi o exame de imagem mais solicitado, com colelitíase como achado mais frequente. A análise anatomopatológica revelou 19,90% de casos agudos e 80,10% crônicos. Os Critérios de Tóquio de 2018 demonstraram sensibilidade de 77,40%, especificidade de 58,40% e acurácia de 66,10% para o diagnóstico de colecistite aguda.

Conclusão: Os Critérios de Tóquio de 2018 demonstraram utilidade no diagnóstico de colecistite aguda, com sensibilidade satisfatória. No entanto, a especificidade indica alguma imprecisão na exclusão de casos que não são de colecistite aguda. A acurácia global é aceitável para a classificação da presença ou ausência da condição.

PALAVRAS-CHAVE: Colecistite aguda. Colelitíase. Guia de prática clínica. Diagnóstico. Sensibilidade. Especificidade.

[1]Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brasil;

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INTRODUCTION

Acute cholecystitis (AC) is a condition that involves sudden inflammation of the gallbladder. In 90-95% of cases it is related to cystic duct obstruction, mainly due to cholelithiasis. In the presence of gallstones, the clinical picture is called acute calculous cholecystitis.[1] Risk factors for gallstones include female sex, obesity, genetics, hormonal exposure (particularly to estrogen), and multiparity.[2-5] Inflammation can also occur in the absence of stones, characterizing acute alithiasic cholecystitis. This condition can also be classified as chronic (CC), resulting from recurrent episodes of AC.[6]

The clinical picture involves pain in the right upper quadrant, fever, nausea and vomiting. During physical examination, it is common to identify Murphy's sign.[1,7] In 25% of cases, after 24 hours of its onset, the gallbladder is palpable.[8] In the clinical context, it is important to distinguish pain resulting from cholelithiasis from that associated with AC, as well as to make the differential diagnosis with other causes of acute abdomen, such as acute appendicitis, perforated peptic ulcer, among others.[3,9] AC is one of the leading causes of acute abdomen and hospitalization worldwide; therefore, it is essential to conduct an evaluation that takes into account the signs of local inflammation and laboratory and radiological tests.[10,11]

The diagnosis is established by means of abdominal ultrasound, the gold standard for the detection of gallstones, which is preferred.[12,13] In clinical management, CT18 is a way to assist professionals in decision-making in relation to the disease. It considers 3 variables (A, B and C), with A being a picture with signs of local inflammation (Murphy's sign and/or pain/tenderness/mass in the right hypochondrium); B systemic signs of inflammation (fever and/or elevated CRP and/or leukocytosis); and C imaging findings compatible with CA. Suspicion is raised when there is at least 1 item in criterion A and 1 in B; the diagnosis is definitive when all criteria (A, B and C) are met.[14]

Gold-standard for the treatment of AC is videolaparoscopic cholecystectomy.[2,3] It stands out compared to laparotomy, due to reduced recovery time, postoperative pain, and infectious complications.[15] In the absence of adequate treatment, possible complications include gallbladder perforation, biliary peritonitis, pericholecystic abscess, and biliary fistula.[2,3]

The present study aimed to verify the sensitivity, specificity and diagnostic criteria of AC according to Tokyo Criteria (CT18), as well as to evaluate the clinical, laboratory and imaging differences between AC and CC.

METHOD

The study was approved by the Research Ethics Committee of Faculdade Evangélica Mackenzie, Curitiba, PR, Brazil under number 6,082,824. The identities of the participants have been and will continue to be protected in accordance with the guidelines established in Resolution 466/12 of the National Health Council.

It consists of a retrospective cohort, with data collected from 825 electronic medical records. All patients who underwent cholecystectomy by the General Surgery Service of the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil, between January 2019 and January 2021, were included. Cases without an anatomopathological diagnosis of cholecystitis were excluded.

Information was collected on the presence of pain in the right upper quadrant, abdominal defense, nausea/vomiting, and Murphy's sign. Laboratory tests were also analyzed, which included leukocyte counts, CRP values, rodsis, AST levels, TGP, amylase, lipase and gammaGT. In addition, imaging tests and anatomopathological results were considered.

The sample was divided according to the anatomopathological result into AC and CC. All variables were analyzed in both groups, and the data collected were tabulated and evaluated according to the TC18. The criterion "fever", contemplated by the CT18, was excluded due to difficulty in obtaining it in the medical records analyzed.

Statistical analysis

The data were analyzed with the IBM SPSS Statistics v.29.0 computer program. Quantitative variables were described as percentages. The Wald test was used to assess the significance of the variables, and the estimated measure of association was the Odds Ratio with 95% confidence intervals (95%CI). The quality of the diagnostic criteria in the prediction of the anatomopathological result (gold standard) was analyzed by estimating values of sensitivity, specificity, accuracy, and positive and negative predictive values. For the calculations of predictive values, the prevalence of CC estimated by the study sample was considered. In all statistical tests, p-values < 0.05 indicated statistical significance.

RESULT

Data were collected from 825 electronic medical records of patients undergoing cholecystectomies at the hospital. However, 20 were excluded due to lack of compliance with the CT18 inclusion criteria. Thus, the analysis was conducted with a total of 805 patients. The laparotomy approach was the most used approach, corresponding to 84.30% of the cases (n=674), while the laparoscopic approach was the most used approach, corresponding to 15.80% (n=126). In the study, 160 patients were diagnosed with AC (19.90%) and 645 with WC (80.10%), based on the anatomopathological result.

According to the CT18 data mentioned above, criterion A corresponds to signs of local inflammation; B to systemic signs mediated by inflammation; and C to imaging findings compatible with CA.

Regarding criterion A, 98.70% reported pain in the region of the upper right quadrant of the abdomen, positive Murphy's sign in 35.80%, and abdominal defense in only 2.60%. It is relevant to highlight that 100% of the patients evaluated had alterations in criterion A.

There was statistical significance (p<0.001) for Murphy's sign, as it was positive in 49.30% of those with AC, while in those with CC, the percentage was 29.60% (RE 2.31, 1.54 - 3.48, Table 1). When this criterion was evaluated in relation to the anatomopathological result, all patients with AC presented alterations, resulting in a sensitivity of 100%, specificity of 0%, and overall accuracy of 31.30%, which indicates an unsatisfactory overall performance of this criterion in the diagnosis of AC (Table 2).

When analyzing criterion B, it was observed that 62.80% had a leukocyte count in the normal range (3,600 to 11,000/mm3), 35.70% leukocytosis (leukocytes >11,000/mm3) and 1.50% leukopenia (leukocytes <3,600/mm3). Statistical analysis of the data referring to criterion B revealed that leukocytosis was 2.93 times more likely to occur in cases of AC compared to cases of CC. In 69.70% of the cases, the CRP was altered. The results indicated that the increase was more prevalent in CC (82.80%) than in AC (59.50%, p=0.001). The variable fever was excluded from the analysis. Criterion B was shown to be altered by 54.90%. A little more than 75% of those with AC presented alterations in criterion B, while in CC, only 43% (Table 1). When evaluating criterion B, the sensitivity obtained was 75.30%, the specificity was 57%, and the overall accuracy was 63.8% (Table 2).

Regarding criterion C, 99.20% of the cases presented alterations in the imaging exam. Abdominal ultrasonography was used in 80.80% (n=516), being the most common examination. Regarding the results of imaging exams, lithiasis was identified in 85.60%, followed by other findings (27.70%) and thickening (21.90%, Table 1). Criterion C had high sensitivity (99.30%), low specificity (0.80%) and overall accuracy of 23.90% (Table 2). The finding of gallbladder thickening on imaging was highly significant (p<0.001), with an OR of 8.69 (5.58 – 13.5, Table 1).

Considering the combination of criteria, as suggested by the TC18, the sum of the "A+B" criteria showed alteration in 56.40% of the cases, while "A+B+C", 56.10% (Table 1). When analyzed together in relation to the AP result, the "A+B" criteria were shown to be sensitive (76.40%), specificity of 56.90% and overall accuracy of 64.80% (Table 2). The results reveal a notable association, with an OR of 4.29 (2.66 - 6.91, p<0.001). In this context, 76.40% of the cases of AC met both criteria based on anatomopathological analysis, while in those with CC the percentage was 43.10% (Table 1). When analyzing the "A+B+C" criteria in relation to pathological results, the sensitivity obtained was 77.40%, specificity of 58.40% and overall accuracy of 66.10% (Table 2). The results highlight an even more significant association when the 3 criteria were associated (OR 4.82, 2.93 - 7.90, p<0.001). Thus, changes in the sum of the "A+B+C" criteria were observed in 77.40% of the patients diagnosed with AC, while with CC this percentage was 41.60% (Table 1).

Other laboratory findings were analyzed. The hepatic markers AST and AST were altered in 43.70% and 52.40%, respectively; gammaGT, 64.60%; pancreatic enzymes, 49.10% in lipase and 27.40% in amylase; roadsis altered by only 7.10%; GOT, TGP and lipase, identified by OR of 0.41 (0.25 - 0.69), 0.43 (0.26 - 0.70) and 0.45 (0.27 - 0.75) respectively. Therefore, it

TABLE 1 — Tokyo Criteria (CT18) variables and sum of A+B and A+B+C in relation to anatomopathological results

			Everyone	Chronic cholecystitis	Cholecystitis acute		
Criterion	Variable	Classif.	n (%)	n vs. CC	n (% vs. CA)	p*	OR (95%CI)
A	QOD pain (n=453)	No	6 (1.30%)	4 (1.30%)	2 (1.40%)	0.916	0.91 (0.17 - 5.04)
		Yes	447 (98.70%)	307 (98.70%)	140 (98.60%)		
	Murphy+ (n=453)	No	291 (64.20%)	219 (70.40%)	72 (50.70%)	<0.001	2.31 (1.54 - 3.48)
		Yes	162 (35.80%)	92 (29.60%)	70 (49.30%)		
	Abdominal defense (n=453)	No	441 (97.80%)	305 (98.10%)	136 (95.80%)	0.168	2.24 (0.71 - 7.08)
		Yes	12 (2.60%)	6 (1.60%)	6 (4.20%)		
	Criterion A Changed (n=453)	No	0 (0.00%)	0 (0.00%)	0 (0.00%)	-	-
		Yes	453 (100%)	311 (100%)	142 (100%)		
B	Leukocytes (n=395)	<3600	6 (1.50%)	183 (73.50%)	71 (48.60%)	<0.001	2.93 (1.91 - 4.5)
		3600-11000	248 (62.80%)	183 (73.50%)	71 (48.60%)		
		>11000	141 (35.70%)	66 (26.50%)	75 (51.40%)		
	CRP (n=198)	<1	60 (30.30%)	45 (40.50%)	15 (17.20%)	0.001	3.27 (1.67 - 6.42)
		>1	138 (69.70%)	66 (59.50%)	72 (82.80%)		
	Criterion B Changed (n=395)	No	178 (45.10%)	107 (40.90%)	36 (27.70%)	<0.001	4.06 (2.58 - 6.37)
		Yes	217 (54.90%)	154 (59.10%)	110 (75.30%)		
C	Lithiasis (n=575)	No	83 (14.40%)	56 (12.90%)	27 (19.30%)	0.062	0.62 (0.37 - 1.02)
		Yes	492 (85.60%)	377 (87.10%)	113 (80.70%)		
	Thickening (n=575)	No	449 (78.10%)	384 (88.30%)	65 (46.40%)	<0.001	8.69 (5.58 - 13.5)
		Yes	126 (21.90%)	51 (11.70%)	75 (53.60%)		
	Another finding (n=575)	No	416 (72.30%)	327 (75.20%)	89 (63.60%)	0.008	1.74 (1.15 - 2.61)
		Yes	159 (27.70%)	108 (24.80%)	51 (36.40%)		
	Criterion C Changed (n=618)	No	5 (0.80%)	4 (0.80%)	1 (0.70%)	0.855	1.23 (0.14 - 11.08)
		Yes	618 (99.20%)	469 (99.20%)	144 (99.3%)		
A+B	Changed (n=349)	No	152 (43.60%)	119 (59.40%)	33 (32.60%)	<0.001	4.29 (2.93 - 7.90)
		Yes	197 (43.60%)	82 (40.60%)	107 (76.40%)		
A+B+C	Changed (n=330)	No	145 (43.90%)	115 (58.40%)	30 (22.60%)	<0.001	4.82 (2.93 - 7.90)
		Yes	185 (56.10%)	82 (41.60%)	103 (77.40%)		

QSD = right upper quadrant of the abdomen; *=univariate logistic regression model and Wald test, p<0.05

TABLE 2 — Sensitivity, specificity, accuracy, and positive and negative predictive values of criteria A, B, and C and the sum of A+B and A+B+C

Parameter	A	B	C	A+B	A+B+C
Sensitivity (95%CI)	100% (-)	75.30% (68.4% - 82.3%)	99.30% (98% - 100%)	76.40% (69.4% - 83.5%)	77.40% (70.3% - 84.5%)
Specificity (95%CI)	0.00% (-)	57.00% (50.9% - 63.2%)	0.80% (0.2% - 1.7%)	56.90% (50.2% - 63.7%)	58.40% (51.5% - 65.3%)
Accuracy (95%CI)	31.30% (-)	63.80% (59.1% - 68.5%)	23.90% (20.6% - 27.3%)	64.80% (59.7% - 69.8%)	66.10% (61.0% - 71.2%)
VP+ (95%CI)	19.90% (-)	30.30% (26.9% - 34.1%)	19.90% (19.7% - 20.2%)	30.60% (26.9% - 34.6%)	31.60% (27.7% - 35.8%)
VP- (95%CI)	- (-)	90.30% (87.3% - 92.6%)	83.20% (35.7% - 98.8%)	90.70% (87.6% - 93.1%)	91.20% (88.1% - 93.6%)

TABLE 3 — Laboratory variables and symptoms in relation to the result of the anatomopathological examination

Variable	Classification	All n (%)	Chronic cholecystitis n (%)	Acute cholecystitis n (%)	p*	OR (95%CI)
Vomiting (n=607)	No	348 (57.30%)	288 (63.00%)	60 (40.00%)	<0.001	2.56 (1.75 - 3.73)
	Yes	259 (42.70%)	169 (37.00%)	90 (60.00%)		
Nausea (n=607)	No	330 (54.40%)	279 (61.10%)	51 (34.00%)	<0.001	3.04 (2.07 - 4.48)
	Yes	277 (45.60%)	178 (38.90%)	99 (66.00%)		
Rods (n=378)	Unchanged	351 (92.90%)	269 (96.60%)	122 (85.50%)	0.001	4.46 (1.90 - 10.5)
	Changed	27 (7.10%)	8 (3.40%)	19 (13.50%)		
AST (n=284)	Unchanged	160 (56.30%)	97 (48.50%)	63 (69.50%)	0.001	0.41 (0.25 - 0.69)
	Changed	124 (43.70%)	92 (51.40%)	32 (30.50%)		
TGP (n=188)	Unchanged	137 (47.30%)	70 (40.10%)	67 (60.30%)	0.001	0.43 (0.26 - 0.70)
	Changed	151 (52.40%)	109 (60.20%)	42 (39.30%)		
Amylase (n=277)	Unchanged	201 (72.60%)	124 (70.10%)	77 (72.00%)	0.221	0.70 (0.39 - 1.24)
	Changed	76 (27.40%)	54 (29.80%)	22 (22.90%)		
Lipase (n=281)	Unchanged	143 (50.90%)	64 (43.90%)	79 (64.40%)	0.002	0.45 (0.27 - 0.75)
	Changed	138 (49.10%)	82 (56.10%)	37 (36.60%)		
GamaGT (n=277)	Unchanged	98 (35.40%)	62 (34.40%)	36 (37.10%)	0.658	0.89 (0.53 - 1.49)
	Changed	179 (64.60%)	118 (65.60%)	61 (62.90%)		

*Univariate logistic regression model and Wald test. p<0.05

is possible to deduce that CC has a more pronounced association with the alteration of these enzymes compared to AC. On the other hand, among those diagnosed with CC, 3.40% had high levels of rods, while in the AC group, this percentage increased significantly (p=0.001) to 13.50%. This difference resulted in an OR of 4.46 (1.90 - 10.5), indicating that AC is more strongly associated with abnormal rod levels compared to CC (Table 3).

Regarding the symptoms, vomiting (42.70%) was almost equal to nausea (45.60%); 280 individuals (46.10%) did not report any symptoms; in those with CC, 37% had vomiting and AC, 60%. A significant association was found between vomiting and the type of cholecystitis (p<0.001). The OR value was 2.56 (1.75 - 3.73), indicating that AC is more associated with the presence of vomiting than CC. In relation to nausea, a positive association was shown (p<0.001), resulting in an OR of 3.04 (2.07 - 4.48). Therefore, it can be inferred that symptoms of nausea and vomiting are more prevalent in patients diagnosed with AC when compared to cases of CC (Table 3).

DISCUSSION

Although laparoscopic cholecystectomy is the gold standard for the definitive treatment of AC, the majority (84.30%) of the cholecystectomies performed were laparotomy. The discrepancy of this data in relation to the established gold standard - laparoscopic cholecystectomy - may be associated with limited access to technology in the Brazilian public health system, as well as the lack of emphasis on training in laparoscopy.

In its isolated form, Murphy's sign was positive in 49.30% of the patients with AC and 29.60% with CC, totaling 35.80% of the patients analyzed. The study demonstrated that although Murphy's sign has little relevance in the general context, it is more strongly associated with the condition of AC (OD of 2.31). Pain in the right upper quadrant occurred in 98.70% of the total, with no significant differences between the AC and CC groups (p=0.916). In general, criterion A alone was not significant for the diagnosis of AC.

It was observed that 35.70% of the patients had leukocytosis, with a probability 2.93 times greater of occurring in cases of AC than CC. Elevated CRP was found in more than 82% of AC cases. The results emphasize the importance and efficacy of criterion B variables in the Tokyo Classification. The absence of the fever variable, an element of criterion B, was due to the fact that the database had temperature records only when there was a report of fever or hyperthermia confirmed at admission. This resulted in the absence of information in most of the medical records.

In the present study, 99.30% of the patients had abnormal imaging studies. There was no statistically significant association between imaging findings and the differentiation between AC and CC (p=0.855). However, only the finding of gallbladder thickening, present in 21.90% of the cases, proved to be significant for the diagnosis of AC (OR 8.69). These results emphasize the relevance of gallbladder thickening as a differential marker between the 2 types of cholecystitis. It should be taken into account that imaging findings may vary according to the ultrasound device, operator, and criteria used. It is also important to emphasize that it is recommended as the diagnostic method of choice for morphological evaluation of AC (Recommendation 1, level C).[14]

In this study, the confirmatory diagnosis for AC (criteria A+B+C) in relation to cases confirmed by anatomopathological study revealed sensitivity of 77.40%, specificity of 58.40%, and overall accuracy of 66.10%. Thus, it is concluded that the combination of the 3 criteria offers reasonable performance in the detection of AC, presenting a higher probability of correct diagnosis when compared to the isolated criteria, or even with the combination of criteria A+B.

In addition, a statistically significant finding - despite the scarcity of evidence in the literature to support it - concerns the levels of AST and ALT. Laboratory abnormalities of these markers showed a greater association with CC. In the same sense, the previous presence of elevation in lipase levels is correlated with AC; therefore, patients without altered lipase have a lower relative risk of having AC (36.60%[1] compared to CC (56.10%). Although AC can result in elevated lipase and amylase levels, these 2 values are commonly associated with any pancreatic inflammation and are not specific to the diagnosis of AC.[1] In addition, it was found that only 13.50% of the cases of AC presented alterations in rods, although this variable was statistically significant ($p<0.001$). Rodsis was more prevalent in AC than CC (OR 4.46), as well as nausea and/or vomiting (OR 2.56).

CONCLUSION

The results of this study indicate that the 2018 Tokyo Criteria demonstrated good sensitivity for the diagnosis of AC, although its specificity was relatively low. Even so, the global accuracy observed suggests that these criteria have an acceptable capacity to correctly classify the presence or absence of the disease, configuring themselves as a useful tool in clinical practice. Secondarily, other data not included in the CT18 can help in the diagnosis of AC, such as the presence of nausea or vomiting and the finding of gallbladder thickening on ultrasound.

Authors' contributions

Guilherme Andrade Coelho – Conceptualization, Research
Bernardo Huçulak Melo – Methodology,
Maria Eduarda Barcik Lucas de Oliveira - Supervision
Bruna Corchak da Silva – Conceptualization, Writing (original draft)

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