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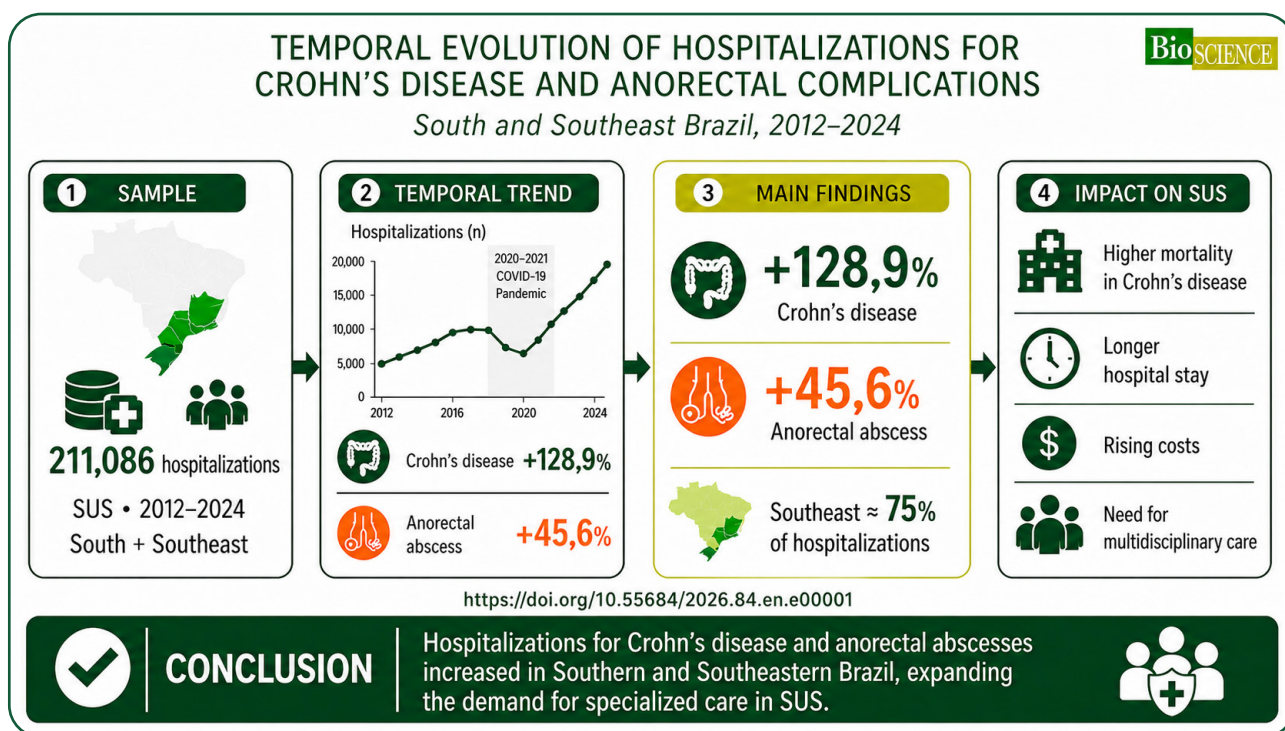
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Temporal evolution of hospitalizations for Crohn's disease and anorectal complications in southern and southeastern Brazil: a population-based study from 2012 to 2024

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Central Message

Hospitalizations for Crohn's disease and its complications in the anal and perianal regions have been increasing significantly in the South and Southeast of Brazil. In just over a decade, hospitalizations for Crohn's disease have doubled and hospitalizations for perianal abscesses have increased by almost 50%. This growth generates a greater need for specialized care and greater public spending on health, highlighting the importance of early diagnosis and multidisciplinary follow-up of patients.

Perspective

The findings help clinical practice by showing that Crohn's disease is no longer a rare condition in Brazil and requires the structuring of specialized care networks. The increase in associated perianal complications reinforces the need for surgeons and gastroenterologists to act in an integrated manner, with early identification of critically ill patients and standardized management protocols. The results also signal to public managers the urgency of planning the allocation of resources for this growing demand, especially in reference centers in the most populous regions of the country.

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ABSTRACT

Introduction: Among the most debilitating complications of Chron's disease are perianal manifestations, including anorectal abscesses and fistulas throughout the course and are associated with significant morbidity, impaired quality of life, and surgical interventions.

Objective: To describe the epidemiology and temporal trends of hospitalizations for anorectal abscesses, anal fistulas and fissures, and Crohn's disease in the Unified Health System of the South and Southeast regions of Brazil between 2012 and 2024.

Method: Retrospective ecological time series study using administrative data on public hospital admissions in the South and Southeast regions between 2012 and 2024. Hospitalizations were identified by the codes of the International Classification of Diseases, tenth revision, corresponding to Crohn's disease, anorectal abscesses, and anal fistulas. The volume of hospitalizations, hospital mortality, length of stay, and costs were analyzed. Temporal trends were evaluated by linear regression and mean annual percentage change.

Results: A total of 211,086 hospitalizations were analyzed. Those due to Crohn's disease increased by 128.9%, while anorectal abscesses grew by 45.6%. In-hospital mortality was higher in Crohn's disease, followed by abscesses and fistulas, with a longer average length of hospital stay, and average cost. Abscesses and fistulas showed a strong male predominance. The Southeast region concentrated approximately 75% of hospitalizations.

Conclusion: Hospitalizations for Crohn's disease and anorectal abscesses have increased substantially in the more developed regions of Brazil, representing an increasing burden on the public health system. The findings reinforce the need for better allocation of resources, early diagnosis, and multidisciplinary management strategies for complex perianal disease.

KEYWORDS: Inflammatory bowel diseases. Perianal disease. Hospitalization. Time series studies. Ecological studies. Unified Health System.

INTRODUCTION

Crohn's disease (CD) is a chronic and relapsing inflammatory bowel disease (IBD) characterized by transmural inflammation that can affect any segment of the gastrointestinal tract. Among its most debilitating complications are perianal manifestations, including anorectal abscesses and fistulas, which occur in approximately 20–40% of patients over the course of the disease and are associated with significant morbidity, impaired quality of life, and recurrent surgical interventions.¹⁻³

Anorectal abscesses (ICD-10: K61) represent acute suppurative infections of the perianal and anorectal spaces, while anal fistulas and fissures (ICD-10: K60) comprise chronic pathological communications between the anal canal and the perianal skin or adjacent structures. Although these conditions may occur in isolation, their coexistence with CD reflects the underlying pathophysiology of transmural intestinal inflammation and constitutes a hallmark of complex perianal Crohn's disease.^{4,5}

In Brazil, the Unified Health System (SUS) provides universal public health coverage and is responsible for approximately 75% of all health care in the country. The SUS Hospital Information System (SIH/SUS) is one of the largest administrative databases of hospital admissions in the world, registering millions of admissions annually and providing a valuable resource for population-based epidemiological analyses.^{6,7}

The South and Southeast regions of Brazil concentrate approximately 56% of the national population and have the highest density of tertiary health services and surgical specialists. This concentration of infrastructure, together with possible differences in the incidence of IBD associated with the degree of urbanization and industrialization, makes these regions particularly relevant for the study

of the burden of hospitalizations due to anorectal complications in the context of CD.⁸⁻¹⁰

Despite the growing global recognition of the epidemiological burden of IBD, particularly in newly industrialized countries, population data on hospitalization patterns for anorectal complications associated with CD remain limited, especially in Latin American contexts.^{11,12} Understanding the temporal trends, demographic distributions, and geographic heterogeneity of these hospitalizations is essential to support public health policies, optimize resource allocation, and identify gaps in the management of complex perianal disease.

The objective of this study was to describe the epidemiology and temporal trends of hospitalizations for anorectal abscesses, anal fistulas and fissures, and CD in the SUS in the South and Southeast regions of Brazil between 2012 and 2024, evaluating the volume of hospitalizations, hospital mortality, length of stay, costs, and demographic and geographic patterns.

METHOD

This study was conducted with secondary, public and unidentified data, and therefore exempted from consideration by the Research Ethics Committee in accordance with Resolution No. 510/2016 of the National Health Council (Brazil).

This is a retrospective ecological time series research based on administrative records of hospital admissions from the SUS Hospital Information System (SIH/SUS, DATASUS). The SIH/SUS records all hospitalizations funded by the public sector in Brazil and contains standardized information on demographics, diagnoses, procedures, outcomes, costs, and length of stay. The data were extracted from the reduced Hospital Admission Authorization (RD-AIH) files for the period from January 2012 to

December 2024, restricted to the federative units of the South (Paraná, Santa Catarina, and Rio Grande do Sul) and Southeast (São Paulo, Minas Gerais, Rio de Janeiro, and Espírito Santo) regions.

Hospitalizations were identified and classified based on the main diagnostic code (DIAG_PRINC) according to the International Classification of Diseases, 10th Revision (ICD-10). Three diagnostic groups were defined: Crohn's disease (K50); anorectal abscess (K61); and fistula and anal fissure (K60). These groups were analyzed independently, since the administrative data do not allow individual linkage between concurrent diagnoses or sequential diagnoses between admissions.

The following variables were analyzed: year of admission (2012–2024); federative unit (seven states in the South and Southeast regions); sex (male, female); age group (< 20, 20–39, 40–59, 60–79, ≥ 80 years); number of hospitalizations; hospital deaths; hospital mortality (proportion of admissions resulting in death); average and median length of stay (in days); total cost of hospitalization; and average cost per hospitalization (in reais, R\$).

Statistical analysis

Descriptive statistics were calculated for all variables, including totals, proportions, means, and medians. Temporal trends in the number of hospitalizations, mortality, length of stay, and costs were evaluated by linear regression of ordinary least squares (OLS) with the year as an independent variable. The mean annual percentage change (AAPC) was estimated by adjusting linear regression to the natural logarithm of the annual hospitalization counts, with the AAPC calculated as $[\exp(\beta) - 1] \times 100$, where β is the regression coefficient. 95% confidence intervals (95% CI) were derived from the standard error of the coefficient. Spearman's correlation coefficients (ρ) were calculated to evaluate monotonic temporal trends. The pre-COVID (2012–2019) and post-COVID (2020–2024) periods were compared by independent sample t-tests. Subgroup analyses were stratified by sex, age group, and state. All analyses were performed in Python 3.12 with NumPy, SciPy and pandas. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

During the 13-year period of the study (2012–2024), a total of 211,086 hospitalizations were recorded in the three diagnostic groups in the South and Southeast regions of Brazil. Fistulas and anal fissures (K60) accounted for the highest proportion of admissions (112,088; 53.1%), followed by anorectal abscesses (K61; 79,018; 37.4%) and CD (K50; 19,980; 9.5%). The total combined cost of these hospitalizations exceeded R\$ 98.4 million over the period included.

Hospital mortality was higher for CD (1.76%), approximately twice that observed for anorectal

abscesses (0.86%) and about 20 times higher than for anal fistulas/fissures (0.09%).¹ The mean length of stay was longest for CD (7.0 days), followed by anorectal abscesses (3.9 days) and fistulas/fissures (1.8 days). The mean cost per hospitalization was higher for CD (R\$ 1,098.39), compared to R\$ 450.56 for abscesses and R\$ 364.28 for fistulas/fissures (Table 1).

TABLE 1 — General descriptive statistics of hospitalizations by diagnostic group, South and Southeast Brazil (2012–2024)

Variable	Crohn's disease (K50)	Anorectal Abscess (K61)	Fistula/Anal Fissure (K60)	Total
Total hospitalizations, n	19,980	79,018	112,088	211,086
Proportion of total, %	9,5	37,4	53,1	100,0
Hospital deaths, n	351	678	96	1,125
Hospital mortality, %	1,76	0,86	0,09	0,53
Average MPR, days	7,0	3,9	1,8	—
Average cost/intern., R\$	1.098,39	450,56	364,28	—
Total cost, million R\$	21,95	35,60	40,83	98,38
Weighted average age, years	40,4	44,7	43,4	—
M:F Ratio	0,93	2,26	1,77	—
Change 2012–2024, %	128,9	45,6	35,6	—
AAPC, % (95% CI)	6,53 (5,03–8,06)	3,02 (2,23–3,82)	1,00 (-2,19–4,30)	—

MPR, average length of stay; AAPC, mean annual percentage change; CI, confidence interval; M:F, male:female.

Temporal trends in hospitalizations

Hospitalizations due to CD showed a more pronounced temporal increase, from 1,036 admissions in 2012 to 2,371 in 2024, corresponding to an increase of 128.9% and AAPC of 6.53% (95% CI: 5.03–8.06%; $p < 0.001$; Spearman $\rho = 0.923$; $p < 0.001$). Hospitalizations for anorectal abscess also showed a significant upward trend, increasing from 5,113 in 2012 to 7,447 in 2024 (increase of 45.6%; AAPC: 3.02%; 95% CI: 2.23–3.82%; $p < 0.001$). In contrast, hospitalizations for anal fistulas/fissures did not show a statistically significant linear trend (AAPC: 1.00%; 95% CI: -2.19–4.30%; $p = 0.555$), although they remained the numerically largest group throughout the period (Figure 1).

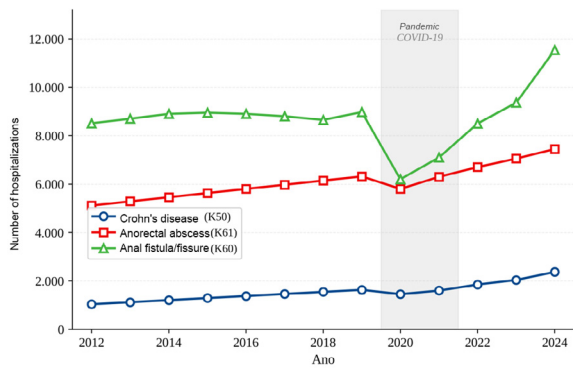


FIGURE 1 — Annual trend of hospitalizations by diagnostic group in the South and Southeast regions of Brazil (2012–2024); horizontal axis: year of admission; vertical axis: number of hospitalizations. The gray band indicates the period of the COVID-19 pandemic

Notable reduction in hospitalizations was observed during 2020–2021, coinciding with the COVID-19 pandemic, particularly for anal fistulas/fissures. The post-pandemic recovery was rapid for all groups, with

2023–2024 values surpassing pre-pandemic levels. Comparison of pre-COVID (2012–2019) and post-COVID (2020–2024) annual means showed significant increases for CD (1,334 vs. 1,862; $p = 0.016$) and anorectal abscesses (5,715 vs. 6,660; $p = 0.025$), but not for fistulas/fissures ($p = 0.899$, Table 2).

TABLE 2 – Comparison of the annual means of hospitalizations in the pre-COVID (2012–2019) and post-COVID (2020–2024) periods, South and Southeast of Brazil

Diagnostic group	Pre-COVID Average (2012–2019)	Post-COVID average (2020–2024)	p-value
Crohn's disease	1,334	1,862	0,016
Anorectal abscess	5,715	6,660	0,025
Fistula/anal fissure	8,673	8,541	0,899

Independent sample t-test comparing annual means of hospitalizations

Hospital mortality trends

Hospital mortality in CD fluctuated between 1.1% and 3.3% over the period, with no statistically significant temporal trend. Mortality of anorectal abscesses ranged from 0.5% to 2.0%, and that of fistulas/fissures remained consistently below 0.4%. The age gradient was striking: in-hospital mortality increased progressively with advancing age in all groups, reaching 12.84% in patients with CD ≥ 80 years of age (Table 3).

Length of stay and costs

The mean length of stay (MPR) for CD showed a decreasing trend over the period (coefficient: -0.148 days/year; $R^2 = 0.702$; $p < 0.001$), MPT of anorectal abscesses showed a modest and non-significant increase, and that of fistulas/fissures remained stable at approximately 1.8 days. The mean cost per hospitalization increased significantly for all three groups (all $p < 0.001$). The average cost of DC went from R\$ 846 in 2012 to R\$ 1.263 in 2024 (coefficient: $+R\$ 19.22$ /year; $R^2 = 0.620$). The total annual cost increased substantially in all groups, reflecting both the increase in the volume of hospitalizations and the increase in unit costs,

Demographic and geographic distribution

Hospitalizations for CD showed a slight predominance of females (male: 48.2%; female: 51.8%; M:F ratio: 0.93). consistent with the known epidemiology of CD in population studies. In contrast, anorectal abscesses and fistulas/fissures showed marked male predominance, with M:F ratios of 2.26 and 1.77, respectively. Regarding age distribution, the highest proportion of hospitalizations due to CD occurred in the 20–39 age group (36.9%), followed by 40–59 years (31.2%) and < 20 years (17.8%). For anorectal abscesses and fistulas/fissures, the peak age was in the 40–59 age group (40.6% and 48.1%, respectively). Hospital mortality increased sharply with advancing age in all groups (Table 3).

The Southeast region concentrated the highest burden of hospitalizations in all diagnostic groups, accounting for approximately 75% of the total in each group (Southeast: CD 75.7% abscess 75.9% fistula

74.2%; South: CD 24.3%. abscess 24.1%. fistula 25.8%). The state of São Paulo alone was responsible for the largest share of hospitalizations in the three groups, followed by Minas Gerais. In the South region, Paraná led for anorectal abscesses and fistulas/fissures, while Santa Catarina had the highest volume of hospitalizations for CD among the southern states.

TABLE 3 – Distribution of hospitalizations by age group and diagnosis group, with in-hospital mortality, South and Southeast Brazil (2012–2024)

Age group	DC n (%)	Abscess n (%)	Fistula n (%)	DC mort. %	Abs. mort. %
<20	3.560 (17.8)	5.734 (7.3)	4.149 (3.7)	0.48	0.19
20–39	7.371 (36.9)	27.971 (35.4)	38.768 (34.6)	0.91	0.23
40–59	6.235 (31.2)	32.103 (40.6)	53.932 (48.1)	1.92	0.69
60–79	2.596 (13.0)	12.218 (15.5)	14.743 (13.2)	4.58	2.53
≥ 80	218 (1.1)	992 (1.3)	496 (0.4)	12.84	7.16

CO=Crohn's disease; Abs = anorectal abscess; death=hospital mortality

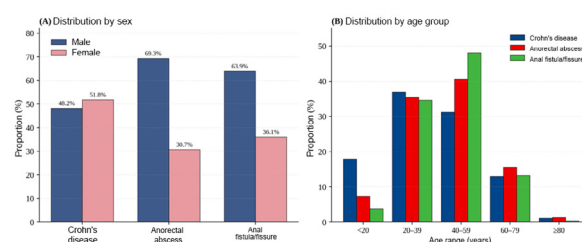


FIGURE 2 – Demographic distribution of hospitalizations by sex (panel A) and by age group (panel B), South and Southeast of Brazil (2012–2024), Horizontal axis panel A: diagnostic group; horizontal axis panel B: age group; vertical axis: proportion of hospitalizations

DISCUSSION

This ecological study analyzed 211,086 hospitalizations related to CD, anorectal abscesses, and anal fistulas/fissures in the South and Southeast regions of Brazil over 13 years, providing a comprehensive picture of the burden of hospitalizations imposed by these conditions in the most developed regions with the largest health infrastructure in the country. The findings reveal significant temporal increases in hospitalizations for CD and anorectal abscesses, associated substantial costs, and notable demographic and geographic disparities.

The most striking finding was the 128,9% increase in hospitalizations for CD between 2012 and 2024, with AAPC of 6,53%. This growth is consistent with global epidemiological trends that demonstrate increasing incidence of IBD in newly industrialized countries.^{8–10} The accelerated upward trend may reflect a real increase in the incidence of the disease, improvement in diagnostic capacity and awareness, greater access to specialized care within the SUS, or a combination of these factors. Similar patterns have been reported in other Latin American countries and in population records from Asia and the Middle East.^{11,12}

Anorectal abscesses also showed a significant upward trend (AAPC: 3,02%), with an increase of 45,6% in the period. Considering that they are a frequent complication of CD, the parallel increase in hospitalizations for K50 and K61 suggests a possible

shared epidemiological factor. However, it is essential to emphasize that the SIH/SUS does not allow individual linkage between these diagnostic codes, and a substantial proportion of hospitalizations for K61 probably represent anorectal abscesses unrelated to CD in the general population.^{13,14} Therefore, these findings should be interpreted as complementary indicators of population burden, and not as direct evidence of a causal relationship at the individual level.

The absence of a significant trend towards hospitalizations for anal fistulas/fissures (AAPC: 1,00%; $p = 0,555$) is remarkable and may reflect the more stable epidemiology of these conditions in the general population, as well as a possible transition to outpatient management of less complex fistulas and fissures. The sharp drop during 2020, which was more pronounced for fistulas/clefts than for the other groups, reinforces this interpretation, as elective surgical procedures were disproportionately affected by pandemic-related restrictions.¹⁵

Hospital mortality was higher for CD (1,76%), consistent with the greater systemic severity and the complication profile of the disease when compared to isolated anorectal conditions. The steep gradient of mortality with advancing age, reaching 12,84% in patients with CD ≥ 80 years, highlights the vulnerability of elderly patients and the need for age-appropriate management strategies.¹⁶

The patterns of distribution by sex observed are consistent with the literature, CD showed an almost equal distribution between the sexes (M:F = 0,93), with a slight predominance of females, reflecting typical findings of population studies of CD.¹⁷ The strong male predominance of anorectal abscesses (M:F = 2,26) and fistulas/fissures (M:F = 1.77) is well established and probably reflects anatomical, hormonal, and lifestyle-related risk factors.¹⁸

The geographic concentration in the Southeast, with São Paulo accounting alone for about 40% of all hospitalizations, reflects both the demographic weight of this region and the higher density of hospital services and referral centers. The South region, although representing approximately 25% of hospitalizations, has a proportionally relevant volume considering its population, which may indicate better diagnostic and therapeutic access in this region.^{19,20}

The economic analysis revealed a progressively increasing financial burden, with average hospitalization costs increasing significantly for all three groups. CD, despite representing only 9.5% of total hospitalizations, generated disproportionately high costs per admission (R\$ 1,098.39), reflecting the higher MPR and clinical complexity associated with hospitalizations for CD. The total combined cost exceeded R\$ 97 million in 13 years, representing a substantial burden on the SUS budget.²¹

Limitations

This study has important limitations. First, the SIH/SUS is an administrative system developed for

billing and reimbursement, not for epidemiological research. The accuracy of diagnostic coding depends on the practices of each facility, and coding errors, underreporting, and overcoding may occur. Second, the exclusive use of the primary diagnosis (DIAG_PRINC) does not capture comorbidities or secondary diagnoses; thus, hospitalization coded as K61 occurring in a patient with CD would not be identifiable as such. Third, the absence of individual identifiers makes longitudinal follow-up impossible; readmissions of the same individual are counted as separate hospitalizations. Fourth, the data reflect only hospitalizations financed by the SUS, not including the private sector. Fifth, ecological design limits causal inference. Sixth, the costs are expressed in nominal reais (\$) without inflationary adjustment. Finally, the restriction to the South and Southeast regions, although it allows for a more homogeneous analysis from the point of view of health infrastructure, limits the generalization of the results to the rest of the country.

CONCLUSION

Hospitalizations for CD and anorectal abscesses increased substantially in the South and Southeast regions of Brazil between 2012 and 2024, with CD demonstrating the most pronounced growth rate. In-hospital mortality remains considerably higher than that of isolated anorectal conditions, with a steep gradient dependent on age. The economic burden is substantial and growing. Marked demographic and geographic disparities highlight inequalities in the burden of disease and access to health care even within the most developed regions of the country. These findings reinforce the need for better allocation of resources, improvement of screening and diagnostic capacity, multidisciplinary management of perianal disease in the SUS, and future epidemiological studies with linkage at the individual level to better characterize the relationship between CD and its anorectal complications.

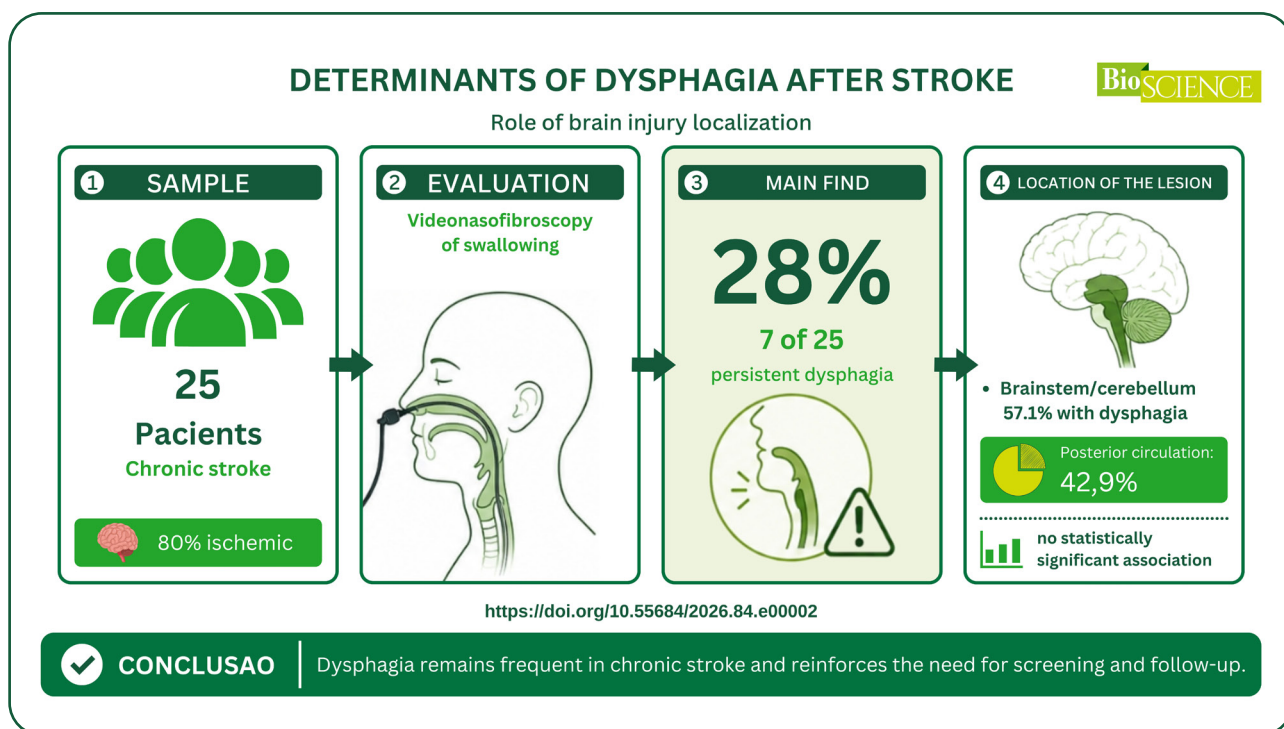
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Determinants of dysphagia after stroke: the role of brain injury location

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Central Message

Stroke is the second leading cause of death in Brazil, surpassed only by acute myocardial infarction. May present clinically as ischemic, thrombotic, embolic or hemorrhagic. Among the classic signs is dysphagia. In swallowing studies, the incidence of swallowing can vary between 41-73%. This variation is justified due to the phases when the diagnosis is made, that is, acute, subacute and/or chronic phases of stroke.

Perspective

The gold standard for diagnosing post-stroke dysphagia is swallowing videofluoroscopy. Videonasofibroscopy is considered a highly accurate test, complementary to clinical diagnosis, and often preferred in clinical settings due to its practicality, but it does not replace videofluoroscopy of swallowing as the gold standard.

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ABSTRACT

Introduction: Cerebrovascular accident (CVA) is one of the leading causes of death in Brazil and, with the increase in life expectancy of the Brazilian population, sequelae are expected to increase.

Objective: To evaluate the association between brain regions of patients diagnosed with stroke in the chronic phase and the presence of dysphagia.

Method: Clinical, cross-sectional, qualitative and quantitative, descriptive and retrospective study with data collection from 25 medical records, in which variables of association between stroke and dysphagia were analyzed, including cause of stroke, diagnosis of dysphagia by videonasofibroscopy of swallowing, compromised brain region and cerebral circulation evaluated by the Swallowing Scale Bamford/ Oxfordshire Community Stroke Project.

Results: Thirteen (52%) patients were men between 61 and 80 years old. Regarding the type of stroke, 20 (80%) were ischemic. Dysphagia remained in seven (28%) in the chronic phase of stroke. There was a predominance of brainstem/cerebellum lesions and concomitant dysphagia in 57.1% of these patients, and even more frequent ischemia with posterior circulation involvement in 42.9%, but without a statistically significant association.

Conclusion: Patients affected by stroke, in the chronic phase, have a high percentage of dysphagia (28%) in outpatient follow-up.

KEYWORDS: Stroke. Dysphagia. Cerebrovascular circulation. Endoscopy. Encephalon.

INTRODUCTION

Cerebrovascular accident (CVA) is the second cause of death in Brazil according to data in DATASUS published in 2024 with 106,182 deaths, being surpassed only by acute myocardial infarction (AMI) which had 119,687.¹ Its incidence worldwide in 2020 was 11.71 million cases, of which 7.59 million were ischemic, 4.12 million hemorrhagic.^{2,3}

Stroke can present clinically as ischemic (ICVA), thrombotic, embolic or hemorrhagic (CVA).⁴ Among the classic signs is dysphagia.⁵ In videofluoroscopy or videonasofibroscopy of swallowing, the incidence of swallowing can vary between 41-73%. This variation is justified due to the phases when the diagnosis is made, that is, acute, subacute and/or chronic phases of stroke.⁶⁻¹³

The use of videofluoroscopy of swallowing in the acute phase is considered the gold standard to evaluate dysphagia, and notably the penetration of food into the larynx and/or aspiration into the trachea.¹⁴

There is no association between the location of acute stroke in the cerebral hemispheres; however, residues in pharyngeal recesses that cause aspiration occur less frequently when the stroke is located in the cerebral hemispheres.^{8,9,15} A Brazilian study demonstrated post-stroke dysphagia in the acute phase in patients with cortical and subcortical involvement, with no association of it in terms of whether the lesion is in the right or left cerebral hemisphere.¹⁶

When evaluated by the Oxfordshire Community Stroke Project (OCSP)¹⁷⁻²⁰ dysphagia predominates with involvement of the anterior and middle cerebral artery. However, there is no difference between dysphagia and compromised topography in either the right or left cerebral hemisphere. However, the involvement of the cerebral circulation of the carotid system predominates in relation to the vertebrobasilar system.^{8:19-24}

The objective of the present study was to correlate the presence of dysphagia in those diagnosed with chronic phase stroke and/or stroke and its correlation with the lesions/regions in the brain detected by imaging in SUS users and treated at the Specialized Rehabilitation Center (CER) – Unesp Marília Auxiliary Unit, Marília Campus, in the speech therapy and neurology clinic.²⁵⁻³⁷

METHOD

This study was approved by the Research Ethics Committee of Unesp Marília under opinion No. 2,858,338 because it was in accordance with the Resolution of the National Health Council (CNS) 466/2012 and Resolution of the National Health Council (CNS) 510/2016

This is a cross-sectional, qualitative and quantitative, descriptive and retrospective clinical study carried out through the collection of data from medical records of the Specialized Rehabilitation Center (CER)/Unesp Marília, in a non-probabilistic sample to evaluate the presence of dysphagia in 25 patients diagnosed with stroke, in the chronic, ischemic and/or hemorrhagic phase, referred from the primary health care network and hospitals in Marília and region, who are treated at the Speech Therapy and Neurology Clinic at the CER of Unesp Marília.²⁶⁻³²

The variables collected were: age, time of stroke occurrence (years), time of follow-up at the CER outpatient clinic (years), gender, age group, education, sedentary lifestyle, smoking, alcoholism, systemic arterial hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, type of stroke, diagnosis of dysphagia by the use of videonasofibroscopy of swallowing, region/lesion in the brain evidenced by imaging exam and association with dysphagia, cerebral circulation affected by the OCSP scale and association with dysphagia, and diagnosis of stroke by magnetic resonance imaging of the skull.

The speech-language pathology diagnosis of dysphagia was made through clinical evaluation of the patients attended, in which the presence or absence of dysphagia was investigated, and later confirmed by videonasofibroscopy of swallowing. In this evaluation, 180 days after the occurrence of the stroke, the presence of pharyngeal residues in epiglottic valleculae and/or piriform recesses were considered indicative of dysphagia.^{25-29,36}

In videonasofibroscopy, a Pentax® nasofibroscope, model FNL 10RP3, coupled to a PSV4000® microcamera system, was used, and a Pentax-branded® light source, model LH-150 PC, without topical anesthesia. The zscan 6.0 software was used to analyze the images of the swallowing videoendoscopy to evaluate the visualization

of the presence of pharyngeal residues (valleculae and/or piriform sinuses) and, if present, the presence of pharyngeal residues (valleculae and/or piriform sinuses) and, if present, the presence of pharyngeal residues (valleculae and/or piriform sinuses) and, if present, the presence of pharyngeal residues (valleculae and/or piriform sinuses) was considered positive for dysphagia.²⁶

The pathophysiology and etiology of stroke was considered according to the TOAST Classification (Trial of Org 10172 in Acute Stroke Treatment) and the Manual of Routines for Stroke Care.^{30,31}

The diagnosis of CVA and/or CVCH was confirmed by a neurologist at the Neurology Clinic of the CER of Unesp Marília, through analysis of imaging tests (cranial tomography and/or cranial magnetic resonance imaging) requested during the anamnesis and physical examination, and or performed in neurology outpatient clinics and/or hospitals in the city of Marília during consultation, and subsequent reassessment of imaging tests in the neurological clinic at the CER for diagnostic confirmation during the consultation. Those who had other diseases of neurological origin in addition were excluded from this study. Some referred to the CER had had a previous stroke, and for this study only the occurrence of the last stroke was considered for the analysis of the data collected in the medical records.

Statistical analysis

Quantitative variables were described as mean, standard deviation, minimum value, and maximum value. The homogeneity of the variances was analyzed by the Levene test. The comparison of means was analyzed by Student's t-test, and when the assumption of homogeneity was violated, the Welch test was used. The relationship between the qualitative variables was analyzed using the chi-square test. The level of significance was set at 5% ($p\text{-value} \leq 0.05$) and the data were analyzed using the Jamovi software.

RESULT

The sample that had a stroke was characterized according to sociodemographic (age, gender, age group, and education) and clinical aspects (type of stroke, time since the occurrence of the last stroke, time of speech-language pathology follow-up at the CER/Unesp Marília/SP, cerebral circulation compromised by the OSCP scale, location of the lesion in the brain region evidenced by imaging exam, presence of dysphagia by videonasofibroscopy of swallowing, diagnosis of stroke

confirmed by cranial resonance imaging, and comorbidities (sedentary lifestyle, smoking, alcoholism, systemic arterial hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation).

Table 1 shows the relationship between age and possible association with dysphagia predominance of older people (68.3 years, standard deviation = 5.2 years); however, there was no statistically significant difference with patients who did not present dysphagia (61.6 years, standard deviation = 11.5 years). The value of $p = 0.057$ suggests that age may be associated with the presence of dysphagia, although it is not statistically significant.

In addition, patients with dysphagia had a shorter time since stroke occurrence, on average 2.7 years, compared to those with stroke without dysphagia, on average 6.3 years, indicating that dysphagia occurs more in acute or subacute phases of stroke; however, $p = 0.091$ does not confirm a statistically significant association.

In this sample, the mean follow-up time with dysphagia and stroke at the neurology outpatient clinic was 1.1 years (mean, standard deviation = 1.6 years), while in those without dysphagia it was four years (mean, standard deviation = 3.4 years), demonstrating a statistically significant association ($p = 0.009$).

TABLE 2 — Analysis of the association between the distribution of absolute (n) and relative frequency of the presence or absence of dysphagia with the variables of the sociodemographic sample and comorbidities of the patients

Variables	Categories	Dysphagia				Total		p-value
		No		Yes		n	%	
		n	%	n	%			
Gender	Women	8	44.4%	4	57.1%	12	48.0%	0.568
	Male	10	55.6%	3	42.9%	13	52.0%	
Age group	20-40 years	1	5.6%	0	0.0%	1	4.0%	0.357
	41-60 years	7	38.9%	1	14.3%	8	32.0%	
	61-80 years	10	55.6%	6	85.7%	16	64.0%	
Elementary School	Incomplete	11	61.1%	6	85.7%	17	68.0%	0.236
	Complete	7	38.9%	1	14.3%	8	32.0%	
Sedentary lifestyle	No	14	77.8%	3	42.9%	17	68.0%	0.093
	Yes	4	22.2%	4	57.1%	8	32.0%	
Smoking	No	15	83.3%	4	57.1%	19	76.0%	0.169
	Yes	3	16.7%	3	42.9%	6	24.0%	
Alcoholism	No	13	72.2%	6	85.7%	19	76.0%	0.478
	Yes	5	27.8%	1	14.3%	6	24.0%	
Hypertension systemic	No	3	16.7%	3	42.9%	6	24.0%	0.169
	Yes	15	83.3%	4	57.1%	19	76.0%	
Diabetes mellitus	No	13	72.2%	5	71.4%	18	72.0%	0.968
	Yes	5	27.8%	2	28.6%	7	28.0%	
Hypercholesterolemia	No	9	50.0%	2	28.6%	11	44.0%	0.332
	Yes	9	50.0%	5	71.4%	14	56.0%	
Atrial fibrillation	No	18	100.0%	6	85.7%	24	96.0%	0.102
	Yes	0	0.0%	1	14.3%	1	4.0%	

Note: p calculated by the chi-square test of association; # Centro Especializado em Reabilitação (CER)/Unesp Marília.

TABLE 1 — Comparison of the mean, standard deviation, minimum and maximum value of the quantitative variables of the sample in relation to the presence of dysphagia in SUS patients with stroke in terms of age, time of stroke occurrence and follow-up time attended at the CER

Variables	Dysphagia								p-value
	No (n = 18)				Yes (n = 7)				
	Average	DP	Minimum	Maximum	Average	DP	Minimum	Maximum	
Age (years)	61.6	11.5	40.0	78.0	68.3	5.2	60.0	73.0	0.057 *
Time of stroke occurrence (years)	6.3	5.2	0.0	21.0	2.7	2.4	0.0	7.0	0.091 **
Follow-up time at CER / UNESP Marília (years)#	4.0	3.4	0.0	11.0	1.1	1.6	0.0	4.0	0.009 *

* p calculated by Welch's test; ** p calculated by Student's t-test; significance level of 5% ($p \leq 0.05$); # Specialized Rehabilitation Center (CER)/Unesp, Marília.

Table 2 presents an analysis of the association of dysphagia in relation to sociodemographic variables and comorbidities, as well as the respective p-values obtained in association tests (chi-square). In general, no statistically significant association was observed between the presence of dysphagia and the variables analyzed, considering the significance level of 5%.

Among women ($n = 4$, 57.1%), there was a higher absolute and relative frequency of dysphagia compared to men ($n = 3$, 42.9%). The p -value = 0.568 is compatible with this distribution, indicating the absence of a statistically significant association between gender and the presence of dysphagia. Thus, although there is numerical variation between the groups, this difference seems to be due to the small sample size and random fluctuation, and not to a systematic effect of gender on the occurrence of dysphagia.

The largest number of patients with dysphagia occurs in the 61–80 year age group, which goes hand in hand with the absolute increase in stroke cases in this age group. However, when comparing the proportion of dysphagia between the different age groups (20–40, 41–60, and 61–80 years), the association test resulted in $p = 0.357$, suggesting that, in the sample studied, age was not statistically significantly associated with the presence of dysphagia. This result should be interpreted with caution, as there are categories with a very small number of patients (e.g., only one individual in the 20–40 age group), which limits the statistical power of the test and increases the chance of type II error (not detecting an association that may exist in the population).

Patients with incomplete primary education represented the majority of the sample ($n = 17$, 68.0%) and concentrated the largest number of dysphagia cases ($n = 6$, 85.7%). However, when the proportions of dysphagia were analyzed between the groups with complete and incomplete primary education, no statistically significant difference was observed ($p = 0.236$). The coherence between the absolute and relative frequencies presented and the p -value suggests that, even with a predominance of low education among patients with dysphagia, this pattern seems to reflect the sociodemographic profile of the population served, and not an independent association between education and dysphagia.

Among sedentary patients ($n = 8$, 32%), a relatively higher proportion of dysphagia was detected than in non-sedentary patients ($n = 17$, 68%). A higher proportion of sedentary lifestyle was observed in those with dysphagia ($n = 4$, 57.1%) compared to those without ($n = 4$, 22.2%). Despite this percentage difference, the result was not statistically significant ($p = 0.093$), which is close to the threshold of statistical significance, but remains above the cutoff point of 5%. This result may indicate a trend of association between sedentary lifestyle and the presence of dysphagia; however, with the sample available ($n = 25$), the test was not able to confirm this relationship with statistical significance.

There was a higher proportion of smoking in those with dysphagia ($n = 3$, 42.9%) than in those without ($n = 3$, 16.7%). The proportion of dysphagia is numerically

higher among smokers ($n = 6$, 24%) than among nonsmokers ($n = 19$, 76%); However, the value of $p = 0.169$ indicates that smoking and dysphagia were not significant in the sample studied. The relative frequencies presented are compatible with a scenario in which observed differences can be explained by random variation, especially considering the small number of smokers with dysphagia. Therefore, there is no robust evidence that smoking, in isolation, is associated with the occurrence of dysphagia in this group.

It was revealed that most patients did not have alcoholism ($n = 19$, 76%), both in those without ($n = 13$, 72.2%) and in those with dysphagia ($n = 6$, 85.7%). The proportion of individuals with alcoholism was higher in those without dysphagia ($n = 5$, 27.8%) compared to those with ($n = 1$, 14.3%). In total, 24.0% of those evaluated reported alcoholism. Despite this numerical difference between the groups, the statistical analysis did not show statistical significance ($p = 0.478$), indicating that there was no association between alcoholism and dysphagia in the sample studied.

It was reported that the prevalence of systemic arterial hypertension was high in both with and without dysphagia, being more frequent in those without ($n = 15$, 83.3%) compared to those with ($n = 4$, 57.1%). Despite this difference, the statistical analysis did not show significance ($p = 0.169$), indicating the absence of a statistically significant association between hypertension and dysphagia.

It was demonstrated that the prevalence of diabetes mellitus was similar among all, with 27.8% ($n = 5$) without dysphagia and 28.6% ($n = 2$) with dysphagia. In total, 28.0% ($n = 7$) had diabetes. Statistical analysis showed no significant difference between those with and without dysphagia ($p = 0.968$), suggesting no relevant association between diabetes and dysphagia.

The analysis of the presence of hypercholesterolemia showed that nine (50.0%) of the patients without dysphagia had hypercholesterolemia, while nine (50.0%) did not. In those with dysphagia, hypercholesterolemia was observed in five (71.4%), while two (28.6%) did not have it. In the total sample, 14 individuals (56.0%) had hypercholesterolemia and 11 (44.0%) did not. There was also no statistically significant association between hypercholesterolemia and dysphagia ($p = 0.332$).

It was found that in the patients without dysphagia, none had atrial fibrillation (0%). In those with, one case of atrial fibrillation was identified (14.3%), while six participants (85.7%) did not. In the total sample, only one patient (4.0%) had atrial fibrillation, while 24 (96.0%) did not.

Finally, there were no statistically significant associations between dysphagia and the variables analyzed (gender, age group, education, sedentary lifestyle, smoking, alcoholism, hypertension and diabetes, hypercholesterolemia, and atrial fibrillation), although sedentary lifestyle and fibrillation presented p values close to the significance threshold, suggesting possible trends that deserve investigation in larger samples.

Table 3 presents the analysis of the association

TABLE 3 — Analysis of the association between the distribution of absolute (n) and relative frequency of dysphagia in terms of the type of stroke, diagnosis of dysphagia by videonasofibroscopy, unilaterality of the lesion/region in the CNS##, impaired cerebral circulation and imaging tests

Variables	Categories	Dysphagia				Total		p-value
		No		Yes				
		n	%	n	%	n	%	
Type of stroke	Hemorrhagic	4	22.2%	1	14.3%	5	20.0%	0.656
	Ischemic	14	77.8%	6	85.7%	20	80.0%	
Videonasofibroscopy of swallowing	Changed	0	0.0%	7	100.0%	7	28.0%	<0.001 *
	Normal	18	100.0%	0	0.0%	18	72.0%	
Region/lesion	Right cerebral hemisphere	5	27.8%	0	0.0%	5	20.0%	0.102
	Right and left cerebral hemisphere	3	16.7%	2	28.6%	5	20.0%	
	Left cerebral hemisphere	7	38.9%	1	14.3%	8	32.0%	
	Brainstem or cerebellum	3	16.7%	4	57.1%	7	28.0%	
Cerebral circulation#	Lacunar syndrome - LACS	3	16.7%	0	0.0%	3	12.5%	0.23
	Partial anterior circulation syndrome PACS	1	5.6%	1	14.3%	2	8.3%	
	Posterior Circulation Syndrome - POCS	3	16.7%	3	42.9%	6	25.0%	
	Total anterior circulation syndrome - TACS	11	61.1%	2	28.6%	13	54.2%	
Skull resonance	No	2	11.1%	3	42.9%	5	20.0%	0.05
	Yes	16	88.9%	4	57.1%	20	80.0%	

Note: * indicates a statistically significant association between dysphagia and videonasofibroscopy of swallowing by the chi-square test for $p\text{-value} \leq 0.05$; ##=CNS central nervous system; # Oxfordshire Community Stroke Project (OCSF) is a clinical classification based on neurological deficits in stroke (Bamford Scale); lacunar syndrome (LACS), total anterior circulation syndrome (TACS - total anterior circulation syndrome), partial anterior circulation syndrome (PACS), and posterior circulation syndrome (POCS). For stroke only, excluding patients with CVA.

between the presence of dysphagia and variables related to the type of stroke, diagnosis by nasovideofibroscopy of swallowing, location of the lesion/brain region in the stroke, cerebral circulation compromised by the Bamford Scale, and magnetic resonance imaging. p-values were calculated using the chi-square test, considering a significance level of 5%.

In the analysis of the type of stroke, it was found that in the patients without dysphagia, four (22.2%) had hemorrhagic stroke and 14 (77.8%) had ischemic stroke. In the patients with dysphagia, one participant (14.3%) had hemorrhagic stroke and six (85.7%) had ischemic stroke. In the total sample, five cases of hemorrhagic stroke (20.0%) and 20 cases of ischemic stroke (80.0%) were recorded. There was no significant difference between patients with and without dysphagia and the type of stroke ($p = 0.656$).

All patients with a diagnosis of dysphagia confirmed by videonasofibroscopy of swallowing ($n = 7$) had dysphagia (100%), while none with normal endoscopic evaluation ($n = 18$) had it. There was a statistically significant association between endoscopic findings on videonasofibroscopy and the presence of dysphagia ($p < 0.001$). These findings reinforce videonasofibroscopy of swallowing as an essential diagnostic method for the detection of dysphagia in the sample studied with high sensitivity and specificity.

Lesions in the left hemisphere were the most frequent ($n = 8$, 32.0%), followed by brainstem/cerebellum ($n = 7$, 28%), right hemisphere ($n = 5$, 20%), and right and left hemisphere ($n = 5$, 20%). Those with lesions in the brainstem or cerebellum had a higher proportion of dysphagia ($n = 4$, 57.1%). Although the distribution of lesions shows a trend toward a greater association between brainstem/cerebellum involvement and clinical outcome, the statistical analysis did not show significance ($p = 0.102$).

Regarding the classification of infarction sites evaluated by the OCSF classification, which evaluates only patients with ischemic stroke, 54.2% ($n = 13$) of

infarctions occurring in the total anterior circulation (TACS), 8.3% ($n = 2$) of infarctions in the partial anterior circulation (PACS), 25% ($n = 6$) of infarctions in the posterior circulation (POCS), and 12.5% ($n = 3$) of lacunar infarctions (LACS). The presence of dysphagia diagnosed by videonasofibroscopy was more frequent among patients classified as POCS ($n = 6$, 42.9%). However, there was no statistically significant association between the clinically involved cerebral circulations and the occurrence of dysphagia ($p = 0.23$).

Regarding magnetic resonance imaging of the skull, it was found that 20 patients (80%) underwent the examination, while five (20%) did not. Among those who did not have it, three (42.9%) were associated with dysphagia; However, among those who underwent the test, four (57.1%) had dysphagia. Statistical analysis showed a trend toward an association between MRI and dysphagia, with a value of $p = 0.05$, indicating proximity to the significance threshold. These findings suggest that cranial MRI may contribute to the identification of dysphagia, although the results should be interpreted with caution.

DISCUSSION

The present study aimed to investigate the presence of dysphagia in stroke with definitive diagnosis by imaging tests (magnetic resonance imaging/cranial tomography), ischemic or hemorrhagic types, in the chronic phase, and association with brain lesions, in a population sample.^{1,2}

According to data from the national and international literature, the diagnosis of ischemic stroke in the present study was present in 80% of the patients, in agreement with other national and international studies, and in another study by the same author.^{2,3,8,9,16,20-23,31,37} The results showed a higher prevalence of stroke in those over 60 years of age, a finding that is in line with the national and international literature. Global data from 2020 indicate that the worldwide prevalence of stroke

reached 89.13 million cases, with a predominance in the most advanced age groups, reinforcing the impact of population aging on the incidence of the disease. Brazilian clinical studies also confirm this trend in the evaluation of post-stroke dysphagia in patients with cortical, subcortical and cerebellar involvement.^{2,16}

In addition, studies that analyzed subcortical and internal capsule lesions identified dysphagia in 35% of the patients, predominantly in the left cerebral hemisphere, with a higher occurrence in elderly individuals.^{22,23} An analysis of the OCSP classification showed that carotid circulation impairment tends to predominate in the elderly.^{8,9,20,21}

In the present study, the incidence of dysphagia in the chronic phase of stroke was 28%, a result that is consistent with the literature. Previous studies have reported divergent incidence rates of dysphagia in clinical evaluation and/or by videonasofibroscopy, being 50% in clinical evaluation six months after the fact, and 2-30% in the chronic phase of stroke in endoscopic evaluation in national and international publications.³²⁻³⁶

These findings reinforce that, although dysphagia is more frequently investigated in the acute phase, a significant proportion of patients maintain the sequelae in the chronic phase, with a direct impact on quality of life and the need for prolonged multidisciplinary follow-up. The convergence between the results of the present study and the percentages described in the references confirms the clinical relevance of dysphagia as a persistent complication of stroke, highlighting the importance of screening protocols and continuous rehabilitation in specialized services.

It should be noted that in this study, patients with stroke and concomitant dysphagia at the time of care at the neurology outpatient clinic had a mean diagnosis of 2.7 years, and those without dysphagia had a mean of 6.3 years. The literature shows that dysphagia is more found in the acute and subacute phases of stroke, with a progressive reduction in chronic evaluations.^{6-11,32-36}

In the present study, it was observed that patients with dysphagia had a significantly shorter mean follow-up time in the CER (1.1 years) compared to those without (4 years), a statistically significant difference ($p = 0.009$). This finding suggests that dysphagia tends to manifest and be diagnosed in earlier stages of outpatient follow-up, reflecting the need for immediate multidisciplinary intervention after the vascular event. The reduced clinical follow-up time in the present study among individuals with dysphagia may be related to the greater initial clinical severity, the need for specialized referrals, or even the interruption of follow-up due to complications. These results reinforce the importance of early screening protocols and continuous follow-up, in order to identify and treat dysphagia from the beginning of care, preventing complications such as aspiration, pneumonia, and malnutrition.^{12-15,22-24,32-36}

The literature indicates that there is no clear association between the affected cerebral hemisphere

and the occurrence of post-stroke dysphagia.^{8,9,16,20,21} However, it is more frequent in cases of lesions of the brainstem, cerebellum, and internal capsule, due to the direct involvement of cranial nuclei and nerves related to swallowing control.^{15,22,23}

The results of the present study confirm this absence of a significant association with the cerebral hemisphere involved in stroke, but reinforce the relevance of analyzing the topography of the lesion. The distribution found in this study suggests that lesions in subcortical structures, brainstem and cerebellum have a greater relationship with dysphagia, and its permanence in the chronic phase.^{22-24,32-36}

The gold standard for diagnosing post-stroke dysphagia is swallowing videofluoroscopy. Videonasofibroscopy is considered a highly accurate exam, complementary to clinical diagnosis and often preferred in clinical environments due to its practicality, but it does not replace videofluoroscopy of swallowing as the gold standard. The diagnosis of certainty when using videonasofibroscopy of swallowing, after clinical evaluation, evidences a statistically significant association between the result of videonasofibroscopy of swallowing and the presence of dysphagia, in agreement with other authors who indicate it as reliable, validated by several studies, and often used as a practical alternative, especially in public services or in bedridden patients for the diagnosis of dysphagia.^{12,13,27-29}

In the acute phase of stroke, studies do not show an association between the location of the stroke, right and/or left cerebral hemisphere, and the presence of dysphagia; however, the presence of aspiration occurs more frequently in individuals who have brainstem stroke, and concomitant absence in the swallowing reflex.^{6,8,9,15,16} There was a predominance of lesions in the left cerebral hemisphere ($n = 8$, 32%), but dysphagia was more common in those with lesions in the brainstem/cerebellum ($n = 7$, 28%), and 57.1% of these patients ($n = 4$) maintained dysphagia in the chronic phase of stroke.³²⁻³⁶

The OCSP classification allows the correlation of clinical and imaging findings with the cerebral circulation involved in ischemic stroke.¹⁷ In the present study, a predominance of events in the total anterior circulation (54.2%) was demonstrated, in line with the literature that describes a higher frequency of involvement of arteries originating from the carotid system.¹⁸⁻²⁰ However, dysphagia was more associated with posterior circulation involvement (42.9%), a finding that suggests a possible relationship between vertebrobasilar lesions and swallowing impairment, given the role of the brainstem and cerebellum in the motor coordination of swallowing. Despite this trend, no statistically significant difference was identified ($p = 0.23$), a result that is similar to previous studies that also did not demonstrate a robust association between the topography of cerebral circulation and the presence of dysphagia, suggesting that additional factors - such as lesion extent, functional impairment, and cortical-subcortical connectivity - should be

considered in understanding the pathophysiology of post-stroke dysphagia.^{18,19}

All patients evaluated were in the chronic phase of stroke, i.e., 180 days after the last ischemic or hemorrhagic event. Despite structural alterations detected in 100% of the CT scans and in 80% of the magnetic resonance imaging, no statistically significant association was observed between the presence of brain lesions on imaging studies and the occurrence of dysphagia. Among the seven patients with dysphagia, 42.9% did not undergo magnetic resonance imaging and 57.1% had lesions confirmed by the examination, suggesting that the simple detection of the lesion does not predict, in isolation, the functional impairment of swallowing.

This finding can be explained by the brain plasticity that occurs after stroke, an adaptive mechanism that allows functional reorganization and partial or total recovery of swallowing over time. Previous studies have shown that dysphagia is very frequent in the acute and subacute phases of stroke, with a significant reduction in the chronic phase due to neural reorganization and motor compensation.³²⁻³⁶

In the present study, none of the sociodemographic or clinical variables analyzed - including gender, age group, education, sedentary lifestyle, smoking, alcoholism, systemic arterial hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation - showed a statistically significant association with the presence of dysphagia. Only sedentary lifestyle and atrial fibrillation showed an association trend, with p-values close to the significance threshold ($p \leq 0.05$), suggesting that these factors may play some modulating role, although they were not confirmed as determinants in the sample studied.

These findings are in line with the literature, which points out that the occurrence of post-stroke dysphagia is more related to the neurological event itself - especially to the location and extent of the brain injury - than to isolated traditional risk factors.^{8,9,16,20,21} Previous studies have shown that variables such as gender, age, or cardiovascular comorbidities do not have a consistent association with the presence of dysphagia, reinforcing that functional swallowing impairment is primarily due to neurological dysfunction.²²⁻²⁴ In addition, investigations in patients in the chronic phase of stroke indicate that brain plasticity and neural reorganization may attenuate the impact of cardiovascular and lifestyle risk factors on swallowing function, explaining the absence of a significant association observed.³²⁻³⁶

The present study showed that dysphagia is a relevant complication in patients affected by chronic stroke, and it remains an important sequela, negatively impacting the prognosis and continuity of treatment.

Although no statistical association was identified between the location of the brain lesion and the occurrence of dysphagia, the literature points to a higher risk in lesions of the brainstem, cerebellum, subcortical structures, and internal capsule, which highlights the importance of early clinical evaluation

and subsequent confirmation by videonasofibroscopy.

Thus, the results of the present study corroborate the hypothesis that post-stroke dysphagia is a direct consequence of neurological damage and the topography of the lesion, while cardiovascular and lifestyle risk factors act more as predisposing factors for the vascular event than as determinants of the presence or absence of dysphagia. Furthermore, the present study corroborates the hypothesis that, in the chronic phase of stroke, the presence of dysphagia is not directly associated with structural changes detected by imaging tests, but rather with the extent of the lesion, the involvement of critical regions and, above all, the brain plasticity that allows the return of swallowing function to normality in a significant portion of patients. The results highlight the need for systematic protocols for screening and monitoring swallowing in post-stroke patients, including those in the chronic phase, in order to prevent complications such as aspiration pneumonia, malnutrition, and early mortality.

Despite the limitations of the study, such as the small sample size and retrospective design, the findings contribute to the understanding of the relationship between chronic stroke and dysphagia in the context of the SUS and point to the importance of multicenter studies with a larger number of patients, which can deepen the analysis of the association between cardiovascular risk factors, lifestyle, and the topography of the lesion.

CONCLUSION

Patients affected by stroke in the chronic phase have a high percentage of dysphagia (28%) when they are in outpatient follow-up. Although no statistical association was identified between the location of the brain lesion and the occurrence of dysphagia, a higher risk was found in lesions of the brainstem, cerebellum, subcortical structures and internal capsule, which highlights the importance of early clinical evaluation and subsequent confirmation by videonasofibroscopy.

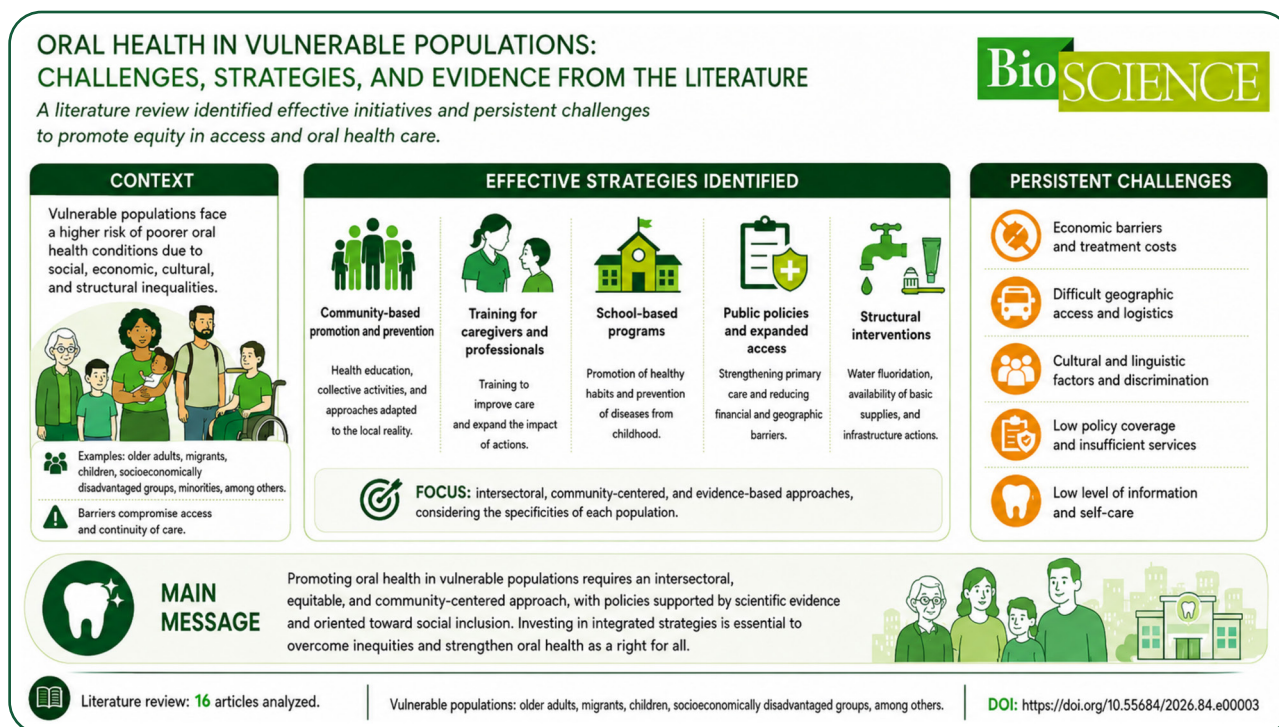
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Oral health in vulnerable populations: challenges, strategies and evidence from the literature

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Central Message

The promotion of oral health is a fundamental strategy to mitigate the risks of health problems enhanced by social inequalities. It should involve educational, preventive, and awareness-raising actions aimed not only at improving oral health, but also at training individuals to adopt healthy habits. Several initiatives have been implemented around the world, focusing on approaches that consider the specificities and needs of these populations.

Perspective

The analysis of the literature allowed us to identify various initiatives aimed at promoting oral health in vulnerable populations, evidencing important advances, but also persistent challenges. Effective strategies highlighted include promotion and prevention actions at the community level, caregiver training, school programs, public policies to expand access, and structural interventions such as water fluoridation and the provision of basic supplies

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ABSTRACT

Introduction: Oral health is an essential component of general health and well-being, playing a crucial role in the quality of life of individuals. However, social, economic and cultural inequalities often result in unequal access to dental care, especially in vulnerable populations.

Objective: To identify in the existing literature databases on oral health promotion initiatives in vulnerable populations and to identify effective strategies and persistent challenges.

Method: We used 16 articles in this review, studies on oral health in vulnerable populations, such as the elderly, migrants, and children.

Results: The discussion about access to dental care for vulnerable populations reveals a complex scenario, in which several social, economic, cultural, and structural barriers compromise equity in access to oral health care.

Conclusion: The promotion of oral health in vulnerable populations requires an intersectoral, equitable, and community-centered approach, with policies supported by scientific evidence and oriented towards social inclusion. Investing in integrated strategies that consider the specific contexts of these populations is essential for overcoming inequities and strengthening oral health as an integral part of the right to health.

KEYWORDS: Vulnerable population. Oral health. Health promotion. Social inclusion.

INTRODUCTION

Oral health is an essential component of general health and well-being, playing a crucial role in the quality of life of individuals. However, social, economic and cultural inequalities often result in unequal access to dental care, especially in vulnerable populations.

The word vulnerable brings great debate about its definition and researchers believe there is little or no consensus. And they point out that different uses and understandings of the term “vulnerable” have implications for the framing of research questions, the allocation of resources, and the delivery of health care.^{1,2}

The World Dental Federation – FDI (2019)³ defines this population as people who are at higher risk of health care disparity due to their general condition or status, such as being a member of ethnic, religious, or linguistic minorities, children, the elderly, the socioeconomically disadvantaged, the under-insured, or those with certain medical conditions. They face significant barriers that limit their access to adequate oral health services, increasing the prevalence of oral diseases and compromising their overall health.

This population ends up not having access to traditional prevention and treatment services, so their health plummets with a higher prevalence of comorbidities that lead to premature death - called by some researchers as the “precipice of inequality”. Some researchers have proposed a new type of health care called “inclusion health,” aimed at “correcting health and social inequalities among the most vulnerable and marginalized in the community.”^{4,5}

The promotion of oral health is a fundamental strategy to mitigate the risks of diseases that enhance these inequalities. It involves educational, preventive, and awareness-raising actions that aim not only to improve oral health, but also to train individuals to adopt healthy habits. Several initiatives have been implemented around the world, focusing on approaches that consider the specificities and needs of these populations.

However, despite the efforts, the effectiveness of interventions and programs to promote oral health

in vulnerable populations is still a topic that lacks systematic analysis. The existing literature points to the need to understand which strategies have been most effective, what challenges are faced in the implementation of these initiatives, and how the results can be optimized.

This article reviews the existing literature on oral health promotion initiatives in vulnerable populations, with the aim of investigating the effectiveness of different approaches in vulnerable patients (children, institutionalized older adults, people with disabilities, and low-income communities), exploring the challenges faced in implementing these approaches, and factors that contribute to the success or failure of these programs.

METHOD

Systematic review of the literature seeking to answer the question: “What are the possible strategies for the dental care of patients in vulnerable situations?” The databases chosen for the search were PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Scielo (<https://www.scielo.br/>). The following descriptors were used: “oral health”, “health promotion”, “vulnerable populations” and “interventions”, according to DeCS/MeSH (<https://decs.bvsalud.org/>).

The results were filtered based on inclusion criteria, which consisted of: studies published in the last 10 years; research that addressed interventions or programs to promote oral health in vulnerable populations; and articles available in English and Spanish. Scientific articles that were not related to the subject studied, technical documents, legislation, manuals, letters, publications of conference proceedings, dissertations, theses, comments, opinions, correspondence, editorials and reports, articles in other languages, and those not available for reading were excluded.

Data were extracted in a systematic manner, recording the following information from each selected study: authors and year of publication, study objective, methodology used, main results and conclusions, and recommendations for oral health practice in vulnerable populations.

RESULT

The search resulted in 32 articles according to the keywords used. Of these, 16 were selected after applying the inclusion and exclusion criteria. By reading the articles in full, the data were synthesized with the following parameters: main author and main findings (Table).

DISCUSSION

The vulnerable population faces barriers to accessing dental care. There are several social, cultural, economic, structural and geographical factors. These barriers also influence the definition of “vulnerable people”, with different opinions among the authors.^{1,3,5,11} Katz et al. in 2020¹ explored in their article ways in which the definition of vulnerable can serve to confuse the nature of public health, and if it does, help to understand the ways in which society is

structured.

The World Dental Federation in 2019³ recognizes the different needs in vulnerable countries and populations, as well as the difference in their health systems, and encourages various actions such as education, research and finance, in order to improve access to care and reduce inequality in oral health.

In children, inequalities of carious lesions are observed by family education and income levels in a vulnerable population. There is a limitation regarding the daily use of fluoride toothpastes, regular visits to the dentist, and factors related to nutrition and diet. Martignon et al. in 2024¹⁴ observed in their study significant socioeconomic inequalities in the number of tooth surfaces affected by carious lesions, and reported that it can be considered an initial marker of vulnerability to the development of more extensive lesions. This finding poses challenges in terms of the

TABLE — Synthesis of the main findings on oral health promotion in vulnerable populations

	Authors (Year)	Key findings
1	Visschere L et al. (2016) ⁶	The greatest need for treatment was observed in the older age group and the highest mean bacterial plaque was observed in the elderly with greater dependence on care. Oral health in the elderly in Belgium is poor. The need for restorative and prosthetic treatment is high, and oral hygiene levels are problematic. Age, residence, and care dependence seem to have some influence on oral health parameters.
2	Watt RG et al. (2019) ⁷	Action to improve access to and quality of dental care for vulnerable adults and to tackle oral health inequalities among vulnerable adults. The burden of oral diseases disproportionately affects vulnerable groups compared to the general population. Addressing these unfair, unfair and preventable inequalities in oral health requires coordinated strategic action at clinical and population levels. Collectively, the dental profession has a responsibility to provide appropriate, high-quality clinical care and to be an advocate for supportive policies to protect and promote good oral health.
3	Velázquez-Cayón RT et al. (2022) ⁸	Prevalence of dental caries is the main situation along with the lack of good oral habits and commitment to health and oral care. The group of people between 15 and 20 years of age in Morocco was considered to have a higher incidence of oral diseases (dental caries and periodontal diseases). They also had fundamental deficiencies related to dental care and hygiene habits, as well as those related to the quality and type of food.
4	Macdonald ME et al. (2022) ⁹	They proposed solutions for research and practice, including co-engagement and co-production with peoples who were vulnerable. In doing so, the paper advances the potential of oral public health to advance research and practice that involves complexity in our work with vulnerable populations.
5	Fernández-Bonet J (2023) ¹⁰	The Vasco Government gradually implemented the Children's Dental Care Program (PADI) and the fluoridation of water for public consumption. These measures have managed to reduce the rates of childhood caries in the territory, until they are among the lowest in Europe. Before giving the green light to the possible fluorization situation, it is essential to accurately determine the carious condition of the most vulnerable population. To this end, rigorous prospective studies should be carried out, both in the adult and child populations, and compare the CAO and SiC indices of the city with and without access to the fluoridated water network.
6	Wisner B (2016) ¹¹	Among the many readings of vulnerability, the economic policy/ecological policy perspective provides deep insight into the role of global capitalism and the resulting underdevelopment it supports. The many other approaches to vulnerability, the range of other frameworks, models, metrics, and tools discussed are useful, but they only inform palliative measures. They do not reveal the root causes of vulnerability and therefore cannot point to reforms and transformations that can change a system based on greed, conflict and the destruction of nature. A participatory approach to vulnerability will not change the world in the short term, but multitudinous struggles in this and other domains of daily life – health, food, energy, biodiversity, shelter, transport and more – can eventually coalesce into a critical mass of resistance to current underdevelopment and positive affirmation of concrete alternatives.
7	Patel R et al. (2019) ¹²	Two nursing homes were available for program delivery, which resulted in the training of 64% (n = 87) of the care team. The training program involved videos and resources and was delivered flexibly with the support of an oral health educator and a dental therapist. There was an improvement in self-reported knowledge and confidence after training; however, only 54% (n = 45) completed the post-training questionnaire. This study suggests that co-producing an oral care training package for nursing home staff is possible and welcome, but challenging in this complex and changing environment. More work is needed to explore the feasibility, sustainability, and impact of doing so.
8	Mejía R et al. (2020) ¹³	The population that benefited the most was the vulnerable. The most attended were: in terms of gender, female; age group, children between 3 and 8 years old and adults aged 36 years and over. The most commonly performed dental procedure in children was dental prophylaxis, and in adults, supragingival scaling. The application of the curriculum of the Dentistry course focused on health promotion and contextualized learning from its use for the development of the community makes it an entity with greater social commitment. The community that receives the benefits becomes an active body in the processes of oral health promotion. Vulnerable and displaced populations are receptive to the oral clinical treatments offered to them.
9	Martignon S (2024) ¹⁴	Approximately one-third of the children included in this study exhibited tooth surfaces affected by moderate/extensive caries, while 84% exhibited early caries. The estimate indicated an absolute difference of 12.4% in the prevalence of moderate/extensive carious lesions among children living in households with the lowest levels of education compared to the highest. These children were also 6.7 times more likely to exhibit early cavities compared to those living in households with higher levels of education. Significant socioeconomic inequalities in early childhood caries have been observed in these vulnerable populations, highlighting the importance of upstream and downstream interventions that raise awareness among stakeholders and improve community and individual practices to address this.
10	Freeman R et al. (2020) ⁵	While oral health continues to improve globally, an important consequence of this approach is that it exacerbates the social exclusion that many people are already experiencing due to the constellation of economic, political, cultural, and individual factors. In contrast, based on the theoretical literature on social exclusion, intersectionality, and otherness, we suggest that dentistry could act as an agent of social inclusion as a more responsive and comprehensive form of oral health care and service delivery. This article advances a theoretical framework for inclusive oral health and an action plan to show how inclusive oral health can become a solution in the arsenal to address the global phenomena of inequalities in oral health, and inclusive is supported by theories of social exclusion, intersectionality, and otherness. We proposed an inclusive oral health framework for all those interested in helping people marginalized by social exclusion. We believe that it is by providing theoretical framework to situate a compelling policy agenda, along with an action plan for new service systems based on research evidence, that the core principles of inclusive oral health can ensure that dentistry will become an agent to address the global phenomena of extreme oral health and the social inequalities that follow social exclusion.
11	FDI World Dental Federation (2020) ³	Unfortunately, the enormous technological and scientific advances that have recently progressed to address many dental conditions are not uniformly available to all populations and the underserved and vulnerable face persistent and systemic barriers to accessing oral health care. These barriers are numerous and complex and include, among others, social, cultural, economic, structural and geographical factors. This policy statement presents vision for access to adequate oral health care for underserved and vulnerable populations throughout the human life cycle. FDI recognizes the distinct and varied needs of underserved and vulnerable populations from different countries and the vast differences in their health systems. However, this statement encourages oral health advocates and dental professionals to take action on behalf of underserved and vulnerable populations and to take the necessary steps to improve access to oral health care, reduce oral health inequality, address oral health illiteracy, promote the concept of Universal Health Coverage, and improve oral health.
12	Katz AS et al. (2019) ¹	In our experience, researchers often use the word “vulnerable” strategically to attract resources, political interest, and public concern. At the same time, we propose that the vagueness associated with terms such as “vulnerable” masks the structural nature of public health problems. This vagueness can serve the political function of obscuring power relations and limiting the discussion of transformational change.

development of public policies and strategies to improve oral health. World Health Organization in 2019¹⁵ recognizes primary care teams as fundamental in the prevention and control of caries, as it ensures the promotion and maintenance of health. Pitts et al. in 2019¹⁶, report that the International Association of Pediatric Dentistry defined some preventive actions to raise awareness, such as avoiding sugar intake before the age of two; limiting sugar intake after this age; brushing teeth twice a day using 1000 ppm of fluoride toothpaste; and visiting the dentist from the first year of life.

In 1980, Fernández-Bonet¹⁰ surveyed those who had a very high rate of dental caries, which is a great concern of the population. To lessen the impact, the government implemented the Children's Dental Care Program and water fluoridation. The program initially offered annual follow-up and dental care for permanent teeth for schoolchildren aged 7 to 15 years. Given the fact that carious lesions develop gradually, it is important to expand the program and adopt measures to raise awareness and encourage families, changing the individual approach to one that prioritizes prevention and promotion.

Oral health in the elderly is of great importance, as it interferes with speech and eating, in addition to interfering with appearance and social life.⁸ Elderly people who live in nursing homes or with caregivers at home have limitations in taking care of their oral health, which ultimately leads to poor oral health and the need for dental care.¹² Visschere et al. in 2016⁶, considered people who lived in nursing homes or home care homes as vulnerable, and observed that oral health was very poor among them, which could be influenced by age, where they lived, and dependence on care. They suggested the development of actions for new dental services with an emphasis on prevention and health promotion and better access to dental care. The biggest concern and challenge to be faced is to identify the elderly to prevent oral health from worsening.

Patel et al. in 2019¹² suggested a training program for caregivers in nursing homes because they observed, based on evidence, that many dental diseases were preventable; Therefore, counseling and interventions for the elderly and their caregivers would be vital. They recognize the need for oral care of these elderly, but did not have training or skills, justifying the lack of oral health care due to restrictions in the workplace (lack of instruments), difficulties in communication, problems in the behavior of the elderly, lack of time and low priority to oral health.

Watt et al. in 2019⁷ suggested two actions for the vulnerable population. The first aimed to improve access to and quality of dental care by prioritizing the assessment of dental needs in certain regions so that they were adequately addressed, providing the necessary treatment and monitoring, and prevention to reduce future risk of disease. The other aimed to tackle inequalities in oral health, then talk about the progressive policies that are needed to address economic disadvantage and broaden participation

and access to education.

The discussion about access to dental care for vulnerable populations reveals a complex scenario, in which several social, economic, cultural, and structural barriers compromise equity in access to oral health care. Vulnerability is not a single concept, it varies according to different contexts and approaches.

Freeman et al. in 2020⁵ defined vulnerability as social exclusion, and then talked about how dentistry could be acting in the social inclusion of this population. This inclusion could be in three ways: 1) with health and social assistance policies requiring oral health services in addition to medical care; 2) with research to identify the reconfiguration of dental services and support the development of innovative solutions; and 3) with dental education, which would be training at undergraduate and graduate levels to train qualified professionals and raise awareness about social exclusion, to reduce difficulties in dental services.

As Macdonald et al. point out in 2022⁹, oral health research and practice in vulnerable populations are not new subjects; However, growth in this area encourages new research. They also report three actions to seek solutions with the vulnerable population, namely; 1) dialogue and knowing from the population how they would like them to be; 2) inclusion of this vulnerable population in actions aimed at helping them; and 3) integrate discourse on social and structural determinants, education, and policy on vulnerability.

CONCLUSION

The analysis of the literature allowed us to identify various initiatives aimed at promoting oral health in vulnerable populations, evidencing important advances, but also persistent challenges. The effective strategies highlighted include promotion and prevention actions at the community level, training of caregivers, school programs, public policies to expand access, and structural interventions such as water fluoridation and the provision of basic inputs. However, significant challenges persist, such as the scarcity of resources, the low priority given to oral health in certain public policies, and the need for professional training aimed at working in contexts of vulnerability. Thus, the promotion of oral health in vulnerable populations requires an intersectoral, equitable, and community-centered approach, with policies supported by scientific evidence and oriented towards social inclusion.

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Bariatric surgery and female sexuality: is there an improvement in sexual function after weight loss?

Hosannah Leite Filho^{1,2}, Daniel Vieira de Oliveira^{2,3}, Mariano Palermo⁴, Rui José da Silva Ribeiro⁵, Paz Piatanesi⁶, Paulo Afonso Nunes Nassif⁷

BARIATRIC SURGERY AND FEMALE SEXUALITY: IS THERE IMPROVEMENT IN SEXUAL FUNCTION AFTER WEIGHT LOSS?

Evaluation of sexual function in women with morbid obesity before and after Roux-en-Y gastric bypass.

OBJECTIVE



To evaluate the sexual function of women with morbid obesity undergoing bariatric surgery at three time points: preoperative, and 6 and 12 months postoperative.



74 women
Age: 36.2 ± 8.3 years
Procedure:
Roux-en-Y gastric bypass



Instrument: FSFI
Assesses 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. Score > 26.55 = satisfactory sexual function.

METHODS



Preoperative



Roux-en-Y gastric bypass



Evaluation at 6 and 12 months

BMI (kg/m²)

42,7

± 4,0

31,8

± 3,5

30,0

± 3,6

Preoperative

6 months

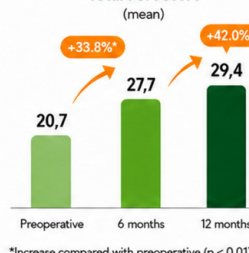
12 months



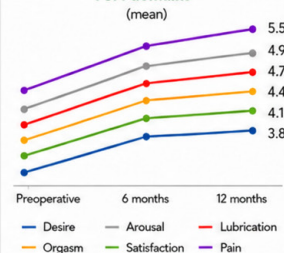
Significant weight reduction after surgery. This reduction was associated with improved sexual function.

RESULTS

Total FSFI score (mean)



FSFI domains (mean)



Significant improvement in sexual function as early as 6 months, with maintenance and further increase at 12 months postoperatively.



CONCLUSION: Women with morbid obesity have a high prevalence of sexual dysfunction. Bariatric surgery promotes a significant improvement in sexual function, as early as 6 months, with maintenance and further increase at 12 months postoperatively.



KEYWORDS

Sexual dysfunction.
Morbid obesity.
Bariatric surgery.

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Central Message

Obesity is associated with specific sexual problems, including lack of desire, poor performance, low fertility, reduction in frequency, and even resistance to sexual encounters, negatively affecting sex life. The high rates of comorbidities associated with morbid obesity are part of the multifactorial mechanism underlying sexual dysfunction. Most candidates for bariatric surgery have this dysfunction, and obese women face greater difficulties in this area when compared to men.

Perspective

To evaluate the sexual function of morbidly obese women undergoing bariatric surgery at three time points: preoperatively, six and 12 months postoperatively after Roux-en-Y gastric bypass.

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ABSTRACT

Introduction: Severe obesity is most effectively treated with bariatric surgery. The resulting weight loss is expected to improve obesity-related conditions, including sexual dysfunction.

Objective: To evaluate the sexual function of morbidly obese women undergoing bariatric surgery using a questionnaire validated at three time points: preoperatively, six months and twelve months later.

Method: A quantitative, descriptive and analytical cross-sectional, quasi-experimental study was carried out with a convenience sample of women over 18 years of age, with class III obesity, submitted to Roux-en-Y gastric bypass. The questionnaire adopted was the Female Sexual Function Index (FSFI), which evaluates six domains: desire, arousal, lubrication, orgasm, satisfaction and pain. Scores above 26.55 translate satisfactory sexual function and lower scores define sexual dysfunction.

Results: A total of 74 women were evaluated from 36.2 ± 8.3 years, BMI before surgery was 42.7 ± 4.0 , after six months 31.8 ± 3.5 and after 12 months 30.0 ± 3.6 . The mean total FSFI score obtained in the preoperative period was 20.7. After six months, 27.7 ($p < 0.01$), and after 12 months, 29.4 (increase of 42.0% compared to the preoperative period). Both in terms of the total score and the isolated domains of the FSFI, an association was observed between improved sexual function and reduced BMI.

Conclusion: There was a significant improvement in sexual function as early as six months after surgery, as well as in the other domains alone.

KEYWORDS: Sexual dysfunction. Morbid obesity. Bariatric surgery

INTRODUCTION

Over the past few years, there has been a growing interest in the quality of life of individuals due to their relationship with health and chronic diseases. Studies in large number have investigated the relationship between quality of life and specific health conditions, including obesity.

At the other end of the malnutrition scale, obesity is a blatant public health problem, growing but still neglected and has reached epidemic proportions globally, with at least 2.8 million people dying each year as a result of the consequences. Previously associated with high-income countries, obesity is now also present in low- and middle-income countries. The prevalence of obesity has grown significantly in recent decades, becoming a serious public health problem, affecting, indistinctly, any age group, ethnicity and sex.

For a long time in human history, weight gain, as well as fat accumulation, was seen as signs of health and prosperity. Today, however, obesity is considered a chronic disease and with a high risk for numerous of other chronic diseases, including diabetes, cardiovascular diseases and cancer. Overweight and obesity are also associated with psychological disorders, including depression, eating, distorted body image, and low self-esteem. The prevalence of anxiety and depression is three to four times higher among obese individuals. In addition, obese individuals are also stigmatized and suffer social discrimination.¹

Obesity is also associated with specific sexual problems, including lack of desire, poor performance, low fertility, reduced frequency, and even resistance to sexual encounters, negatively affecting sex life.² The high rates of comorbidities associated with morbid obesity are part of the multifactorial mechanism underlying sexual dysfunction. Most female candidates for bariatric surgery have this dysfunction, and obese women face greater difficulties in this area when compared to men.

Quality of life is considered a multidimensional construction that includes several aspects. When discussed in relation to obesity, health and weight are the most used dimensions. Particularly relevant to people with morbid obesity and those who undergo bariatric surgery are body image and sexual functioning.³

The operation is considered an important therapeutic measure for weight reduction in case of documented failure of clinical treatment in patients with a degree of severe obesity and/or associated with serious diseases.^{3,4} Among the techniques used for this procedure, Roux-en-Y gastric bypass is performed with low mortality rates and demonstrates high efficiency, especially if the impact on weight loss and control of comorbidities is taken into account.⁵ This procedure aims to reduce weight and promote weight loss through the restriction of food intake or malabsorption, or by combining these.⁴

By reducing weight, individuals report improvements in their psychosocial state⁶, raising their self-esteem and greater interaction in society, as well as improved sexual function. After bariatric surgery, individuals report statistically and clinically significant benefits in health- and weight-related quality of life. Many of these improvements are reported during the period of rapid weight reduction and before patients achieve their maximum weight loss.⁷

Analyzing the female sexual function (SP) of morbidly obese patients is important because it is little studied and little reported in the literature, especially in Brazil. It is also important to evaluate the role of bariatric surgery in the impact of weight loss on the sexual function of these women in our country.⁸

The objective of this study was to evaluate the sexual function of morbidly obese women undergoing bariatric surgery through a questionnaire validated at three moments: preoperatively, six and 12 months after Roux-en-Y gastric bypass.

METHOD

This study was approved by the Research Ethics Committee of the Universidade Estadual de Feira de Santana, in Feira de Santana, BA, Brazil, under opinion number 1.033.680/2015 and CAAE number 39234214.1.0000.0053. All patients were only admitted to the study after signing the Informed Consent Form (ICF).

This is a quantitative, descriptive and analytical cross-sectional, quasi-experimental cohort study, carried out with a convenience sample composed of women with grade III obesity, with the application of the Female Sexual Function Index (FSFI).

Women over 18 years of age who underwent Roux-en-Y gastric bypass by the Obesity Surgery Service of Feira de Santana, BA, at the São Matheus and Unimed hospitals, and who agreed to answer the proposed questionnaires, after signing the Informed Consent Form (ICF) were selected. They answered a validated sexual dysfunction (SP) analysis questionnaire for their gender, the Female Sexual Function Index (FSFI).⁹ The FSFI assesses female sexual function through 19 questions graded from 0 to 5, covering six domains: desire (questions 1 to 2), arousal (questions 3 to 6), lubrication (questions 7 to 10), orgasm (questions 11 to 13), satisfaction (14 to 16) and pain (questions 17 to 19). In all, the points obtained can reach a maximum of 95, and the values of each domain are submitted to different weights to obtain a final score. Scores above 26.55 translate satisfactory sexual function and scores below this value, sexual dysfunction.¹⁰

By means of such tools, we proceed to an analysis in three stages. In the first moment, referring to the preoperative phase, the patients under the outpatient regime answered two questionnaires – the FSFI and another structured one containing the preoperative clinical data – self-administered in a reserved room, only numbered and, later, inserted in a collection box. These same questionnaires were reapplied six months after surgery, which constituted the second moment of the analysis. Finally, the same questionnaires were applied 12 months postoperatively.

The inclusion criteria were being a woman, having an indication for bariatric surgery; having attended pre-surgical and post-surgical follow-up appointments; agree to participate in the research and have signed the ICF.

The exclusion criteria were refusal to participate in the research, submission to previous or ongoing pelvic surgery and/or radiotherapy; history of neurological diseases; sexual inactivity in the last six months; inadequate filling (blank or left any items unanswered); or non-adherence to follow-up for at least six months postoperatively.

Statistical analysis

The data were processed electronically using the statistical program Social Package for the Social

Sciences – SPSS for Windows, version 22.⁰

RESULTS

A total of 74 women were evaluated, aged 36.2 ± 8.3 years, BMI before surgery 42.7 ± 4.0 , after six months 31.8 ± 3.5 and after 12 months 30.0 ± 3.6 , showing a change in the classification of these patients with obesity from grade III to grade I. Most individuals (68.5%) were married or in a stable union. Regarding religion, 41 were Catholic (55.4%). The ethnic profile comprised 32 browns (43.2%), 17 blacks (23.0%) and 25 whites (33.8%). Regarding education, most of them had completed higher education, equivalent to 33.8%, followed by 32.4% with complete secondary education (Table 1).

TABLE 1 – Sociodemographic and clinical characteristics of the 74 women who underwent bariatric surgery.

Age (years)	36.2 ± 8.3	%
Height (m)	1.63 ± 0.6	
Weight (Kg)		
Before	113.6 ± 12.5	
After six months	84.5 ± 9.7	
After 12 months	79.7 ± 9.4	
BMI (kg/m ²)		
Before	42.7 ± 4.0	
After six months	31.8 ± 3.5	
After 12 months	30.0 ± 3.6	
Marital status (n = 74)		
Single	19	25,7
Married/Common-law	51	68,9
Separated/Divorced	4	5,4
Skin color (n = 74)		
White	25	33,8
Brown	32	43,2
Black	17	23,0
Education (n = 74)		
Incomplete elementary school	1	1,4
Complete elementary school	8	10,8
Incomplete high school	4	5,4
Complete high school	24	32,4
Incomplete higher education	12	16,2
Complete higher education	25	33,8
Religion (n = 74)		
Catholic	41	55,4
Protestant	29	39,2
Spiritist	1	1,4
Other religion	2	2,7
Ignored	1	1,4

The mean total FSFI score obtained in the preoperative period was 20.7, reflecting the picture of sexual dysfunction. Six months after the operation, the score increased to 27.7, i.e., an increase of 33.8% compared to the preoperative period, which already represents an improvement in sexual function ($p < 0.01$). After 12 months, the FSFI corresponded to 29.4, which is equivalent to 42.0% more than the preoperative period. Both in terms of the total score and the isolated domains of the FSFI, an association was observed between improved sexual function and reduced BMI.

All domains after six and 12 months of surgery

when compared to the preoperative period were statistically significant, i.e., $p < 0.05$. When analyzing each one individually, the desire domain obtained the greatest variation in the two postoperative moments compared to the preoperative period, corresponding to an improvement of 44.9% after six months and 55.1% after 12. Arousal has second best value, with an improvement of 40.6% and 53.1% in the two moments studied (Table 2 and Figure 1).

TABLE 2 — Mean values of the variables and FSFI analyzed before, after six and 12 months of bariatric surgery

	PO n	6M n	12M n	p value
Desire	2,9	4,2	4,5	< 0.001
Excitement	3,2	4,5	4,9	< 0.001
Lubrication	3,7	4,6	4,8	< 0.001
Orgasm	3,4	4,5	4,6	< 0.001
Satisfaction	3,4	4,7	4,9	< 0.001
Pain	3,8	5,0	5,5	< 0.001
Total FSFI	20,7	27,7	29,4	< 0.001

PO = preoperative; 6M = six months postoperatively; 12M = 12 months postoperatively

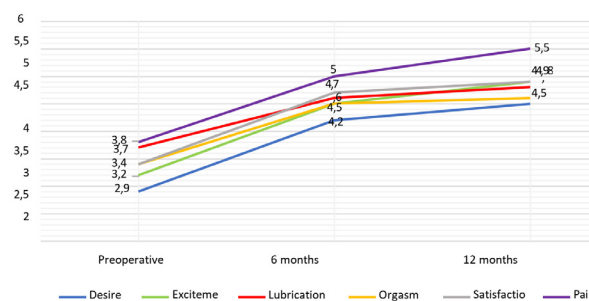


FIGURE 1 — Mean values of the domains analyzed before, after six and 12 months of bariatric surgery

When asked about their perception of their SP at the times studied, the majority ($n = 19$) in the preoperative period, corresponding to 26% of the sample, evaluated it as very dissatisfied. Another 19% ($n = 14$) were reasonably dissatisfied; 16% ($n = 12$) were indifferent; 28% ($n = 21$) reasonably satisfied; and 11% ($n = 8$) reported being very satisfied (Figure 2).

After six and 12 months of bariatric surgery, there was a decrease in the number of women who considered themselves very dissatisfied, 10% ($n = 7$) and 5% ($n = 4$) respectively. There was also a reduction for the item reasonably dissatisfied, corresponding to 7% ($n = 5$) at both times. For those who reported indifference in their SP, after six months there was a reduction to 9% ($n = 7$), while the value increased to 19% ($n = 14$) at 12 months of the study. The values were more expressive in terms of improvement in sexual function: 39% ($n = 29$) reported being reasonably satisfied at six months, while 31% ($n = 23$) 12 months after bariatric surgery. For those who self-rated themselves as very satisfied, they corresponded to 35% ($n = 26$) at six months and 38% ($n = 28$) at 12 months (Figures 3 and 4).

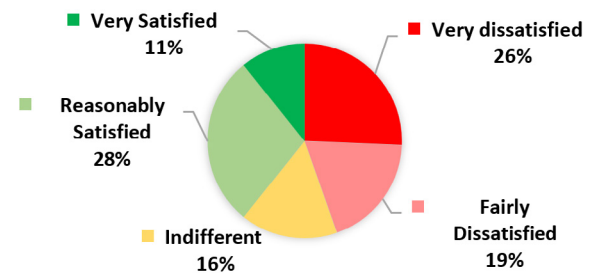


FIGURE 2 — Self-assessment of their sexual function in the preoperative period of the 74 women studied

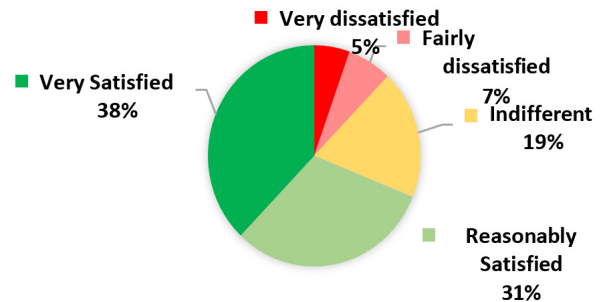


FIGURE 3 — Self-assessment of their sexual function six months after bariatric surgery ($n = 74$)

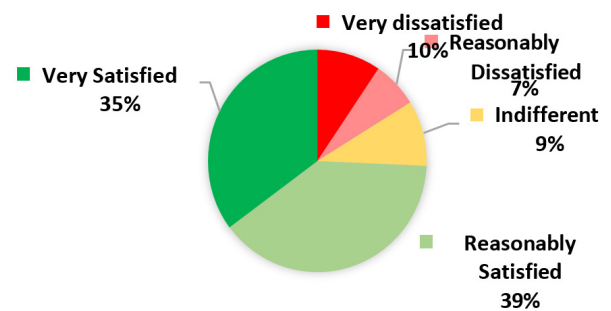


FIGURE 4 — Self-assessment of their sexual function 12 months after bariatric surgery ($n = 74$)

DISCUSSION

This study demonstrates that morbidly obese women have a high prevalence of sexual dysfunction, and there is a significant improvement in it after bariatric surgery. The data show that the effect after 12 months is even greater than after six.

Currently, studies on the relationship between body weight and sexual functioning are minimal.¹¹ Although there are few analyses investigating the association between female sexual functioning and obesity, the present study shows that bariatric surgery has a great impact on the improvement of sexual function in women with morbid obesity, which coincides with other studies carried out.^{4,6,12} These patients experience significant improvement in weight loss with improvement in various physical aspects, diseases, well-being, and quality of life.⁴

Kim et al.¹³ conducted an eight-week study of 46 overweight or obese women who received weight-reduction medication (sibutramine) along with behavioral therapy and used the FSFI for sexual function analysis. Weight reduction was significantly associated with improved sexual functioning, specifically in arousal and orgasm scores ($p < 0.05$). This study corroborates the idea that weight reduction

positively affects sexual function.

Kolotkin et al.¹⁴ conducted a cross-sectional study with 1,158 participants with obesity prior to weight loss treatment, in order to examine the association between sexual quality of life and obesity. The results revealed a statistically significant negative correlation between the quality of sexual life. This study also demonstrates sexual dysfunction in the preoperative sample.

In the study by Sarwer et al.³ in a prospective cohort of 106 women evaluated through the FSFI in the preoperative period and two years after the operation, showed an increase from 20.3 to 24.8 in the mean total FSFI score, as well as improvement in all domains. Two domains, orgasm and pain, did not reach statistical significance. In this study, women also reported improvement in these domains. Although there was a small difference in the mean age in the aforementioned study - 40.5 years - compared to this study, which consisted of younger people aged 36.2 years, the differences in the results of the domains should reflect the particularities of each sample analyzed.

Goitein et al.¹⁵ that evaluated 34 women, comparing FSFI scores before and six months after the operation, also did not achieve statistical relevance in all domains. Improvements of 25% in the mean total score ($p = 0.006$), 17% in the desire domain ($p = 0.18$), 29% in arousal ($p = 0.025$), 24% in orgasm ($p = 0.046$), 35% in satisfaction ($p = 0.001$), 23% in lubrication ($p = 0.011$) and 34% in pain ($p = 0.027$) were evaluated. In contrast, this study found statistical significance in all domains. This disparity may be associated with the fact that the aforementioned study had a significantly smaller sample, as well as possibly due to cultural differences, given that the study comprises individuals from Israel, whose cultural environment, historically, is marked by less sexual freedom.

Bond et al.¹⁶ evaluated 54 women at two time points: pre- and six months after gastric bypass in Roux-en-Y by videolaparoscopy. The mean age was 43.3 years and the method of analysis of sexual function was the FSFI. When analyzed at the moment before the operation, 63% had sexual dysfunction. Afterwards, 68% showed improvement in sexual function, and only one worsened. Thus, it is considered that there is a significant improvement in the period of six months after the procedure, which coincides with the values found in this study. There was improvement in all domains, but only desire and lubrication reached statistical significance, showing that the improvement in sexual function seems to be independent of the surgical technique.¹⁶

In a publication by Efthymiou et al.¹⁷ sexual function and BMI evolution were analyzed in 80 patients – 50 women and 30 men. The analysis in question was performed in four times after the operation: T1, referring to the preoperative period; T2, one month later; T3, six months later; and T4, one year later. For women, the FSFI questionnaire was applied, whose domains

showed statistically significant improvement between T1 and T4. In this period, the mean scores showed an improvement of: 45% in the desire domain, 43% in arousal, 34% in lubrication, 39% in orgasm, 34% in satisfaction, 33% in pain and 28% in total satisfaction. This study demonstrates equivalent results showing that the desire domain has greater improvement compared to the others, followed by the arousal domain.

The FSFI is the most accepted instrument in the diagnosis of female sexual dysfunctions in research. However, this questionnaire aims only at the sexual context, allowing the grading of sexual dysfunctions and, also, comparing the results before and after clinical and/or surgical therapeutic interventions. However, they do not identify the factors that may interfere negatively or positively with the score.

There is strong evidence of a link between body weight and mental disorders, among a number of factors that influence the relationship between common mental disorders and obesity, such as depression and anxiety.¹⁴ These should be studied, analyzing the degree of satisfaction of these women with this aspect of their life, in addition to their long-term sexual function. Clarifying these pathways is necessary to inform treatment guidelines for clinical practice in overweight or obese individuals suffering from mental health problems and/or impaired sexual functioning.

It is also important to make a more accurate assessment of the impact of comorbidities and changes in the improvement of sexual function. It is known that vascular disorders also interfere with sexual performance, and laboratory analyses and their pathophysiological associations can add even more to the understanding of the causes of sexual dysfunction.

The results of this research could have important implications for public health policy and practice and put sexual function higher on the agenda to help reduce obesity. It is important to emphasize that this is a theme that is still little portrayed in Brazilian literature, especially regarding the female sex.

The relationship between sexual functioning and obesity is highly complex, and although there is strong evidence to support the association between these two variables, studies looking at the impact of obesity on sexual functioning to illustrate the complex interaction between these two variables, is much needed

CONCLUSION

This study demonstrates a high prevalence of sexual dysfunction in women with morbid obesity in the preoperative period, and a significant improvement in sexual function at six and 12 months after bariatric surgery, as well as improvement in all domains alone. Sexual function still shows better results at 12 months. Further studies are needed to better assess the relationship of physical, clinical, and psychological components to female sexual function.

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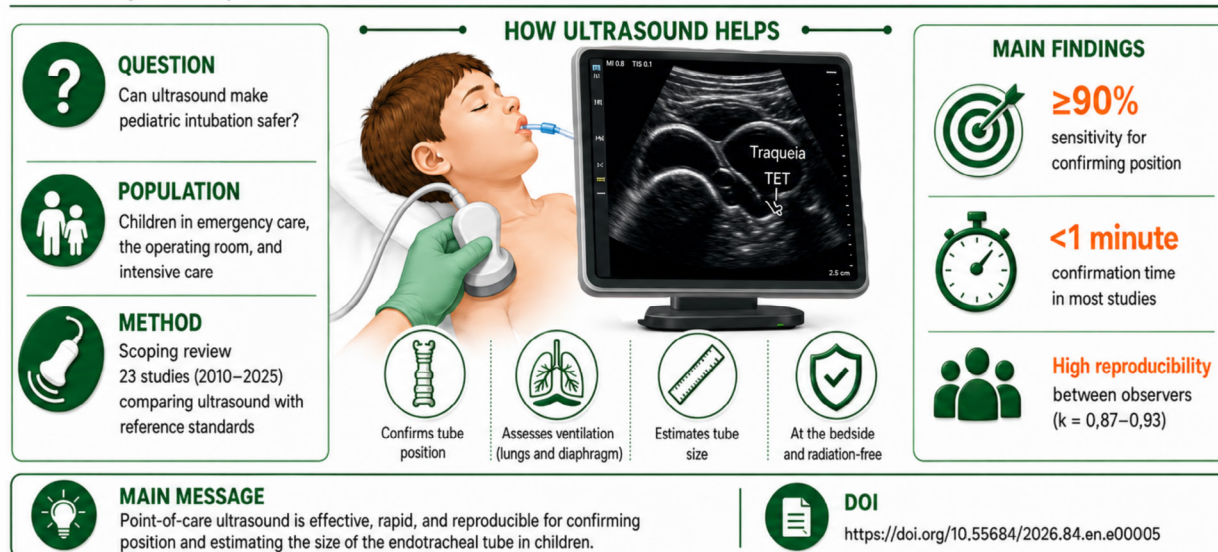
Can bedside ultrasound make pediatric intubation safer?

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Fernanda Marcondes Ribas¹, Edgardo Emilio Serra², Valeria Daniela Robles³

POINT-OF-CARE ULTRASOUND IN PEDIATRIC INTUBATION

More safety, more speed, no radiation.

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Central Message

Rapid and accurate confirmation of endotracheal tube positioning and caliber is critical in pediatric practice. Traditional methods, such as radiography and capnography, have limitations related to time, radiation exposure, and the inability to assess depth or selectivity. Thus, mapping and synthesizing the evidence on the use of ultrasonography to confirm the positioning, depth, and caliber of the endotracheal tube in pediatric populations is interesting in the care of children

Perspective

Beside ultrasonography is an effective, fast, and reproducible method for confirming the positioning and estimating the caliber of the endotracheal tube in pediatrics. It can assist with care; however, large-scale implementation requires standardization of protocols and structured training.

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ABSTRACT

Introduction: Rapid and accurate confirmation of endotracheal tube positioning and caliber is critical in pediatric practice. Traditional methods, such as radiography and capnography, have limitations related to time, radiation exposure, and the inability to assess depth or selectivity.

Objective: To map and synthesize the evidence on the use of ultrasonography (US) to confirm the positioning, depth, and caliber of the endotracheal tube in pediatric populations.

Method: Scoping review conducted according to the PRISMA-ScR guidelines. The PubMed, Embase, and Cochrane Library databases were searched in September 2025, with no language restriction. Clinical studies comparing US with radiography, capnography, bronchoscopy, or anatomical formulas were included. Those with samples smaller than ten participants, exclusively adult populations, or simulations without clinical data were excluded. Two independent reviewers screened and extracted the data. The findings were narratively synthesized in five domains: tracheal versus esophageal distinction, depth and selectivity, caliber estimation, time to confirmation, and reproducibility.

Results: Were included 23 studies published between 2010 and 2025, covering emergency, operating room, and pediatric intensive care settings. Ultrasonography generally showed sensitivity $\geq 90\%$ and confirmation times of less than one minute.

Conclusion: Bedside ultrasound is an effective, rapid, and reproducible method for confirming the positioning and estimating the caliber of the endotracheal tube in pediatrics. Large-scale implementation requires standardization of protocols and structured training.

KEYWORDS: Airway ultrasonography. Pediatrics. Endotracheal intubation.

INTRODUCTION

Rapid and accurate confirmation of endotracheal tube (ETT) positioning is essential for airway safety in pediatrics. Conventional methods, such as auscultation, observation of blurring, and radiography, may have limitations related to delay and operational accuracy. Capnography is useful for assessing ventilation, but does not provide information on the depth or selectivity of the ETT. Bedside ultrasonography (US), in turn, avoids radiation exposure and has been shown to be consistently faster than radiography, although it may, in some reports, be slightly slower than capnography.¹⁻³

Point-of-care US (POCUS) allows direct visualization of tracheal structures and pleurodiaphragmatic assessment. In pediatric populations, studies conducted in the emergency department, intensive care unit, and operating room report sensitivity often $\geq 90\%$, variable specificity, and confirmation time of less than one minute, with high interobserver agreement ($\kappa \approx 0.87-0.93$).^{1,3} The main technical approaches include suprasternal and tracheal scans, evaluation of pleural sliding and diaphragmatic movement, as well as direct visualization of the tip of the tube and the use of a cuff filled with saline solution. The most commonly used reference standards are radiography, capnography, and, to a lesser extent, bronchoscopy. This set of methods reinforces the role of US as a multimodal tool, which adds anatomical assessment - including depth assessment - to the functional surveillance provided by capnography.^{2,4}

Recent literature syntheses indicate high performance of US in confirming intubation and assessing the depth of ETT in different pediatric age groups, although there is still heterogeneity among techniques, protocols, and standards of comparison.^{5,6} There are still gaps in the standardization of procedures and methodological reporting, with a predominance of single-center studies and significant variation in the

experience of operators.

The objective of this scoping review was to map and synthesize the evidence on the use of US in confirming the positioning and assessing the depth of ETT in pediatric populations, describing the techniques employed, reference standards, diagnostic performance, execution times, and reproducibility, in order to support integrated clinical protocols and guide future multicenter research.

METHOD

This scoping review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). The aim of this study was to identify and synthesize the evidence on the use of US to confirm the positioning and estimate the size of ETT in pediatric populations. Comprehensive searches were conducted in PubMed/MEDLINE, Embase, and Cochrane Library in September 2025, with no language restriction. The search strategy combined controlled vocabulary (MeSH/Emtree) and free terms related to ultrasonography, endotracheal intubation, and pediatric population, connected by Boolean operators (AND/OR). Relevant review references were also manually examined to identify additional studies. Clinical studies that evaluated ultrasound for confirmation of ETT or caliber estimation, compared with reference standards such as radiography, capnography, bronchoscopy, or anatomical formulas, were included. Prospective and retrospective designs, diagnostic accuracy studies, and systematic reviews were considered eligible. Series with fewer than 10 participants, studies exclusively in adults and investigations based only on simulations without clinical data, were also excluded. Two independent reviewers screened titles, abstracts, and full texts, resolving disagreements by consensus. The extracted data included clinical scenario, ultrasound technique, reference standard, diagnostic metrics (sensitivity,

specificity, accuracy, and predictive values), time to confirmation, and interobserver agreement (κ). Due to the methodological heterogeneity between the studies, the results were synthesized in a narrative manner and organized into five domains: tracheal versus esophageal distinction, depth and selective intubation, caliber estimation, time to confirmation, and reproducibility. No meta-analysis or formal assessment of risk of bias was performed, in accordance with the scope of PRISMA-ScR. This study used only secondary data in the public domain; therefore, there was no need for approval by the Research Ethics Committee or to obtain informed consent.

RESULTS

The search included 23 articles directly related to the topic that were compiled in this review (Table).

DISCUSSION

The search identified 76 records in the PubMed, Embase, and Cochrane Library databases. After removing duplicates, 55 titles and abstracts were screened and 31 full texts evaluated. Eight studies were excluded because they were based on simulations with no clinical outcomes or because they did not provide relevant diagnostic data. In total, 23 clinical trials were included in this scoping review (Table).

The studies covered the period from 2010 to 2025 and were conducted in several countries in Asia, Europe, and North America, covering a wide variety of settings, operating rooms, emergency services, and pediatric ICUs. Different methodological designs were identified, including prospective cohorts, diagnostic accuracy studies, and systematic reviews.^{1,5,6} The populations evaluated included neonates, infants, children, and adolescents up to 17 years of age, with sample sizes ranging from 42 to 155 participants per study.^{1,3}

The sonographic approaches were grouped into four main categories: 1) integrated airway and lung protocols, such as TRUCE and 5-AIR;^{2,3} 2) visualization of the saline-filled cuff in the suprasternal notch or between the tracheal rings, as in the TR.U.S.T.;⁴ 3) isolated pleural and/or diaphragmatic evaluations;^{6,7} and 4) subglottic measure protocol to predict the tube gauge.^{17,18} Chest X-ray and capnography were the most frequently used reference standards, followed by bronchoscopy, fluoroscopy, or comparison with traditional anatomical formulas.^{1,9}

In the set of pediatric studies, the diagnostic accuracy of US for confirmation of intubation and depth estimation varied according to the technique and the level of experience of the operators.^{1,5} The most comprehensive systematic review, consisting of 33 studies and 1,934 examinations, reported accuracy between 90.6% and 100% for confirming intubation and between 66.7% and 100% for depth assessment, demonstrating superior performance

of ultrasound approaches compared to traditional anatomical formulas for choosing the ETT caliber.^{5,10}

Among the integrated protocols, the TRUCE (with suprasternal and bilateral pleural windows) showed correct identification of ETT in 97.4% of the cases, compared to 83.2% on radiography, with a sensitivity of 98% and interobserver agreement of 96.8% ($\kappa = 0.53$).¹ The 5-AIR protocol, which combines real-time tracheal US and pleurodiaphragmatic assessment, achieved a sensitivity of 100% for detection of selective intubation, an overall accuracy of 96%, and faster than capnography and auscultation - with a median of six seconds for confirmation of tracheal position versus 15 seconds (capnography) and 12 seconds (auscultation).²

Among the techniques based on salinized cuffs, the TR.U.S.T. protocol had a sensitivity of 98.8%, specificity of 96.4%, a positive predictive value of 96.5% and a negative predictive value of 98.8% with a mean examination time of four seconds and excellent reproducibility ($\kappa = 0.93$).⁴ In settings with less training, performance was reduced: in a pediatric ICU, a simplified pleural protocol demonstrated a sensitivity of 77% and specificity of 68% compared with radiography, although with faster confirmation (POCUS: two minutes; radiography: 10 minutes).⁶

The evaluation of the ETT depth also showed consistent performance. Studies comparing diaphragmatic ultrasound to radiography showed a sensitivity of 0.91 for detecting tracheal position and a specificity of 0.50 for selective intubation in the source bronchus, with a mean confirmation time eight minutes shorter than that of radiography.⁸ In critically ill children, US has shown high reliability for estimating depth, with the tracheal ring method being the most accurate among the techniques evaluated.^{4,9} In an elective setting, the use of US-guided pleural sliding outperformed auscultation in identifying suboptimal tube positioning.^{3,8}

For the choice of ETT caliber, the measurement of subglottic diameter by US showed superior performance to age-based formulas. In a cohort of 118 children aged 1-5 years with microcuff tubes, the agreement between the diameter estimated by US and the best clinical fit was 99.2%, compared with 77.1% by the age formula, with correlation $r = 0.994$ and $\kappa = 0.986$. Primary use of US could have avoided approximately 22% of tube changes.¹⁷ Additional results confirmed that the minimum subglottic transverse diameter measured by US more accurately guides ETT selection than traditional methods, including in patients with reinforced tubes.¹⁸ A quantitative synthesis of 33 studies reported US accuracy between 23.3% and 100%, depending on the outcome and the protocol used.¹⁰

In general, confirmation of positioning by US was faster than radiography: 4-6 seconds in integrated protocols (TR.U.S.T. and 5-AIR) and a few minutes in isolated pleural approaches.^{2,4,6} Comparative studies have recorded a mean reduction of 8-10 minutes in the time to confirmation compared to radiography.^{8,13}

TABLE — Synthesis of references directly related to the theme (23 articles).¹⁻²³

Author and year	Type of study	Objective	Method	Conclusion
Gautam et al. ¹ 2025	Prospective observational study (diagnostic accuracy)	To evaluate the accuracy of three-point ultrasonography (TRUCE) to confirm the position of ETT in children, using chest X-ray as the reference standard.	155 children (3 months to 12 years) intubated in the emergency room and pediatric ICU; US at three points (sternal notch and bilateral anterior thorax) compared with radiography, with interobserver agreement.	Three-point US identified the correct position of the ETT in 97.4% (vs. 83.2% on radiography), with a sensitivity of 98%; effective, sensitive, safe and reproducible method at the bedside.
Baruah et al. ² 2024	Prospective observational study	To compare the accuracy and timing of the 5-point airway ultrasound protocol (5-AIR) with capnography and auscultation in confirming intubation and ETT positioning.	75 children (2 to 12 years old), ASA I and II, undergoing elective surgery; Real-time tracheal US followed by pleural and bilateral diaphragmatic US, compared to quantitative capnography and auscultation.	The 5-AIR was fast and accurate (sensitivity 100% and overall accuracy 96% for positioning), confirming tracheal position faster than capnography; useful as a complement to clinical signs.
Tessaro et al. ³ 2015	Prospective feasibility study (diagnostic accuracy)	To evaluate the accuracy of tracheal ultrasound of the saline-filled cuff (T.R.U.S.T.) to confirm the correct depth of ETT insertion in children.	42 children in surgery; US in the sternal notch during endotracheal vs. endobronchial positioning, confirmed by bronchoscopy and assessed by two blinded reviewers.	Accurate and rapid method (sensitivity 98.8%, specificity 96.4%; $\kappa=0.93$; mean 4 s scan) to confirm the correct depth of the ETT.
Datta et al. ⁴ 2024	Prospective cross-sectional study (diagnostic accuracy)	To evaluate the diagnostic accuracy of airway US to confirm the depth of ETT in critically ill children.	62 children (2 months to 17 years) intubated with cuffed ETT in the pediatric ICU; three techniques (sternal notch, cricoid and tracheal rings) with salinized cuff, compared to radiography.	US is a good method to confirm the depth of ETT; The tracheal ring method had the best accuracy ($\kappa=0.87$) and is easy to perform.
Wani et al. ⁵ 2021	Prospective non-randomized clinical trial	To evaluate the use of POCUS to determine the position of the ETT cuff in relation to the cricoid cartilage in the pediatric population.	80 patients (1 to 78 months); after intubation, identification of the salinized cuff and the tracheal/cricoid rings in the longitudinal plane by POCUS.	POCUS is a fast and effective means to identify the position of the ETT cuff in relation to the cricoid, with applications in the perioperative, emergency room, and ICU.
Guerder et al. ⁶ 2021	Single-center prospective study (diagnostic accuracy)	To evaluate the performance of a simplified pulmonary ultrasound (POCUS) to confirm the positioning of the ETT in the pediatric ICU and to compare time with radiography.	71 critically ill children with urgent intubation; pleural sliding sign compared to radiography; operators with 1-hour training.	Pleural ultrasound, although faster than radiography (2 vs. 10 min), was inadequate to identify selective intubation (sensitivity 77%, specificity 68%) in an unaccustomed team; Useful at the bedside by trained operators.
Bharathi et al. ⁷ 2022	Comparative prospective study	Predict the appropriate size of the ETT by the subglottic diameter measured by US, compared to age/height-based formulas and clinical methods.	27 children (2 to 15 years old); intubation with ETT of a predetermined size by US; Optimal size defined by the leak test (cuff leak).	The subglottic diameter by US is an easy, effective, and noninvasive way to predict the size of the ETT, with higher accuracy than the age and height formulas.
Pillai et al. ⁸ 2018	Prospective observational study	To evaluate the utility of minimum transverse subglottic airway diameter (MTDSA) by US for screening ETT in children with congenital heart disease.	51 children (1 day to 5 years) undergoing cardiac surgery; size of the ETT guided by MTDSA, with better fit by the escape test and comparison with Cole's formula.	The MTDSA by US predicted the best ETT in 87.8% of cases (vs. 27.5% of the age formula); safe and accurate method in the pediatric cardiac population.
Gupta & Ahluwalia ⁹ 2022	Systematic review and meta-analysis	To evaluate the accuracy of the ultrasound correlation vs. standard age formulas in predicting ETT size in pediatrics.	Systematic review (PubMed, Cochrane, Embase) with 48 studies (1,978 patients) and 18 independent correlations; registered in PROSPERO.	Ultrasound is an effective modality for estimating the size of the ETT, which is higher than the age/height formulas (combined correlation 0.824); non-invasive, cost-effective and reproducible technique.
Liu et al. ¹⁰ 2023	Systematic review	Summarize the applications of airway US at each step of endotracheal intubation in pediatric patients.	Systematic review (MEDLINE, Embase, Cochrane, and Chinese database) with 33 studies and 1,934 US examinations; diagnostic accuracy as the outcome.	Ultrasound confirms intubation (accuracy 90.6 to 100%), depth (66.7 to 100%), and ETT size (23.3 to 100%), surpassing traditional methods; Unified protocol required.
Congedi et al. ¹¹ 2022	Systematic review and meta-analysis	To evaluate the efficacy of US in the adequacy of ETT positioning in full-term and preterm newborns and to compare time with other methods.	Meta-analysis of 14 studies (602 TTET assessments) in the neonatal ICU and delivery room; radiography as the gold standard in about 80% of cases.	POCUS is a fast and effective technique to identify the correct intubation in neonates (pooled sensitivity 93.4%), being faster than radiography.
Levkovitz et al. ¹² 2023	Prospective observational feasibility study	To examine the reliability of a new sonographic method to assess the position of ETT in neonates.	42 exams in 33 neonates; distance from the tip of the ETT to the right pulmonary artery by US compared to the X-ray (gold standard).	The US measurement of the ETT distance to the right pulmonary artery had excellent accuracy ($\kappa=0.82$; specificity 100%); Further clinical feasibility studies are needed.
Dennington et al. ¹³ 2012	Prospective pilot study	To determine whether bedside US demonstrates the location of the ETT tip in preterm and term newborns.	30 newborns with position confirmed by radiography; US with 13 MHz linear transducer; measurement of the distance from the tip of the TET to the carina.	US visualized the position of the ETT in all neonates (good correlation with radiography; examination < 5 min); Requires additional validation prior to routine use.
Huang et al. ¹⁴ 2022	Prospective educational study (simulation)	To evaluate the effectiveness of a simulation-based domain curriculum to train clinicians with no US experience to assess the position of neonatal ETT.	29 neonatologists; theoretical class and simulation session with 3D trachea/aorta model (phantom); performance checklist and pre/post evaluations.	Simulation-based training with 3D model has improved knowledge and skill in the ultrasound evaluation of TET by inexperienced operators.
Rajasekhar et al. ¹⁵ 2018	Prospective observational study	To compare whether subglottic diameter by US or little finger width correlates better with ETT outer diameter (OD) in children.	60 patients (6 months to 8 years), ASA I and II, undergoing elective surgery; preoperative measurements of subglottic diameter (USGD) and little finger width (LFB); Lin's agreement.	Neither USGD nor LFB were reliable predictors of ETT ND (low agreement: 0.29 and 0.46, respectively).
Lin et al. ¹⁶ 2016	Systematic review	To describe the available data on the accuracy and feasibility of bedside US to verify tracheal tube position in children.	Systematic review (MEDLINE, Embase) of 9 articles (cervical, pulmonary/diaphragmatic and direct tip visualization); quality rated by QUADAS.	Beside US is feasible and useful as an adjunct in tracheal tube confirmation (transtracheal sensitivity 0.92 to 1.00); Randomized multicenter studies are lacking.
Alonso Quintela et al. ¹⁷ 2014	Comparative prospective study	To evaluate the usefulness of bedside ultrasound compared to capnography and radiography for tracheal intubation in children and neonates.	31 intubations in 26 patients (pediatric and neonatal ICU); Simultaneous tracheal ultrasound and capnography, thoracic ultrasound vs. radiography, with time recording.	US was as effective as capnography (although slower) and as effective and faster than radiography; It can reduce the routine use of post-intubation radiography.
Jaeel et al. ¹⁸ 2017	Literature review	To review the literature on the use of US for ETT positioning in the pediatric population.	Search in the Ovid and MEDLINE databases for US for intubation and positioning of ETT in infants and children.	Ultrasound for ETT verification is well tolerated and can complement the determination of correct positioning, associated with radiography and capnography; there is a lack of studies in technique and training.
Salvadori et al. ¹⁹ 2021	Prospective study	To establish the reliability of US to assess the position of ETT in the neonatal ICU, the time required, and the tolerance of patients.	71 newborns; distance from the tip of the ETT to the right pulmonary artery by US compared to the distance from the tip to the carina on X-ray (Lin's agreement; Bland-Altman).	ETT ultrasound is a fast, tolerable, and highly reliable method (mean time 3.2 min), with the potential to reduce radiation exposure in neonatology.
Zaytseva et al. ²⁰ 2020	Prospective observational study	To define the optimal depth of the ETT from the gingiva in neonates and to compare the POCUS with the radiograph in the confirmation of the ETT tip.	Intubated neonates; measurements of the lip and gums during the radiography; POCUS (10 MHz heart probe, high parasternal window); linear regression by weight.	Marking on the gum (≈ 5.2 cm + weight in kg) is feasible; POCUS rapidly confirms the position of the ETT tip with accuracy similar to radiography (ICC 0.95).
Recker et al. ²¹ 2024	Systematic review	Synthesize the evidence on applications, benefits, challenges, and educational strategies of POCUS in neonatology.	Systematic review (SPIDER scheme and MeSH terms) with 68 publications; narrative synthesis of the findings.	POCUS represents a significant advance in neonatal medicine (including the confirmation of ETT), reducing invasive procedures; requires training and standardized guidelines.
Saravia et al. ²² 2023	Systematic review	To determine the ability of US to assess the subglottic airway in pediatrics to estimate the appropriate size of the ETT.	Systematic review (PubMed, Scopus, Embase) of 16 studies (1,633 children) with transcervical laryngeal ultrasound from the MTDSA.	Transcervical laryngeal US is a reliable predictor of ETT size (prediction in 48 to 100% vs. 24 to 95% of age formulas), with implications for the prevention of trauma by intubation.
Yang et al. ²³ 2024	Randomized controlled trial	To explore the use of US to determine MTDSA in the selection of cuff-reinforced ETT model in children.	110 children (3 to 6 years) randomized into three groups (MTDSA by US, age formula, and height formula); comparison of predictive accuracy and complications.	The measurement of MTDSA by US was more accurate (87.2% vs. 54.3% and 47.2%), reducing tube changes and complications; helps the choice of cuff-reinforced ETT in pediatrics.

Reproducibility was high when the operators had formal training, with interobserver agreements often higher than $\kappa = 0.9$.^{3,4}

In summary, the 23 clinical studies included corroborate the diagnostic efficacy and operational applicability of bedside ultrasound to: 1) confirm tracheal intubation; 2) detect inadequate depth or selective intubation, and 3) estimate the optimal ETT caliber in pediatrics.^{10,17,18} The methodological variation observed reflects both the versatility of the technique and the need for standardization and training. Performance is maximized when tracheal, pleural, and diaphragmatic windows are combined in integrated protocols and when subglottic measurement is used to guide tube choice.^{3,5,17}

This scoping review demonstrates that bedside US is an accurate, rapid, and reproducible method for confirming the positioning of ETT in pediatric patients. The reported sensitivity is often $\geq 90\%$, while the specificity varies according to the technique and reference standard used.^{1,3,5} Confirmation times are mostly below one minute, and interobserver agreement remains high ($\kappa \approx 0.87 - 0.93$).^{3,4}

Integrated protocols that combine tracheal and pulmonary windows tend to have superior performance, whereas isolated approaches - such as pleural-only assessment - demonstrate greater variability in specificity.^{2,6} The analysis of the studies shows consistently high sensitivity and more heterogeneous specificity, reinforcing the role of US as a multimodal verification tool, complementary to other diagnostic methods, rather than as an isolated test.^{1,5}

From an operational perspective, ultrasound surpasses radiographs in terms of confirmation time and, in some series, it was also faster than auscultation. Although capnography may be occasionally faster, it does not provide information on the depth or selectivity of ETT with the same anatomical resolution.^{3,8,21} In comparative terms, typical times range from 4-17 seconds for US, approximately 14-20 minutes for radiography, and approximately six seconds for capnography in a specific study.^{2,4} These findings support the role of US as an immediate decision-making tool, capable of reducing delays and unnecessary radiation exposure.^{2,8}

The predictive values reported, when available, were high, with positive predictive values in the range of 90% and variation of the negative predictive value according to the scenario and the technique employed. Likelihood ratios described in some studies reinforce the clinical robustness of US within well-defined protocols.^{4,5} The high reproducibility (κ to 0.93) observed in different contexts confirms the interobserver consistency and supports the incorporation of US into pediatric care flows conducted by trained operators.^{3,4,16}

The main limitations of the body of evidence include small sample sizes, predominance of single-center studies, heterogeneity in protocols and reference standards, and incomplete blinding

between operators and evaluators, which increases the risk of measurement bias.^{1,5,6} There is also a scarcity of data from prehospital contexts and underreporting of relevant clinical outcomes, such as severe desaturation, need for reintubation, and pulmonary complications.^{5,6,13} Such limitations restrict the generalization of the results and make it difficult to perform comparable meta-analyses between techniques.^{5,10,23}

In practical terms, the integration of US with ETT confirmation algorithms immediately after intubation should be prioritized, with the use of standardized sequences that combine suprasternal or tracheal window and bilateral pleural evaluation, in addition to the observation of diaphragmatic movements when necessary.^{2,3,6,22} In environments with slow or unavailable radiography, ultrasound allows confirmation in a few seconds and can reduce the occurrence of inappropriate positioning.^{2,8} Capnography should remain a complementary method for monitoring continuous ventilation, whereas US provides anatomical information on depth and selectivity that capnography alone is not able to provide.^{1,4,21}

Regarding the research agenda, the need for standardization of protocols (with definition of anatomical landmarks, cutoff points, and window sequence), the establishment of minimum training curricula, and multicenter validation with adequate blinding are highlighted.^{5,6,19} Pragmatic trials comparing integrated diagnostic routes (US + capnography) with usual practices are essential to assess impact on clinical outcomes, process times, and costs.^{5,10} Studies in prehospital settings and cost-effectiveness analyses are priorities to expand the safe adoption of US in systems with different levels of resources.^{5,20}

In summary, airway ultrasound in pediatrics is a rapid, sensitive, and highly reproducible method for confirming ETT positioning, with the potential to reduce delays and radiation exposure.^{3,4,16} Considering the variability of specificity between techniques, its optimal use occurs within integrated protocols, applied by trained professionals and in complementarity to capnography, until standardized multicenter studies establish definitive parameters guided by robust clinical outcomes.^{5,6,23}

The technique has demonstrated consistent applicability in different clinical contexts, emergency, operating room, and intensive care, when performed by adequately trained operators.^{3,6} Despite the growth of the body of evidence, methodological heterogeneities, lack of standardization of protocols, and scarcity of multicenter studies with objective clinical outcomes persist.^{5,6,10} The consolidation of US as a standard for verification in pediatrics requires large-scale validation, definition of consensual anatomical landmarks, and structured incorporation into training in anesthesiology, intensive care, and pediatric emergency medicine.^{5,10}

CONCLUSION

Beside ultrasound demonstrated high diagnostic performance, speed, and reproducibility in confirming the positioning of ETT in children and neonates. Integrated protocols that combine tracheal, pleural, and diaphragmatic windows achieve sensitivities close to 100% and confirmation times of a few seconds. In addition to confirming the position, subglottic measurement by US was shown to be superior to age-based formulas in determining the ideal tube size, reducing exchanges and potentially the risk of mucosal injury.

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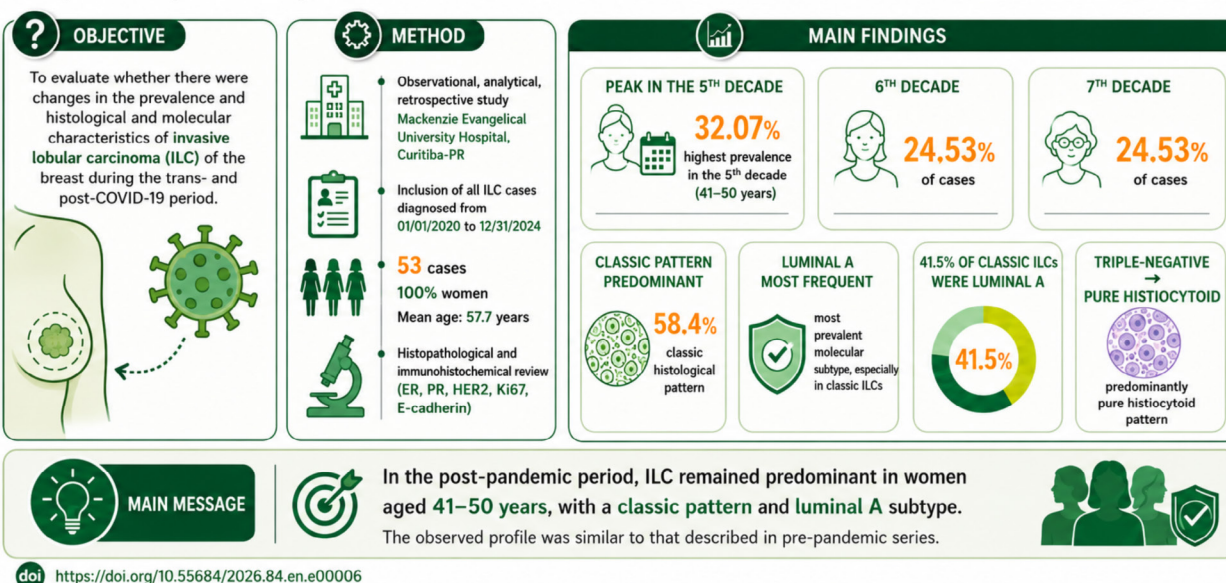
Lobular breast carcinoma after COVID-19: what has changed in prevalence and molecular profile?

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LOBULAR BREAST CARCINOMA AFTER COVID-19: WHAT CHANGED IN PREVALENCE AND MOLECULAR PROFILE?

Retrospective study of cases diagnosed between 2020 and 2024

BioSCIENCE



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Central Message

The COVID-19 pandemic has significantly impacted health services around the world, with the suspension of elective operations and the prioritization of care for severe cases. In this context, it is plausible to hypothesize that the epidemiology of invasive lobular carcinoma of the breast may have undergone changes, with a possible increase in the incidence of cases diagnosed in more advanced stages, perhaps due to the interruption of screening and timely treatment.

Perspective

It is appropriate to evaluate possible changes in the prevalence and characteristics of invasive lobular carcinoma of the breast in the post-pandemic period, with emphasis on distribution by age group, histological patterns, and molecular subtypes. Thus, it will be possible to assess how much the pandemic may have influenced the prevalence and characteristics of this carcinoma in the post-pandemic period, with emphasis on distribution by age group, histological patterns, and molecular subtypes.

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ABSTRACT

Introduction: Invasive lobular carcinoma (CLI) is a type of cancer that originates in the mammary glands. It is distinguished by presenting multiple histological and molecular patterns, with the main subtypes being luminal (A and B) and triple negative. The COVID-19 pandemic has significantly impacted health services, with the suspension of elective operations and the prioritization of care for severe cases.

Objective: To evaluate the possible changes in the prevalence and characteristics of CLI in the post-pandemic period, with emphasis on the distribution by age group, histological patterns, and molecular subtypes.

Method: The prevalence of carcinoma was identified by core biopsy and/or segmental resection of the breast, within the histological standards of lobular carcinomas, and the comparison of histological findings was based on the immunohistochemical profile of the tumors (molecular classification).

Results: The highest prevalence was between the fifth and seventh decades, peaking in the fifth (41-50 years) similar to pre-pandemic data. The classic histological pattern of the CLI was the most common in all age groups. Among the classical CLIs, luminal molecular subtype A was the most prevalent. There was no statistically significant difference between the prevalence of luminal CLI B and triple negative. Triple-negative tumors predominantly exhibited the pure histiocytoid pattern.

Conclusion: There was a higher prevalence of CLI in women in the fifth decade, with a predominance of the classic pattern and the luminal subtype A in the post-pandemic period.

KEYWORDS: Lobular breast carcinoma. Breast neoplasms. COVID-19. Molecular characterization. Tumor biomarkers.

INTRODUCTION

Invasive lobular carcinoma (CLI) is a special breast neoplasm, occupying the second place in prevalence among all breast cancers, especially in the postmenopausal age group.¹ It originates in the lobules and terminal ducts of the mammary gland (terminal lobular duct unit), presenting unique biological and molecular characteristics, which are the result of the inactivation of the CDH1 gene and the consequent absence of the E-cadherin protein, providing this neoplasm with a multicenter/multifocal pattern, perhaps bilateral, in addition to infiltrative and diffuse growth, contrasting with the more cohesive pattern of highly prevalent breast neoplasms.²

Its diagnosis is based on the characteristic growth pattern and phenotype of the neoplastic cells with the respective subtypes: classical, alveolar, solid, tubulolobular, pleomorphic and mixed lobular type.^{3,4} Despite the histological particularities, the treatment of CLI is mainly based on clinical staging and TNM, which depends on the size of the primary tumor, the presence of regional lymph node metastases and their number, as well as the presence of distant organ metastases.³

It is important to emphasize that there are differences in prognosis between two tumors of the same clinical stage and the same histopathological characteristics. That is why priority is given to individualized therapy, which depends on the molecular characteristics of breast cancer, individualized by genotyping, emphasizing that different molecular subtypes have varying prognosis. Standard prognostic factors depend on age, disease stage, tumor grade, histological type, status of resection margins, and presence of lymphovascular invasion.⁵ Predictive markers of therapeutic response are the ER and HER2 receptors, which is why determining the status of the hormone receptors ER, PR and HER2 is considered an essential factor to make additional decisions about the therapy of this cancer.^{6,7}

It is important to recognize that the COVID-19 pandemic has significantly impacted health services around the world, with the suspension of elective

operations and the prioritization of care for severe cases. In this context, it is plausible to hypothesize that the epidemiology of CLI may have undergone changes, with a possible increase in the incidence of cases diagnosed in more advanced stages due to the interruption of screening and timely treatment.⁸

Within this semantics, The present study aimed to analyze the prevalence and clinical-pathological characteristics of CLI cases, with emphasis on the distribution by age group, histological patterns and molecular subtypes, diagnosed in a high-complexity hospital in southern Brazil, between the years 2020 and 2024, which marks the trans and post-COVID-19 pandemic period.

METHOD

This research was approved by the Human Research Ethics Committee of the Evangelical Mackenzie Faculty of Paraná, Curitiba, PR, Brazil – CAAE no. 81810124.4.0000.0103. It was conducted in accordance with the applicable ethical principles. The anonymity of the patients and the confidentiality of the data collected were guaranteed. It was observational, analytical, and retrospective and was carried out at the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil. The prevalence of carcinoma was identified by core biopsy and/or segmental resection of the breast, within the histological standards of lobular carcinomas, and the comparison of histological findings was based on the immunohistochemical profile of the tumors (molecular classification).

All cases of CLI diagnosed at the hospital in the period from January 1, 2020 to December 31, 2024 were included.

Data were collected from medical records, including demographic information (age, gender), diagnostic data, histopathological report, and immunohistochemistry.

The histopathological slides were reviewed by a pathologist specialized in the breast to confirm the diagnosis and classify the tumors according to the histological standards (classical, alveolar, solid,

trabecular, pleomorphic, histiocytoid and with signet ring cells).

Immunohistochemistry

Immunohistochemical studies were performed to determine the expression profile of the following markers: hormone receptors (estrogen and progesterone), HER2/NEU, Ki67 and E-cadherin. The results were used to classify tumors into molecular subtypes (Luminal A, Luminal B, HER2-enriched, and Triple Negative) and to analyze the expression of E-cadherin in the different histological patterns of CLI.

Statistical analysis

Descriptive statistical methods (absolute and relative frequencies, means, medians, standard deviations) were used to present the results. To compare the histological and immunohistochemical characteristics of the tumors, appropriate statistical tests were used, such as chi-square or Fisher's test for categorical variables, and Student's t-test or Mann-Whitney test for continuous variables. The level of statistical significance was set at 5% ($p < 0.05$).

RESULTS

Epidemiology of the data

There were 53 cases of CLI diagnosed between January 1, 2020 and December 31, 2024. Of these lobular carcinomas, all cases found (100%) affected the female gender with a mean age of 57.7 years.

The incidence was between the fourth (between 31-40 years) and tenth decade of life (between 90-100 years). Quantification between the age groups was heterogeneous and is shown in Table 1.

TABLE 1 — Incidence of lobular carcinomas diagnosed between 2020 and 2024

Decade of life	Number of cases	Percentage
4th	2	3.77 (c)
5th	17	32.07 (a)
6th	13	24.53 (a)
7th	13	24.53 (a)
8th	7	13.2 (b)
9th	0	0 (d)
10th	1	1.88 (c,d)

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$

In the 4th decade (between 31-40 years), only two cases were diagnosed. Among the histological patterns found, one was classic lobular carcinoma and the other was pleomorphic lobular carcinoma and histiocytoid. Table 2 shows the characteristics of the tumors found in this age group, as well as their molecular classification.

TABLE 2 — Histological pattern, number of cases, and molecular classification of lobular tumors diagnosed in the 4th decade of life between 2020 and 2024

Histological pattern	Number of cases	Molecular classification
Classic	1 (a)	Luminal A
Pleomorphic lobular and histiocytoid	1 (a)	Luminal A

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$.

In the 5th, 6th and 7th decades of life, the patterns were heterogeneous, both in terms of histological classification and molecular classification. Tables 3, 4 and 5 reveal the patterns for these age groups.

Interestingly, there were some tumors, especially of classical pattern, that were classified as Luminal B; however, all tumors of this molecular classification revealed the same immunohistochemical profile, i.e. estrogenic and progesterone positive, without HER2/NER overexpression.

TABLE 3 — Demonstration of the histological pattern, number of cases, and molecular classification of lobular tumors diagnosed in the 5th decade of life between 2020 and 2024

Histological pattern	Number of cases (n = 17)	Molecular classification
Classic	1 (b)	inconclusive
Classic	12 (a)	Luminal A
Classic + cells in signet ring	1 (b)	Luminal A
Histiocytoid	1 (b)	Triple negative
Pleomorphic	1 (b)	Luminal A
Tubulolobular	1 (b)	Luminal A

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$

TABLE 4 — Demonstration of the histological pattern, number of cases, and molecular classification of lobular tumors diagnosed in the 6th decade of life between 2020 and 2024

Histological pattern	Number of cases (n=13)	Molecular classification
Classic	1 (b)	inconclusive
Classic	4(a)	Luminal A
Classic	1 (b)	Luminal B
Classical + pleomorphic	1 (b)	Luminal A
Classical + pleomorphic	1 (b)	Luminal B
Classic + pleomorphic + alveolar	1 (b)	Luminal B
Pleomorphic + solid	1 (b)	Luminal B
Pleomorphic	1 (b)	Luminal A
Tubulolobular	1 (b)	Luminal A
Histiocytoid	1 (b)	Triple negative

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$

TABLE 5 — Demonstration of the histological pattern, number of cases, and molecular classification of lobular tumors diagnosed in the 7th decade of life between 2020 and 2024.

Histological pattern	Number of cases (n=13)	Molecular classification
Classic	7(a)	Luminal A (a)
Classic + honeycomb + signet ring	1 (b)	Luminal A
Classic + honeycomb + solid	1 (b)	Luminal B
Classic + pleomorphic	1 (b)	Luminal B
Histiocytoid	1(b)	Inconclusive
Histiocytoid	1 (b)	Luminal B
Histiocytoid + pleomorphic	1(b)	Luminal A

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$

TABLE 6 — Shows the histological pattern, number of cases, and molecular classification of lobular tumors diagnosed in the 8th decade of life between 2020 and 2024

Histological pattern	Number of Cases (n=7)	Molecular classification
Classic	1 (b)	inconclusive
Classic	4(a)	Luminal A
Pleomorphic	1 (b)	Luminal A
Solid + honeycomb	1 (b)	Luminal A

Values followed by the same letter in parentheses are statistically similar, $p > 0.05$

No cases were found in the 9th decade of life. In the 10th there was only one diagnosed as lobular carcinoma in the signet ring, with molecular classification of Luminal B.

DISCUSSION

In the present study, the prevalence of lobular carcinomas and their respective molecular patterns was evaluated according to age group in the cases diagnosed during the study period.

The results found corroborate the scientific literature in pre-pandemic periods, demonstrating that lobular carcinoma of the classic variant is still the most frequent histological type among lobular carcinomas of the breast, corresponding to 58.4% of cases.⁹ This finding is in agreement with several studies that point to the classic variant as the most prevalent, accounting for up to 80% of lobular carcinomas in some geographic ranges of the globe, especially the United States of America.¹⁰

The analysis of the age distribution of the patients revealed a higher prevalence of lobular carcinomas in the fifth decade of life (41-50 years), with 32.07% of the cases diagnosed in this range. This period corresponds to the moment of menopausal transition, in which several hormonal changes occur that can influence the development of breast cancer.

Although the fifth decade of life stood out as the most prevalent, a significant incidence of lobular carcinomas was also observed in the sixth (51-60 years) and seventh (61-70 years) decades of life, with identical percentages of 24.53%. Despite these differences, there was no statistical significance between the fifth, sixth, and seventh decades, suggesting that advanced age and cumulative alteration of epigenetics may also be a risk factor for the development of this type of invasive lobular breast cancer.¹¹

These results indicate that most classic lobular carcinomas (41.50%) have the luminal A pattern, characterized by the expression of hormone receptors (estrogen and progesterone) and absence of HER2 receptor expression. This molecular profile is associated with a better prognosis and greater sensitivity to hormone therapy. These results corroborate data in the literature, which sometimes shows even a higher percentage, reaching 55-70% in terms of the prevalence of these tumors among other institutions.¹²

The analysis of hormone receptor expression and HER2/NEU in all histological subclasses of lobular carcinomas revealed that most of them have the luminal A pattern, regardless of the histological variant. This finding suggests that luminal A molecular profile is a common factor in most lobular carcinomas, regardless of their microscopic appearance.¹³

In the cases in which the pleomorphic pattern was identified, it was observed that most of them (six cases between 8-75%) were associated with mixed carcinomas, i.e., tumors that present characteristics of

different histological patterns. Lobular carcinomas, in which the pure pleomorphic pattern is predominant, were less common (2-8 cases - 25%).¹¹

Regarding triple-negative carcinomas, in which there is no expression of hormone receptors and HER2, ER and PR concomitantly, it was observed that all cases (100%) exhibited a single histological pattern, which was pure histiocytoid.¹⁴ This pattern is a rare variant of CLI, characterized by the presence of tumor cells with morphology similar to histiocytes, i.e., abundant and eosinophilic cytoplasm. This histological pattern has been associated with more aggressive CLI behavior, with a higher risk of extranodal metastasis and local recurrence. This molecular profile is associated with a worse prognosis compared with other subtypes of CLI, due to the lack of specific targeted therapies and the greater aggressiveness of the tumor. Curiously, not all those who present the mixed histiocytoid profile present heterogeneity of molecular profile, ranging from Luminal A or B. However, due to the scarcity of the number of these tumor patterns, the literature fails to establish a molecular pattern establishing a global prevalent pattern, and this study is an initiator in this perspective.^{14,15}

The results of the present study are valuable on the clinical and histopathological profile of CLI five years after the COVID-19 pandemic, contributing to a better understanding of this disease and to the development of more effective diagnostic and treatment strategies.

Limitations

It is important to note that this study has some limitations, such as the sample size and the retrospective nature of the analysis. Future studies with larger samples and a prospective design are needed to confirm our findings and deepen our knowledge about lobular carcinoma of the breast.

CONCLUSION

The identification of specific histological and molecular patterns in different age groups can contribute to a better understanding of CLI biology and optimize treatment strategies, especially in the context of possible changes resulting from the COVID-19 pandemic.

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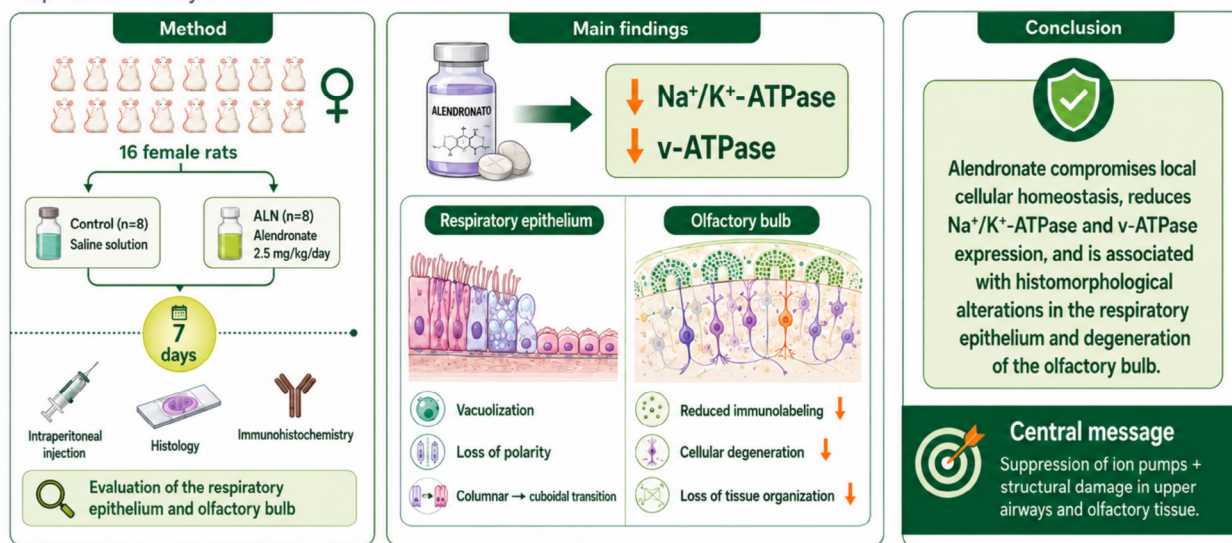
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Alendronate impairs key ion pumps and triggers structural damage in the upper airway mucosa and olfactory bulb

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Alendronate reduces Na⁺/K⁺-ATPase and v-ATPase and causes damage in the upper airways and olfactory bulb

Experimental study in rats



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Central Message

Alendronate compromises local cellular homeostasis due to energy-ionic suppression (loss of ATPases), negatively affecting the histomorphology of the nasal turbinates, the nasal septum, and the integrity of the olfactory bulb.

Perspective

It is opportune to evaluate possible alterations in protein expression and histomorphological characteristics of the upper airways and central nervous system in the long term after interruption or prolongation of alendronate treatment, with emphasis on the distribution of lesion severity, patterns of cellular degeneration, and tissue recovery capacity. Thus, it will be possible to assess the extent to which chronic alendronate administration may have influenced the prevalence and characteristics of cellular and structural alterations in the respiratory epithelium and olfactory bulb, with emphasis on dosage distribution, histological patterns, and ATP-dependent ion transport mechanisms.

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ABSTRACT

Introduction: Alendronate (ALN) is bisphosphonate used in clinical practice to reduce the adverse consequences of bone pathological condition.

Objective: This study aimed to investigate the effects of alendronate (ALN) administration on the immunoexpression of Na⁺K⁺ATPase and v-ATPase within the upper airway mucosa and olfactory bulb of rats.

Method: Sixteen animals were equally distributed into control and experimental groups, with the latter receiving daily intraperitoneal doses of ALN (2.5 mg/kg). After 7 days, the rats were euthanized, and their heads were processed for histological evaluation and immunohistochemical quantification of both target proton pumps to assess tissue structural integrity.

Results: On the seventh day, the animals were euthanized, and their heads were processed for histological and immunohistochemical examinations. Specimens treated with ALN exhibited a decreased presence of Na⁺K⁺ATPase and v-ATPase in both the respiratory epithelium and the olfactory bulb. These findings coincided with vacuolization and a loss of polarity within the respiratory epithelium, alongside profound cellular degeneration in the olfactory bulb.

Conclusion: It can be concluded that the administration of alendronate may alter the histomorphology of the respiratory epithelial, additionally compromising olfactory bulb integrity due to the down-regulation of the expression of Na⁺K⁺ATPase and v-ATPase expression.

KEYWORDS: Alendronate. Respiratory epithelium. Olfactory bulb. v-ATPase. Na⁺K⁺ATPase.

INTRODUCTION

Alendronate (ALN) is a common bisphosphonate used in clinical practice to reduce the adverse consequences of pathological condition that culminates in osteolysis such as osteoporosis, otospongiosis, Paget's diseases, osteogenesis imperfect, multiple myeloma or bone metastasis due to invasiveness of neoplasms.¹⁻²

The effect of alendronate on bone modulation is vast and its fundamental action is associated with reducing the osteoclast number and viability.³ Besides that, alendronate seems to promote osteogenesis in craniofacial defects.⁴⁻⁶ Despite its importance, the use of alendronate may cause numerous collateral effects, among them erosive mucositis and toxic effects on Schwann and neuronal cells.⁷⁻⁹

Several anatomical areas are composed of bone and cartilage and may be affected by alendronate. Among them, includes the nasal septae and turbinates that support adjacent structures such as respiratory epithelium.¹⁰

The upper airway tract is covered by a thinner epithelium composed of ciliary pseudostratified columnar epithelium with goblet cells that possess an important action in respiratory organ physiology since they regulate inhaled air temperature and humidity and filter foreign particles.¹¹ However, a portion of the specialized olfactory epithelium known as the olfactory bulb consists of multiple cell types. One of these cells is a bipolar cell known as olfactory receptor neuron. At its basal surface, it gives rise to a small-diameter, unmyelinated axon that transmits smell signals between the olfactory epithelium and the primary olfactory brain.¹²

Several proteins act for appropriate histophysiology action of respiratory epithelium and olfactory bulb. In this context, Brezillon et al.¹³ highlight that proteins exhibiting ATPase activity seem to play a crucial role in the arrangement of the respiratory epithelium. This is because these ATP-dependent proteins are accountable for the formation of junctional complexes at the interface between basal and ciliated cells. Additionally, these proteins support the integrity of the interface basolateral

epithelium on columnar cells, and ATP appears to aid in the anchoring of intermediate filaments like actin and cytokeratins.

Recognizably, the Na⁺K⁺ATPase pump is an important protein whose ATPase activity has maintained an ionic composition of its cytoplasm, maintaining low sodium, and high potassium, and keeping a neutral Hydrogenionic potential (pH). Besides that, several studies have demonstrated the importance of Na⁺K⁺ATPase on the modulation of tight junction development, permeability, and cell polarity¹⁴ and acts like an ion transporter either in neural axon and plasmatic membrane of the epithelium and neuroepithelial cells as occurs in olfactory bulb cells.¹⁵

Conversely, the v-ATPase is a transmembrane protein that possesses fundamental action either in epithelial or neuroepithelial cells. Intracellular v-ATPases play a crucial role in intracellular acid-base regulation, working on protein processing and degradation, vesicle trafficking, and the coupled transport of small molecules.¹⁶

Thus, the purpose of this study was to evaluate the effect of ALN on the respiratory epithelium of the nasal mucosa and olfactory bulb, while simultaneously verifying the immunoexpression of Na⁺K⁺ATPase and v-ATPase in order to understand the cellular mechanisms underlying ALN-related mucosal and neuronal toxicity

METHOD**Animals**

The Ethical Committee for Animal Research gave its approval to this work, which complied with the regulations of animal use and the Principles of Laboratory Animal Care (NIH Publication 85-23, revised in 1985). In this investigation, sixteen female rats (*Rattus norvegicus albinus*, Holtzman) weighing between 240 and 260 g at two months of age were used. The animals were housed in a room with a 12-hour light/dark cycle, regulated humidity (52%±5%), and ad libitum access to food and water.

Randomly, eight newborn rats received 1 ml of sterile 0.9% saline solution (control group); while eight rats received 2.5 mg/kg/day of alendronate trihydrate

(Biolife, Curitiba, Brazil; lot number: 14042132C) for seven days (ALN group). Intraperitoneal injections of saline and alendronate solutions were given every day until the seventh day, when an isoflurane overdose led to euthanasia and immediately the entire heads of rats were removed.

Histological procedure

The surgical specimens were collected instantaneously after the euthanasia process and they were placed in a 4% formaldehyde fixative solution, which was made by mixing paraformaldehyde with 0.1 M sodium phosphate at a pH of 7.2, for 48 hours at a temperature between 18 and 20°C. Each sample was dehydrated in graded quantities of ethanol, clarified in xylene, and embedded in paraffin after being decalcified for 21 days in 7% Ethylenediaminetetraacetic Acid Tetrasodium (EDTA) containing 0.5% formaldehyde in 0.1 M sodium phosphate (pH 7.2).

From each specimen, sequential 3- μ m-thick histological sections were cut in the anterior-posterior direction in accordance with the coronal anatomic plane. The slices were placed on silanized slides (Sigma-Aldrich Chemie, Steinheim, Germany) in order to detect Na⁺K⁺ATPase and v-ATPase using immunohistochemistry.

Immunohistochemistry

Each slide composed of specimens with a thickness of three micrometers was deparaffinized in xylene and after ten minutes in each of ninety-five and seventy percent alcohol, they were hydrated in 70% alcohol. A 1% pepsin solution (pH 1.8) (Sigma-Aldrich, Germany) was used for the antigen retrieval process, which lasted for one hour at 37°C. After 20 minutes of room temperature cooling, they were given a 10-minute soak in distilled water and subsequently, they were immersed in 0.1% hydrogen peroxide (H₂O₂) (Thermo Fisher Scientific, US) for fifteen minutes, to endogenous peroxidase activity was inhibited. After five minutes of running tap water washing, the specimens were immersed in phosphate-buffered saline (Sigma-Aldrich, Germany) for a further five minutes. The primary antibodies anti- α 1-Na⁺K⁺ATPase (Santa Cruz Biotechnology Inc., sc-166848, CA, USA, dilution factor: 1:180) and v-ATPase (Santa Cruz Biotechnology Inc.: sc-166848, CA, USA, dilution factor: 1:150) were incubated overnight for the samples. In order to identify the primary antibodies, a labeled streptavidin biotin antibody-binding detection system (Universal HRP immunostaining kit – Diagnostic Byosystem Universal HRP Immunostaining Kit, Diagnostic Byosystem, Foster City, CA, USA) was employed for 30 minutes. Following this, the sample was immersed in dimethane chromogen (Universal HRP immunostaining kit – Diagnostic Byosystem Universal HRP Immunostaining Kit, Diagnostic Byosystem, Foster City, CA, USA) for a duration of 15 minutes, resulting in a brownish precipitate at the antigen site. Harris's hematoxylin was used for two minutes as a counterstain on the specimens. For every sample that omitted, a negative control was carried out.

Image analyses

Using a digital camera (Samsung, South Korea) and a light microscope, images of the histological and immunohistochemical sections were taken at magnifications of $\times 100$ and $\times 200$. At a resolution of 300 dpi, 110 $\times$ 65 cm digital photographs were taken and stored.

For the histological and immunohistochemical evaluation, the microscopy images were processed using Adobe Photoshop version 11.0 for Mac. For each image obtained, all area of the nasal cavity was considered for evaluation and it was composed of entire nasal septae recovered by respiratory epithelium. In serial posterior slices, it was considered areas that presented integral internal capsular region of the olfactory bulb for analysis. However, since the histological is a limited technique used to obtain the olfactory bulb in surgical pieces, it was possible to analyze only areas of the olfactory bulb posteriorly to the ethmoid bone, and all findings were presented in accordance with the layers that the original Cajal depiction of the olfactory bulbs frontal region described.¹⁷

Each micrograph was submitted to the Image J software (<https://imagej.nih.gov/ij/>), and positivity for Na⁺K⁺ATPase and v-ATPase cells (detected by brownish color in membrane and cytoplasm of cells of interest) were manually counted and tagged. It was considered 5,000 cells for specimens and the area accounted for was randomized chosen. The results were transformed in the percentage of positivity.

Statistical analysis

The Shapiro-Wilk test was used to establish normalcy, and the nonparametric Kruskal-Wallis test was used to identify statistically significant group differences. A significance criterion of $p < 0.05$ was established.

RESULTS

The Na⁺K⁺ATPase and v-ATPase expression immunohistochemical data are represented respectively present on Figure 1, while the immunohistochemistry illustration is given in Figure 2.

Respiratory epithelium

On the 7th day of evaluation, the control group exhibited a respiratory epithelium with normal histological characteristics. In contrast, numerous regions of intraepithelial vacuolation and alterations in epithelial polarity were observed in the specimens that received ALN. Furthermore, the ALN-treated specimens demonstrated a transition from columnar to cuboidal epithelium, as well as areas showing a loss of basolateral adhesion within the epithelium. Moreover, the regions where these microscopic modifications were detected coincided with the loss of expression of Na⁺K⁺ATPase and v-ATPase proteins (Fig. 1). In the control group, these proteins were expressed throughout the membrane and cytoplasm of the ciliated pseudostratified columnar epithelium, as well as on the membrane of goblet cells lining the respiratory tract.

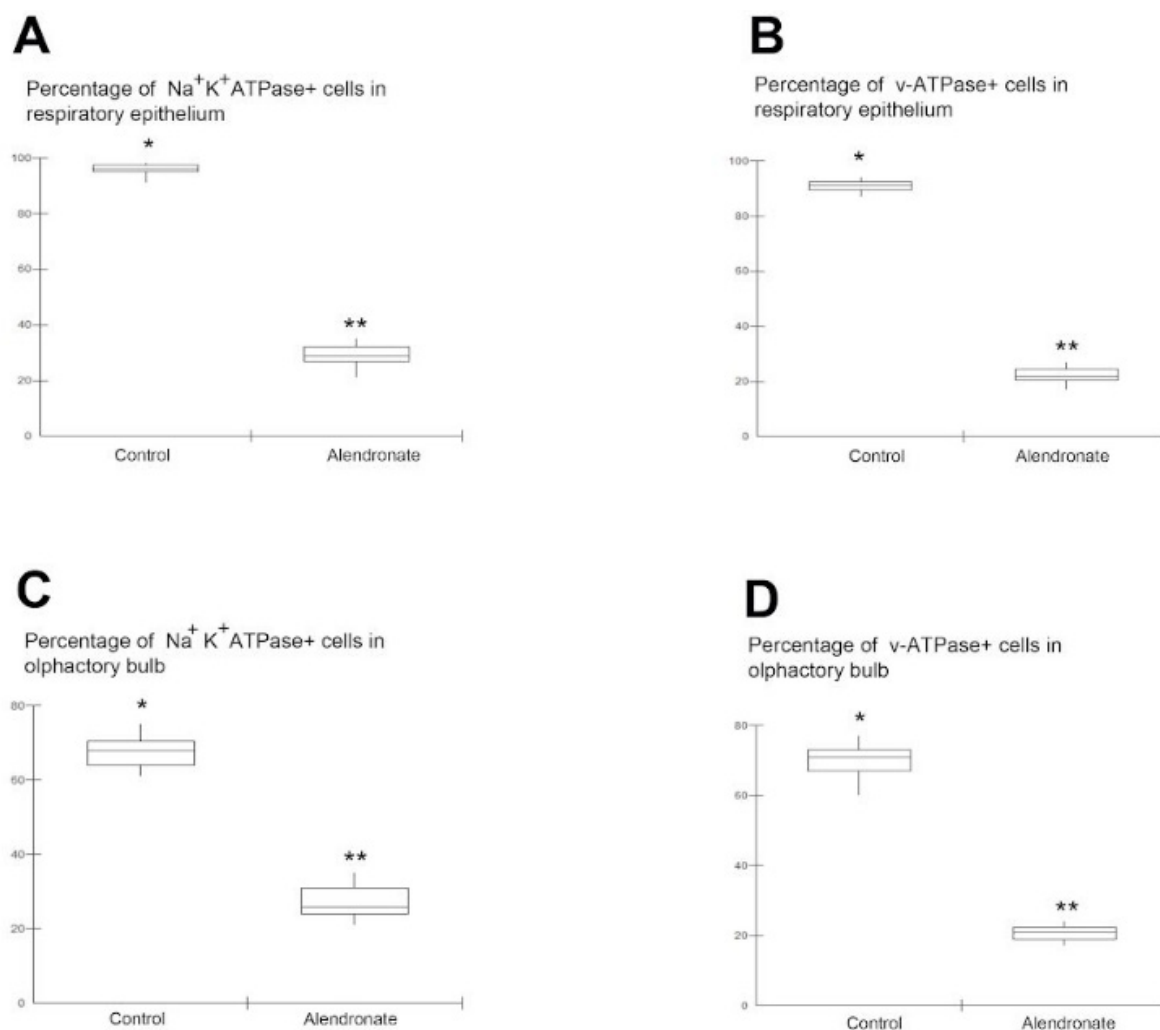


FIGURE 1 — Box plot diagram revealing the median, maximum, and minimum values of Na⁺K⁺ATPase as well as v-ATPase on respiratory epithelium and olfactory bulb in the course of the study. The same superscript character (asterisk) is not statistically different, $p > 0.5$.

Both Na⁺K⁺ATPase (Figs. 2A and E) and v-ATPase (Figs. 2B and F) shared the same expression pattern in the alendronate-treated specimens (Figs. 2B and F for Na⁺K⁺ATPase; Figs. 2C and G for v-ATPase); however, the number of positive cells was significantly lower (Fig. 1). Interestingly, the epithelial lining at the apex of the nasal turbinates was negative for both evaluated proteins, whereas other topographical regions of the respiratory tract demonstrated substantial areas with a loss of protein positivity. A similar expression pattern was observed in the maxillary sinus; however, the negative epithelial cells of the maxillary sinus displayed a distinct morphology, characterized by squamous to cuboidal epithelial cells.

Olfactory bulb

Significant differences also were seen in the olfactory bulb for Na⁺K⁺ATPase and v-ATPase proteins and histomorphology. On control, all cells that compounded the glomerular layer of the olfactory bulb were positive for Na⁺K⁺ATPase (Fig. 2I) and v-ATPase (Fig. 2K). The glomeruli exhibited immunopositivity for Na⁺K⁺ATPase and v-ATPase either in cytoplasm or membrane while the peripheral tufted cells, that surrounded each

glomeruli body, demonstrated positivity for v-ATPase in membrane axon and dendrite, while Na⁺K⁺ATPase was restricted to neuronal prolongation areas. In the group that received alendronate, the presence of Na⁺K⁺ATPase (Fig. 2J) and v-ATPase (Fig. 2L) was found in few anucleated glomerulus cells, while other cellular bodies of glomeruli were negative. In addition, only sparse axonal and dendritic areas exhibited focal positivity on regions occupied by peripheral tufted cells.

Yet, in the control group, both v-ATPase and Na⁺K⁺ATPase also were well expressed in the inner plexiform layer, an area compatible with grains and white matter layer on the cellular body, axon, and dendrite; however, the mitral cells layer exhibited only expression for v-ATPase. In contrast, the specimens that received ALN demonstrated a loss of positivity for both v-ATPase and Na⁺K⁺ATPase when compared to the control group.

DISCUSSION

In the present study, we demonstrated that the expression of v-ATPase and Na⁺K⁺ATPase were significantly decreased in specimens that received ALN. These results were consistent with areas that revealed

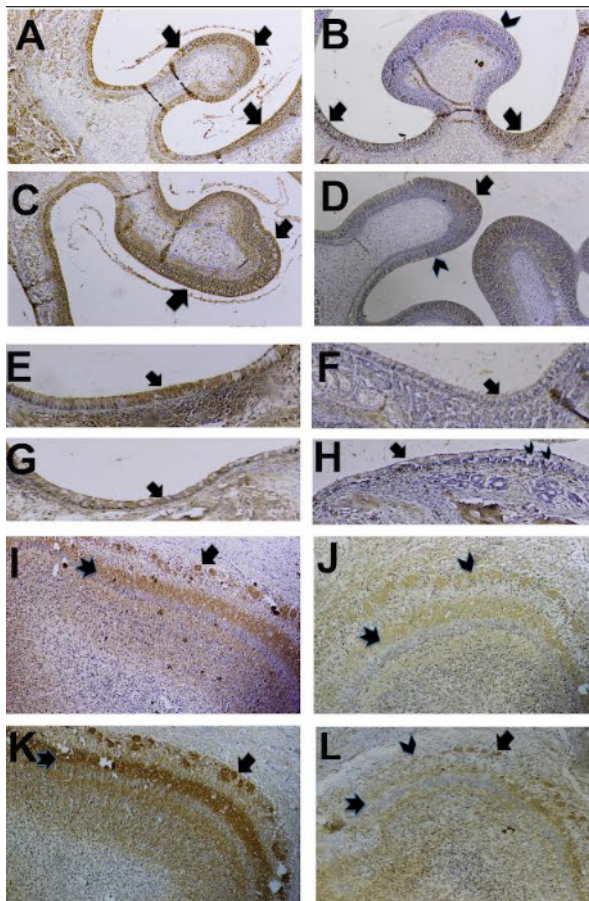


FIGURE 2 — Micrographs A and B demonstrate the pattern of immunoeexpression of Na⁺K⁺ATPase (in brownish color) in respiratory on nasal turbinates for control and specimens that received alendronate respectively. Note the presence of the immunoeexpressions (arrows) for either for Na⁺K⁺ATPase on either control group or alendronate, however, the test group demonstrated areas of loss of immunopositivity for protein (chevron). Micrographs C and D reveal similarly pattern for v-ATPase on control and ALN group. E and G demonstrate immunoeexpression of Na⁺K⁺ATPase and v-ATPase positivity (arrows-brownish color) for control, while F and H reveal loss of positivity for Na⁺K⁺ATPase and v-ATPase on respiratory epithelium (arrows) of ALN group. Note loss of adhesiveness and intraepithelial vacuolization in the alendronate group (chevron). Micrographs I and J show the expression for Na⁺K⁺ATPase (in brownish color) for the control and alendronate groups respectively. Note the intense positivity in glomerular cells (arrow) in the control group, while in the test group cellular degeneration (chevron). Yet, there is an expression for protein (Notched arrow) in the axonal area. Note the organized expression occurred in the control group while in alendronate specimens occur a disorganized and infrequent expression. Micrographs K and L demonstrate that v-ATPase reveals a similar pattern of Na⁺K⁺ATPase. (A to D and I to L- Original magnification ×100; E to H- Original magnification ×200; positivity area occurs in brownish color).

cell degeneration on the olfactory bulb, particularly in its glomerulus bodies of the olfactory bulb, and histological changes of the respiratory lining epithelial tissue.

The previous discovery that ALN inhibits farnesyl pyrophosphate synthase in the mevalonate cascade metabolic pathway may help to explain the loss of membrane ATPase-protein.¹⁸ This inhibitory event

may lead to an accumulation of non-prenylated GTP-binding proteins spread in the cytoplasm of the cell due to suppression of cholesterol. Thus, the binding protein's ability to facilitate protein-protein interaction in the cellular membrane is eliminated in its non-prenylated state, condition that may provide protein denaturation.¹⁹⁻²⁰ It have to be highlighted that when a protein that works as a transmembranic receptor protein is spread throughout the cytoplasm, it may exhibit changes in its tertiary or quaternary protein configuration, and the modification of the level protein organization simulating the denaturation of protein and inhibit either its usual functional action as well as its immunohistochemical detection.²¹⁻²²

It should be taken into consideration that damage of Na⁺K⁺ATPase in the epithelium is also associated with degenerative processes, that inducing hydropic or vacuolar degeneration due to accumulation of Na⁺ in the intracellular compartment, as well as leads to a loss of epithelial cell surface membrane polarity.²³ In addition, there is evidence that associates the loss of Na⁺K⁺ATPase to detachment of the cytoskeleton and surface membrane structures whose results lead to numerous cellular physiopathological adaptations including damage of cell-cell contact as well as cell-extracellular matrix adhesion.²⁴ Consequently, loss of Na⁺K⁺ATPase seems to be also relevant to the functional action of respiratory epithelium, since this protein also collaborates for mucociliary clearance and airway lining fluid. It should be highlighted that ciliated epithelial cells that compound the respiratory epithelium are important in propelling mucus up the airway, thereby removing particulate material.¹¹

In addition, either suppression of Na⁺K⁺ATPase or v-ATPase not only may induce damage in respiratory histophysiology, but also seems to facilitate secondary infections since this epithelium also is associated with sinus development and also It controls the flow of water and ions into the mucus in the airways, secretes lactoferrin, lysozyme, and antimicrobial peptides (cathelicidins and β -defensins), and releases reactive oxygen and nitrogen species to annihilate pathogens that invade the respiratory tract.²⁵⁻²⁶

Conversely, loss of Na⁺K⁺ATPase as well as v-ATPase on bulb olfactory coincided with structural changes in the morphology of this organ. It is noteworthy that Na⁺K⁺ATPase is important for depolarization and repolarization of the membrane, a condition that is also important for neurotransmission.²⁷

Specifically, the v-ATPase is a biomarker of specialized proton-secreting cells. This protein is present in lateral membrane in a subpopulation of olfactory sensory cells and the microvilli of the apical plasma membrane of sustentacular cells. It was also discovered that, when produced in olfactory neurons, v-ATPase typically assumed a greater subapical location in olfactory sustentacular cells. Typically, v-ATPase may be associated with CO₂ detection when expressed in olfactory neurons, aiding in signal transduction that supports respiratory tract homeostasis and cellular integrity.²⁸ Supporting this hypothesis, the

lack of expression of v-ATPase seems to have contributed to the intracellular acidity of the sensory epithelium of the olfactory bulb, and this situation may be suggested herein since the integrity of the glomerular cells showed an evident degenerating cellular situation.²⁹

CONCLUSION

Herein, we demonstrated that Alendronate induces loss on Na⁺K⁺ATPase and v-ATPase expression, situations that may modify the histophysiology of the respiratory epithelium of the nasal cavity, as well as degeneration of the olfactory bulb.

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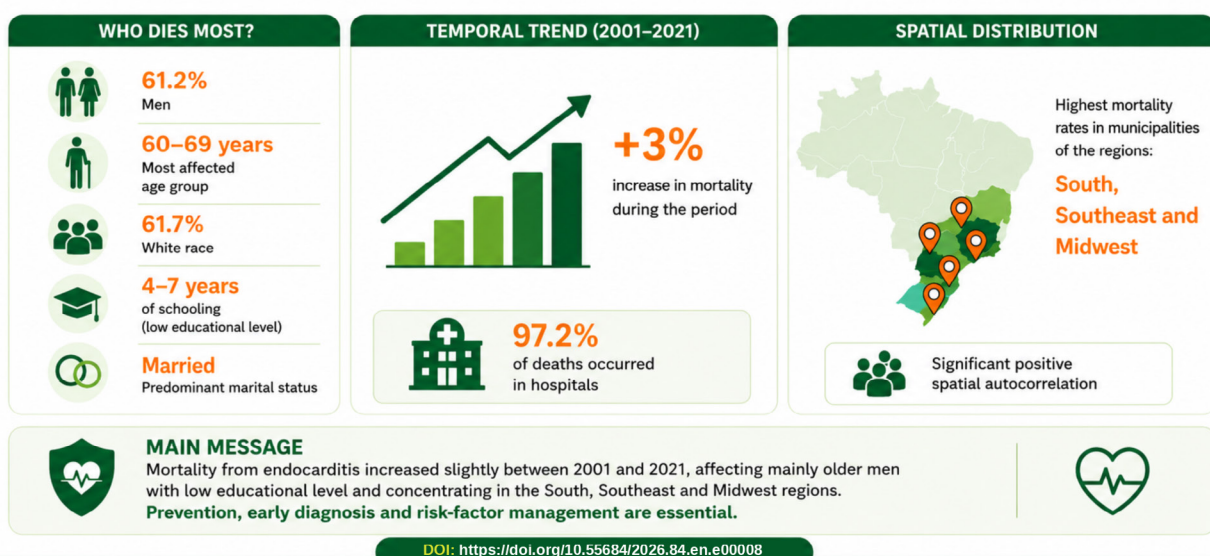
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Endocarditis in Brazil: what do two decades of mortality reveal?

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ENDOCARDITIS IN BRAZIL: WHAT DO TWO DECADES OF MORTALITY REVEAL?

Analysis of mortality from acute and subacute endocarditis between 2001 and 2021



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Central Message

Infective endocarditis is a serious condition caused by infection of the endocardium, prosthetic valves, or cardiac devices. Its incidence has increased worldwide. In 2019, the highest incidences occurred in tropical and southern Latin America. Mortality also increased, being higher in southern Latin America, Oceania and high-income North America. Thus, analyzing the epidemiological profile, temporal trends, and spatial distribution of mortality from acute and subacute endocarditis in Brazil is important to identify patterns and priority areas for intervention

Perspective

As mortality due to endocarditis showed a slight increase in the studied period, concentrating in vulnerable population groups and in specific regions of the country, the need for regional strategies for prevention, early diagnosis, and adequate management of cardiovascular risk factors is reinforced. With this, better results can be presented in terms of their frequency and mortality.

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ABSTRACT

Introduction: Infective endocarditis is a serious condition caused by infection of the endocardium, prosthetic valves or cardiac devices. Its incidence has increased worldwide, currently being 1.5-11.6 cases per 100,000 people and in-hospital mortality rates ranging from 17.5-30%.

Objective: To analyze the epidemiological profile, temporal trends, and spatial distribution of mortality from acute and subacute endocarditis in Brazil between 2001 and 2021, identifying patterns and priority areas for intervention.

Method: Epidemiological study with temporal and spatial analysis, using death data from the Mortality Information System (SIM/DATASUS) and population data from the IBGE to calculate crude and standardized rates.

Results: Between 2001 and 2021, 15,448 deaths from acute and subacute endocarditis were recorded in Brazil, with an approximate increase of 3% in mortality over the period. The highest frequency was observed in individuals aged 60–69 years (21.22%), males (61.20%), white (61.67%), with low schooling (4–7 years of schooling) and married marital status. Most deaths occurred in a hospital environment (97.24%). The spatial analysis showed a higher concentration of mortality in the South and Southeast regions, with emphasis on specific municipalities. There was significant positive spatial autocorrelation.

Conclusion: Mortality from endocarditis showed a slight increase in the period studied, concentrated in vulnerable population groups and in specific regions of the country, reinforcing the need for regional strategies for prevention, early diagnosis, and adequate management of cardiovascular risk factors.

KEYWORDS: Endocarditis. Spatio-temporal analysis. Mortality records.

INTRODUCTION

Infective endocarditis (IE) is a serious condition caused by infection of the endocardium, prosthetic valves, or cardiac devices. Its incidence has increased worldwide, currently being 1.5-11.6 cases per 100,000 people and hospital mortality rates ranging from 17.5% to 30%.¹ O Global Burden of Disease Study showed its growth, with 1.09 million cases registered in 2019 and an age-adjusted rate of 13.8 per 100,000 people, compared to 9.9 in 1990. In 2019, the highest incidence rates occurred in tropical and southern Latin America. Mortality rates also increased, ranging from 0.7 to 0.9 per 100,000, being higher in southern Latin America, Oceania and high-income North America.²

It is important to note that the epidemiological profile of IE has changed, contributing to high morbidity and mortality. The incidence has grown among patients with risk factors, such as advanced age, comorbidities, prosthetic valves, and cardiac devices. In addition, an increase in cases of IE of nosocomial origin has been reported in the literature.¹ Moreover, other epidemiological characteristics such as predisposing factors and causative microorganisms are different between geographic regions. Predisposing factors include rheumatic heart disease, which is very present in developing countries such as Brazil, as well as degenerative heart disease or intravenous drug use, which are more common in developed countries. However, in Latin America, synthesized data on characteristics and trends of the IE are scarce.²

The etiology of IE shows an increase in cases of *Staphylococcus aureus* and a significant reduction in viridans group streptococci in North America, while in Latin America no changes were observed over the decades. Globally, *S. aureus* is predominant, with variation of secondary microorganisms.²

A study conducted with data from Latin America showed that the main cardiovascular risk factors

were a history of heart valve disease (24.3%), followed by the presence of prosthetic heart valve (23.4%). The most frequent comorbidities were hypertension (38.1%) and diabetes mellitus (15.8%). Previous surgical or endoscopic procedures, catheter or indwelling device, and previous procedures were associated with IE in 21.9%, 20.9% and 5.6%, respectively.²

The main clinical manifestations are fever, dyspnea, Osler's nodules, petechiae, malaise, presence of heart murmur, with the possibility of developing complications, the main ones being heart failure, embolic events and septic shock.²

In a systematic review analyzing blood culture data in 41 studies, including 4032 blood cultures, 23.9% had negative blood cultures.² Several factors influence this occurring, such as inadequate microbiological techniques and previous use of empirical antibiotic therapy before the diagnostic analysis.³

The main surgical indications are left ventricular ejection dysfunction due to heart failure and/or valve dysfunctions, failure in clinical treatment, and echocardiographic vegetation greater than 10 mm. Emergency surgery may also be indicated due to severe cardiocirculatory shock.³ Techniques such as Ozaki aortic valve repair and transaortic mitral valve repair with autologous pericardium stand out.

IE has important complications on patients due to the high proportion of future complications such as development of heart failure (36.4%) or embolic events (27.1%), leading to the need for surgery. Surgery was reported in 42% of cases in a systematic review looking at IE in Latin America, lower than the Euro-Endo registry, which reported 51.2% and a Japanese national study, 61%. Regarding mortality associated with the surgical treatment of endocarditis, studies analyzing in-hospital mortality found an overall in-hospital mortality of 25.1% (37 studies with n of 1027/4095) and overall mortality, including late and unspecified periods, of 26.6%.²

METHOD

This is an epidemiological study of secondary data analysis in health with a focus on temporospatial analysis. Data on cases of death due to acute and subacute endocarditis 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 came from DATASUS.

For the analysis of the mortality trend due to acute and subacute endocarditis in Brazil, the period from 2001 to 2021 was selected, in order to better understand the outcome in this historical series. For the study population, individuals were selected, according to data available from the Department of Informatics of the Unified Health System (DATASUS) for adults who were registered with deaths from acute and subacute endocarditis. 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 133 of the International Classification of Diseases (ICD-10) was adopted. Information on the epidemiological profile and frequency of deaths from acute and subacute endocarditis were compiled 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 100,000 inhabitants as a reference for this coefficient. While 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 100,000 inhabitants.

Initially, the temporal trend of mortality due to acute and subacute endocarditis 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 analysis of the temporal pattern was performed using the Joinpoint Regression Program 5.0.2 2023 software. Next, the spatial distribution of mortality from acute and subacute endocarditis in Brazil was analyzed. Initially, the mean mortality of them in Brazilian municipalities 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 through 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.

To identify spatial clusters, the Global and Local Moran's 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 $p < 0.05$ to be significant. If the hypothesis of dependence is accepted, the Local Index of Spatial Association (LISA) was 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 (Figure 4). The Moran Map graphically demonstrates the degree of similarity between neighbors, being represented by four quadrants: 1) high-high (upper right quadrant) which 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) that correspond to municipalities that have low mortality rates and are close to municipalities 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) that correspond to municipalities that have low mortality rates and are close to municipalities that have high mortality rates.

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 the Ethics Committee.

RESULTS

After a meticulous analysis of the profile of Brazilian victims of acute and subacute endocarditis, a significant prevalence was identified among those aged between 60 and 69 years, totaling 21.22% of the cases. However, it is notable that the incidence of this fatal event is practically comparable in close age groups, with 17.54% of deaths occurring between 50-59 years of age, and 19.37% among 70-79 years of age. In addition, there was a marked predominance of males, representing 61.20% of the cases. At the same time, most of the victims belonged to the white ethnicity (61.67%) and had the marital status of married (45.25%).

Regarding the educational level, it was observed that most deaths occurred among individuals with 4-7 years of complete schooling, comprising 20.46% of the cases, followed by 18.25% among those with 8-11 years of complete schooling. It is crucial to highlight that most cases of mortality due to acute and subacute IE occurred in a hospital environment,

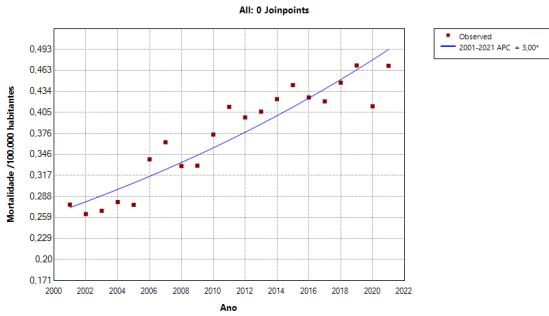
representing 97.24% of the total.

From 2001 to 2021, 15,488 deaths from acute and subacute IE were recorded in Brazil. The average mortality in this period was 0.37/100,000 inhabitants, with the lowest mortality recorded in 2002 (0.26/100,000 inhabitants) and the highest in 2019 (0.47/100,000 thousand inhabitants). The analysis of the temporal pattern of mortality in the period from 2001 to 2021 showed a significant mean increase of 3% per year in the mortality rate per 100,000 inhabitants ($p < 0,05$, Figure 1). Pearson's correlation coefficient was 0,9674 with $p < 0.05$, indicating that there is a significant and proportional linear correlation, with an increase in the mortality rate over the years.

TABLE — Epidemiological profile of individuals who died from endocarditis

	n	%
Child 1 year old	217	1.40%
1 to 4 years	100	0.65%
5 to 9 years	65	0.42%
10 to 14 years old	128	0.83%
15 to 19 years old	289	1.87%
20 to 29 years old	821	5.30%
30 to 39 years old	1144	7.39%
40 to 49 years old	1793	11.58%
50 to 59 years old	2748	17.74%
60 to 69 years old	3286	21.22%
70 to 79 years old	3000	19.37%
80 years and over	1891	12.21%
Age ignored	6	0.04%
Gender	n	%
Men	9478	61.20%
Women	6007	38.78%
Ign	3	0.02%
Color/Race	n	%
White	9552	61.67%
Black	1048	6.77%
Yellow	97	0.63%
Brown	3872	25.00%
Indigenous	21	0.14%
Ignored	898	5.80%
Education	n	%
None	855	5.52%
1 to 3 years	2813	18.16%
4 to 7 years	3169	20.46%
8 to 11 years	2827	18.25%
12 years and over	1583	10.22%
Ignored	4241	27.38%
Marital status	n	%
Single	3740	24.15%
Married	7008	45.25%
Widower	2162	13.96%
Legally separated	1079	6.97%
Other	322	2.08%
Ignored	1177	7.60%
Place of occurrence	n	%
Hospital	15061	97.24%
Other health facility	151	0.97%
Domicile	199	1.28%
Public road	13	0.08%
Other	58	0.37%
Ignored	6	0.04%

Source: Department of Informatics of the Unified Health System (2024)



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 1 Joinpoint.

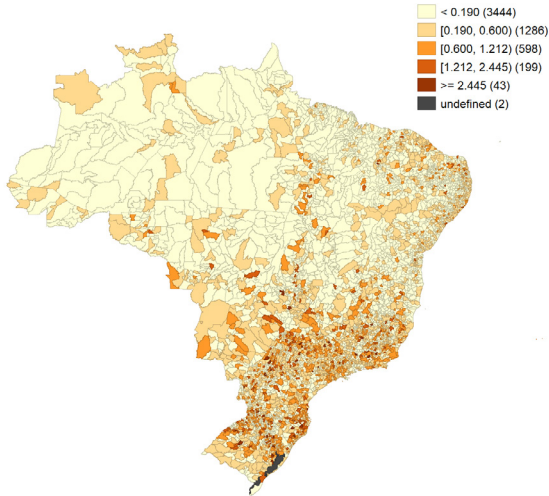
Source: The authors (2024)

FIGURE 1 — Temporal pattern of mortality from acute and subacute endocarditis in Brazil between 2001-2021

Through spatial analysis, Figure 2 shows the spatial dispersion of mortality due to acute and subacute endocarditis in Brazil, with a focus of incidence in the South and Southeast regions, Torre de Pedra, SP (6.15/100,000 inhabitants), Serranos, MG (4.70/100,000 inhabitants), Protásio Alves, RS (4.69/100,000 inhabitants), Ourizona, PR (4.14/100,000 inhabitants) and Porteirão, GO (4.11/100,000 inhabitants) were the five municipalities that presented the highest mortality rate due to acute endocarditis and subacute between 2001-2021.

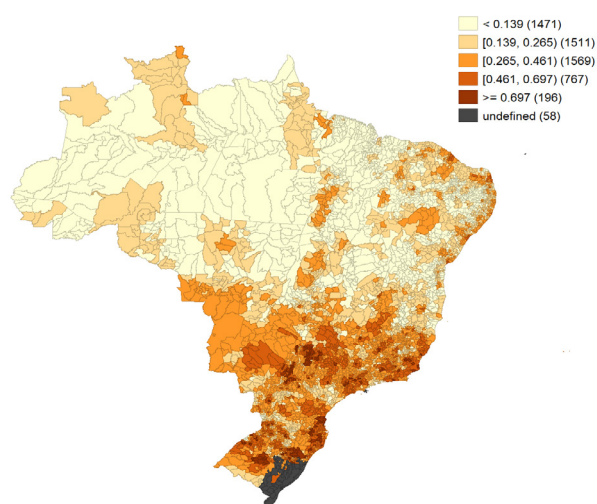
With the smoothing of the crude rates by the local empirical Bayesian method (Figure 3), it is possible to observe a more apparent spatial pattern, with aggregation of municipalities with higher mortality rates in the South, Southeast and Midwest regions. Spatial autocorrelation was identified by the Global Moran Index ($I = 0.779$; $p = 0.01$), demonstrating evidence of positive autocorrelation.

The application of the Local Moran's Index made it possible to identify spatial clusters of both high and low equal values (Figure 4). The high-high pattern was identified mainly in the South, Southeast and Midwest regions, which indicates similarity of the municipalities in these regions for high mortality values from the disease analyzed, while the low-low pattern was identified mainly in the North and Northeast regions, which indicates similarity between the municipalities in these regions for low mortality values from the pathology analyzed.



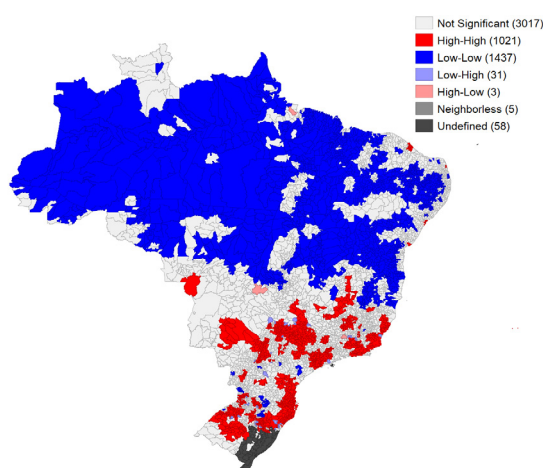
Source: The authors (2024)

FIGURE 2 — Crude mortality rate from acute and subacute endocarditis in Brazil between 2001-2021



Source: The authors (2024)

FIGURE 3 — Mortality rate smoothed by the local empirical Bayesian method for acute and subacute endocarditis in Brazil between 2001-2021



Source: The authors (2024)

FIGURE 4 — Spatial clusters of mortality from acute and subacute endocarditis in Brazil between 2001-2021

DISCUSSION

The temporal and spatial analysis of mortality from IE in Brazil between 2001 and 2021 reveals a complex mosaic of determinants and challenges of public health. IE is a rare condition associated with endocardial infection, but associated with high morbidity and mortality.^{1,2,4-6} The incidence of IE is estimated at 3-10 cases per 100,000 people, but an increase in its incidence has been observed in the last decade (13.8/100,000), especially in tropical countries and Latin America.^{4,5,7} Associated with the case, an increase in mortality was also observed in the period 1990–2019, ranging from 0.7 to 0.9 per 100,000, with Latin America, Oceania, and North America being the regions with the highest mortality rates in 2019.^{5,7}

The increase in mortality due to IE found in this study is in line with recent studies and may be related to recent changes in the epidemiological profile. In a period of about 30 years, mortality due to endocarditis increased by about 2.3 times,

both in men and women, which reflects population growth and the maintenance of high morbidity and mortality.^{1,5} Although there has been an improvement in the population's standard of living, with greater availability of antibiotics to combat rheumatic fever, other risk factors stand out, such as advanced age, comorbidities, cardiac devices, and prosthetic valves.^{1,5} In addition, there is an increase in mortality due to nosocomial endocarditis, which varies between 17-30%, a fact also observed in the present study, in which about 97% of deaths occur in the hospital environment.¹ The vast mortality observed in the hospital environment is explained by several additional risk factors, such as: etiology caused by *Staphylococcus aureus*, negative blood cultures, valve abscess, heart failure secondary to IE, and septic shock.⁷ Thus, considering the great impact of endocarditis and its diagnostic complexity, the optimization of its evaluation and treatment is essential to avoid undesirable clinical outcomes, and specialized and multidisciplinary protocols can be used according to the severity of the condition.

In general, corroborated by the world literature, the incidence of IE is higher in men, which may explain the marked predominance of males as victims of the disease (61.2%) observed in this study.² As a result, it is reported by Urina-Jassir et al,⁵ that there was a predominance of males in 68.5% of the cases, a situation confirmed by Yang et al,⁵ who observed an incidence of 16.2/100,000 in men, compared to 11.6/100,000 in women in 2019. This can be explained by the presence of associated risk factors. Thus, a large percentage of cases are related to preexisting heart disease, mainly valve disease, prosthetic valves, rheumatic heart disease, and congenital heart diseases. Although the epidemiological panorama is different between countries with unequal socioeconomic levels, rheumatic heart disease remains an important cause of mortality in developing countries. It is noteworthy that in developed countries, the presence of intracardiac implantable devices, as well as the use of intravenous medications, diabetes and cancer, have replaced rheumatic heart disease as the main risk factors.^{2,5}

In addition, another factor that draws attention is the prevalence of mortality due to acute and subacute IE in elderly individuals. Recent studies have proven an increase in the burden of diseases, especially in individuals over 60 years of age,⁵ which clarifies the high death rates evidenced between 60 and 69 years of age in this study. This significant increase in old age is multifactorial and refers both to immunosenescence, observed in this population, and to the consequences of their comorbidities.^{5,8,9} With the increase in life expectancy, the population lives longer with multiple comorbidities, degenerative valve diseases, as well as being more susceptible to interventional treatments, such as cardiac device implants (pacemakers) and hemodialysis, which are known risk factors for the disease in question.⁵ In

addition, the high mortality in this population segment is explained by their nutritional deficiencies, as well as their reduced functional capacity, which are recognized as independent predictors of mortality. Thus, it is clear that the disproportion in the mortality of elderly patients is related to multiple comorbidities, long hospitalization and medical devices, requiring a multidisciplinary approach based on increasing the response capacity of the health system due to the variation in epidemiological profiles and considering that the global population aged 80 years and over tends to triple between 2017-2050. Nevertheless, associating early discharge with oral therapies is beneficial because it has been shown to be non-inferior to intravenous therapy exclusively for gram-positive bacteria in IE.⁸

In addition, the incidence of deaths from acute and subacute endocarditis reflects a dispersed pattern, with varied and heterogeneous prevalence in the Brazilian regions, with higher mortality rates in the South, Southeast, and Midwest regions, proven by the smoothing of crude rates by the local empirical Bayesian method and by the analysis of spatial clusters. Due to the lack of national studies on this specific point, such a spatial pattern of unequal distribution of mortality due to IE may be indicative, in part, of variations in living conditions and demographic profiles, in the distribution of health resources, as well as socioeconomic inequalities. This finding may represent the existing difference in access to resources in Brazil, evidencing how health disparities may be rooted in socioeconomic differences, shaping the risk of multifactorial diseases and the responsiveness of the health system due to the monopolization of resources. This fact raises questions about equity in access to health, since the low prevalence of deaths in other regions of the country may be caused by the complete absence of diagnosis, mainly due to precarious access to diagnostic structures and, consequently, underreporting of cases. Therefore, in view of the great diagnostic challenge and increase in incidence and mortality rates, it is clear the need for intervention programs that prioritize, from health promotion to the optimization of access to quality medical care services, and should therefore be multidisciplinary and intersectoral in order to ensure equity in public health.

The association observed between lower schooling and higher mortality from IE consistently reflects the role of social determinants of health in the clinical outcomes of the disease. Large-scale population studies have shown that low educational attainment is independently associated with increased mortality from cardiovascular and infectious causes, even after adjusting for age, sex, and other risk factors, evidencing schooling as a structural determinant of health.^{9,10} Individuals with lower education have greater exposure to risk factors, lower health literacy, and greater difficulty in recognizing early symptoms and seeking timely medical care, which favors late

diagnosis and worse prognosis.¹¹ In addition, low education is often associated with unfavorable socioeconomic conditions, a higher prevalence of chronic comorbidities, and lower adherence to treatment, factors known to be related to increased cardiovascular and infectious mortality.¹² The literature also indicates that populations with lower educational levels are more vulnerable to severe infections and unfavorable clinical outcomes, especially in the elderly and those with chronic diseases. Thus, the findings of this study reinforce that the higher mortality from IE among individuals with low education is not limited to isolated biological factors, but reflects persistent social inequalities, highlighting the need for public policies aimed at strengthening health literacy, expanding access to specialized services, and reducing educational inequities as a strategy to mitigate mortality associated with the disease.⁹⁻¹¹

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. Associated with this, there is a limitation in the analysis of information on population estimates through the indirect method, as the last census dates from 2010. The results found for the general population may not be repeated 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 underestimation of deaths from acute and subacute endocarditis,

Thus, the temporospatial analysis allowed the identification of the Brazilian regions with high mortality from endocarditis and the differences between the mortality rates for acute and subacute endocarditis between the municipalities of the state. 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 endocarditis aggravations.

CONCLUSION

Mortality from acute and subacute endocarditis in Brazil showed a slight increase between 2001 and 2021, with heterogeneous spatial distribution and greater concentration in the South and Southeast regions. Deaths predominantly affected elderly individuals, males and those with a lower level of education, evidencing the influence of clinical and social determinants on disease outcomes. The presence of significant spatial autocorrelation reinforces the need for integrated regional strategies,

aimed at strengthening early diagnosis, qualifying hospital care, and reducing inequalities in access to health services, with the aim of mitigating mortality associated with infective endocarditis in the country.

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ICU and antimicrobial resistance: how to face an ever-increasing challenge?

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REVIEW ARTICLE

ICUs AND ANTIMICROBIAL RESISTANCE: HOW TO FACE AN EVER-GROWING CHALLENGE?

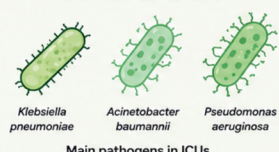
Analysis of the epidemiological dynamics, risk factors, and prognostic impact of antimicrobial resistance in intensive care units

METHOD

- Integrative literature review
- 20 studies analyzed
- Different ICU settings
- Focus: healthcare-associated infections and bacterial resistance

MAIN FINDINGS

PREDOMINANCE OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACILLI



ASSOCIATED WITH GREATER SEVERITY AND MORTALITY



Bloodstream infections and ventilator-associated pneumonia show the worst outcomes

RISK FACTORS

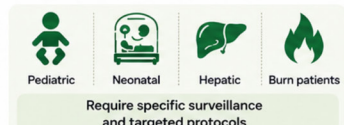
- Prolonged use of invasive devices (mechanical ventilation, central catheter, urinary catheter)
- Prior exposure to broad-spectrum antibiotics
- Nursing staff overload increases cross-transmission

CENTRAL MESSAGE

- Facing antimicrobial resistance in ICUs requires a continuous multidisciplinary approach:
- ✓ Rational use of antimicrobials (stewardship)
- ✓ Rapid diagnosis and epidemiological surveillance
- ✓ Rigorous adoption of preventive measures (bundles)
- ✓ Adequate staffing of healthcare teams

Integrated strategies save lives, reduce costs, and improve outcomes.

MOST VULNERABLE PATIENTS



CLINICAL AND HEALTHCARE IMPACT



OBJECTIVE OF THE STUDY
Analyze the epidemiology, pathogens, risk factors, and prognostic impact of antimicrobial resistance in ICUs.

“Hospital infections in ICUs are preventable. Understanding them is the first step to controlling them.”

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Central Message

Antimicrobial resistance in Intensive Care Units is dominated by Gram-negative bacilli, such as *Klebsiella pneumoniae* and *Acinetobacter baumannii*, which have high mortality rates. The review highlights that long-term use of invasive devices and prior exposure to broad-spectrum antibiotics are the main triggers for these infections. In addition, structural factors, such as nursing staff overload, directly impact cross-bacterial spread. Effective control requires constant epidemiological surveillance and the adoption of rapid molecular diagnostic technologies.

Perspective

The findings reinforce that the mitigation of multidrug resistance in intensive care units depends on a multidisciplinary approach that transcends the prescription of new antibiotics. In clinical practice, the rigorous implementation of packages of preventive measures (bundles) and the rational management of antimicrobials (stewardship) are vital to stop the selective pressure on the hospital microbiota. The adequacy of the sizing of health teams emerges as an administrative intervention with a direct impact on patient safety, reducing fatal outcomes and optimizing the length of hospital stay in highly complex environments.

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ABSTRACT

Introduction: Antimicrobial resistance in critical care units represents one of the main challenges of health care, associated with high morbidity and unfavorable prognostic impact.

Objective: To analyze the epidemiological dynamics, microbiological profile, risk factors, and prognostic impact of antimicrobial resistance in intensive care units, considering different patient profiles.

Method: This is an integrative literature review based on the analysis of 20 scientific articles that investigated healthcare-associated infections, pathogen prevalence, and bacterial resistance in different critical care settings.

Results: There was a predominance of gram-negative bacilli, especially microorganisms associated with high clinical severity, especially in ventilator-associated lung infections and bloodstream infections. Patients in specialized units, such as burns, pediatric, neonatal, and liver units, showed specific vulnerabilities. In addition, inadequacies in the nursing team sizing were associated with increased risk of microorganism dissemination.

Conclusion: The reduction of antimicrobial resistance in these contexts requires an integrated approach, including programs for the rational use of antimicrobials, incorporation of rapid diagnostic methods, strict adherence to preventive measures, and adequacy of the workload of health professionals.

KEYWORDS: Nosocomial infection. Bacterial drug resistance. Critical Care. Sepsis.

INTRODUCTION

Nosocomial infections, also known as healthcare-associated infections, represent one of the greatest challenges in contemporary intensive care medicine. Intensive care units (ICUs) house patients who are in broad clinical severity, requiring therapeutic interventions that, paradoxically, compromise their natural defenses. The prolonged use of mechanical ventilation, central venous catheters, and bladder tubes, which creates direct entry points for opportunistic pathogens, results in infection rates significantly higher than those observed in general wards.^{1,2}

In recent decades, the epidemiology of these infections has undergone critical transformation due to the emergence and global spread of multidrug-resistant bacterial strains. Multicenter studies have shown that gram-negative bacilli, notably *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, have become endemic in many hospitals.²⁻⁴ The production of inactivating enzymes, such as extended-spectrum beta-lactamases and carbapenemases, confers on these microorganisms the ability to resist the main classes of antibiotics available, drastically limiting empirical and definitive therapeutic options.⁵⁻⁷

The impact of this resistance transcends isolated treatment failure. Infection by multidrug-resistant bacteria in critically ill patients is associated with a substantial increase in mortality, prolonged ICU stay, and exponential increase in hospital costs.^{2,3,8} Transmission dynamics are aggravated in highly susceptible subpopulations. In burn units, loss of the skin barrier and systemic immunosuppression facilitate fulminant infections by environmental pathogens.⁹⁻¹¹ Similarly, pediatric patients, premature newborns in neonatal ICUs, and pre-transplant hepatopathic patients face disproportionate risks in the face of exposure to hospital strains.^{1,6,12,13}

Despite advances in infection control policies, the literature points to systemic gaps that perpetuate the spread of resistance. Excessive and often

inappropriate prescribing of broad-spectrum antimicrobials generates strong selective pressure on the patient's microbiota and the environment.^{3,5,7} At the same time, structural factors, such as the work overload of nursing teams, have been increasingly recognized as determining variables in the breakdown of contact protocols and in the occurrence of outbreaks.^{14,15} Understanding the intersection between the epidemiological profile of pathogens, host susceptibility, and the ICU environment is essential for the design of effective containment strategies.

METHOD

This is an integrative review, carried out in the PubMed database, whose formulation of the guiding question and eligibility criteria was based on the PICO strategy: P (Population) – patients hospitalized in Intensive Care Units (ICUs); I (Intervention/Exposure) – nosocomial infections by multidrug-resistant bacteria; C (Comparison) – not applicable / patients without infection or with susceptible infections; O (Outcomes) – associated risk factors, clinical impact, and mortality. As this is a literature review, the study is exempt from evaluation by the Institutional Research Ethics Committee.

The structured search used the combination of the following keywords (DeCS/MeSH) and their corresponding terms: "Cross Infection", "Intensive Care Units", "Drug Resistance, Multiple", "Bacterial Infections" and "Risk Factors" (Risk Factors). The inclusion criteria included original articles (clinical trials, observational cohort studies, retrospective, and prospective) and review articles published from 2003 to March 2025, in Portuguese and English, available in full text. Articles that did not address the topic of multidrug-resistant bacterial infections in the context of intensive care, or that did not present specific data on prognosis, risk factors, or infection control strategies, were excluded. In total, 20 articles were selected to compose this review (Table).

RESULTS

The consolidated analysis of the studies reveals that infections in ICUs are mostly driven by Gram-negative bacilli, which have supplanted Gram-positive cocci in prevalence and complexity of management in several regions.^{2,4,16,17}

Microbiological profile and resistance

The carbapenemase-producing *Klebsiella pneumoniae* and the multidrug-resistant

Acinetobacter baumannii emerge as the most critical pathogens. In large university hospitals, the prevalence of extended-spectrum beta-lactamase-producing *K. pneumoniae* and *Escherichia coli* has shown a sustained annual increase, complicating the empirical approach to bloodstream infections.¹⁸ The scenario is aggravated by the identification of genetic determinants of extreme resistance, such as the blaNDM-1, mcr-1, and blaKPC-2 genes, which

TABLE — Summary of the studies incorporated in this review¹⁻²⁰

Author(s)	Title	Periodical	Objectives	Conclusion
Marin H. Kollef and Carey-Ann D. Burnham (2017)	Ventilator-Associated Pneumonia: The Role of Emerging Diagnostic Technologies	Semin Respir Crit Care Med	To assess the impact of antimicrobial resistance and the role of novel rapid diagnostic technologies in ventilator-associated pneumonia.	Integrating rapid diagnostic tests into protocols maximizes clinical benefits and minimizes bacterial resistance.
J. Yang et al. (2025)	Prognosis analysis and infection-related risk factors of multi-drug-resistant bacteria isolated from a general hospital in China, 2019-2023	Journal of Hospital Infection	To analyze detection trends, prognosis, and risk factors for nosocomial infections by multidrug-resistant bacteria.	The high lethality requires rigorous clinical attention in ICUs and better supervision of antimicrobial use.
Alison J. Carey et al. (2008)	Hospital-Acquired Infections in the NICU: Epidemiology for the New Millennium	Clinics in Perinatology	To describe the epidemiology and propose best practices for the prevention and diagnosis of nosocomial infections in neonatal ICUs.	Rigorous preventive strategies and the use of lumbar puncture are essential in the evaluation of neonatal sepsis.
Xinlong Zhou et al. (2025)	Genome drafting of nosocomial infection CRE <i>Klebsiella pneumoniae</i> confirming resistance to colistin...	Frontiers in Cellular and Infection Microbiology	To investigate the genome of carbapenem-resistant <i>K. pneumoniae</i> isolated during an outbreak in neonatal ICU.	The complexity of outbreaks requires continuous genomic surveillance and strict infection control to avoid therapeutic failures.
Haifaa Hassan Al-Mousa et al. (2016)	Device-associated infection rates, bacterial resistance, length of stay, and mortality in Kuwait: International Nosocomial Infection Consortium findings	American Journal of Infection Control	To report the rates of device-associated infection, bacterial resistance, and mortality in ICUs in Kuwait.	The high infection rates underscore the urgent need to strengthen rigorous infection control programs.
Ziyaettin Karakuzu et al. (2018)	Prognostic Risk Factors in Ventilator-Associated Pneumonia	Med Sci Monit	To analyze the clinical and laboratory factors that affect the prognosis of patients diagnosed with ventilator-associated pneumonia in the ICU.	The SOFA score was shown to be a strong predictor of mortality, and should be continuously monitored for prognostic evaluation.
Elham A. Hassan et al. (2018)	Health care-associated infections in pre-transplant liver intensive care unit: Perspectives and challenges	Journal of Infection and Public Health	To assess the incidence, risk factors, and infection-causing microorganisms in patients with end-stage liver disease.	The high prevalence of multidrug resistance requires effective surveillance, active control measures, and strict antibiotic use policies.
Wendy Irene Sligl et al. (2015)	Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes	International Journal of Infectious Diseases	To describe the epidemiology, susceptibility, and clinical outcomes of ICU-acquired Gram-negative bacteremia.	The high mortality of these bacteremias requires the adoption of appropriate empirical therapy and greater attention to the management of comorbidities.
Abdelraouf A. Elmanama et al. (2013)	Antimicrobial susceptibility of bacterial isolates from burn units in Gaza	Burns	To determine the susceptibility profile of bacteria isolated in clinical and environmental samples from burn units.	The prevalence of multidrug-resistant strains, especially MRSA, requires the immediate implementation of strict infection control measures.
Beomjoon, Kim et al. (2020)	Nosocomial <i>Acinetobacter baumannii</i> infection in children in adult versus pediatric intensive care units	Pediatrics International	To compare the incidence of <i>A. baumannii</i> infection in pediatric patients treated in adult ICUs versus pediatric ICUs.	Paediatric ICUs provide a safer care environment, significantly reducing the risk of nosocomial infections in children.
Oral, Öncül et al. (2014)	Nosocomial infection characteristics in a burn intensive care unit: Analysis of an eleven-year active surveillance	Burns	To describe the rates of nosocomial infection, risk factors, and the bacterial resistance profile in a burn ICU.	The increased risk associated with the burned area makes it vital to know the local microbiological profile to direct appropriate treatment.
Min Xu and Jing Zeng (2024)	Analysis of factors influencing the risk of secondary infection in patients colonized or infected with multidrug-resistant Gram-negative bacteria...	Microbial Pathogenesis	To investigate the factors that influence the emergence of secondary infections in patients with multidrug-resistant Gram-negative bacteria.	The adoption of infection control measures and the rational use of antibiotics are essential to minimize secondary risks.
Ilker Onguc Aycan et al. (2015)	Bacterial colonization due to increased nurse workload in an intensive care unit	Brazilian Journal of Anesthesiology	To evaluate the possible association between the high workload of the nursing team and the development of nosocomial infections in the ICU.	Excessive workload increase and undersizing of staff directly correlate with a higher risk of infection.
Peter Agaba et al. (2017)	Nosocomial bacterial infections and their antimicrobial susceptibility patterns among patients in Ugandan intensive care units: a cross sectional study	BMC Research Notes	To describe the common bacterial infections, resistance patterns, and factors associated with nosocomial infection in Ugandan ICUs.	The high bacterial multi-resistance in critical units reinforces the strict need for antibiotic surveillance and infection control.
D.A. Enoch et al. (2008)	Investigation and management of an outbreak of multidrug-carbapenem-resistant <i>Acinetobacter baumannii</i> in Cambridge, UK	Journal of Hospital Infection	To describe the investigational measures and practical management of an outbreak of multidrug-resistant <i>A. baumannii</i> occurring in intensive care units.	Successful control of the clinical outbreak required a multidisciplinary approach, rapid isolation of patients, and deep environmental cleansing.
V. Bonnet et al. (2019)	Influence of bacterial resistance on mortality in intensive care units: a registry study from 2000 to 2013 (IICU Study)	Journal of Hospital Infection	To assess the direct influence of antibiotic resistance on mortality in patients admitted to intensive care units.	Infections by resistant strains are independently and significantly associated with increased length of hospital stay and mortality.
S. G. Santucci et al. (2003)	Infections in a burn intensive care unit: experience of seven years	Journal of Hospital Infection	To analyze the epidemiological characteristics and record the rates of nosocomial infections in a burn ICU over seven years.	The high rate of infections in these patients highlights the need for continuous surveillance strongly focused on the use of invasive devices.
Sanwar M. Mitharwal et al. (2016)	Intensive care unit-acquired infections in a tertiary care hospital: An epidemiologic survey and influence on patient outcomes	American Journal of Infection Control	To study the epidemiological patterns of ICU-acquired infections and identify their direct impact on patients' clinical outcomes.	The high incidence of infections caused by resistant pathogens is strongly associated with prolonged mechanical ventilation time.
M. Nagao (2013)	A multicentre analysis of epidemiology of the nosocomial bloodstream infections in Japanese university hospitals	Not informed in the article	To analyze current epidemiological trends and resistance profile in bloodstream infections in university hospitals.	Additional efforts are needed to promote serial blood culture collection and significantly improve the prognosis of these infections.
Zhe Wang et al. (2018)	Risk Factors for Carbapenem-resistant <i>Klebsiella pneumoniae</i> Infection and Mortality of <i>Klebsiella pneumoniae</i> Infection	Not informed in the article	To identify primary risk factors and predictors of mortality in infections caused by carbapenem-resistant <i>K. pneumoniae</i> .	The protection of patients' immune function and the adoption of control measures are essential to reduce the risks and lethality of the condition.

confer resistance even to last-line agents in outbreaks within neonatal units.⁶ In prolonged outbreaks, carbapenem-resistant strains of *A. baumannii* demonstrate a remarkable ability to persist in the abiotic ICU environment, requiring drastic infection control interventions for their eradication.¹⁵

Clinical and structural risk factors

The literature is unanimous in pointing to the use of invasive devices as the main catalyst for nosocomial infections. The risk of ventilator-associated pneumonia and central catheter-associated bloodstream infections increases proportionally to the patient's exposure to these interventions.^{2,17,19} Prior use of broad-spectrum antimicrobials acts as a strong independent predictor for superinfection or subsequent colonization by multidrug-resistant pathogens.^{3,7,20} It was evidenced that the increase in the workload of the nursing team and the undersizing of personnel are positively correlated with the increase in the rates of cross-colonization by multidrug-resistant bacteria, demonstrating that structural failures sabotage hygiene and contact precaution practices.¹⁴

Outcomes and mortality

Mortality associated with infections by multidrug-resistant microorganisms in ICUs is severe. Patients who develop resistant bacilli sepsis or nonsusceptible pathogen pneumonia have considerably lower survival rates than those infected with susceptible strains.^{2,16,20} The prognosis is particularly bleak when initial empirical antimicrobial therapy is inadequate, which occurs with high frequency in the face of Gram-negative bacteria with complex resistance profiles.^{4,5,16}

Specific scenarios and vulnerable populations

Epidemiology varies depending on the ICU profile. The Burn Units are characterized by rapid colonization of wounds by aggressive environmental bacteria, with the massive presence of *P. aeruginosa* and *A. baumannii* with extreme resistance, making grafting difficult and increasing mortality.⁹⁻¹¹ In pediatric and neonatal ICUs, newborns and children admitted to adult ICUs are at higher risk of acquiring hospital strain infections than those allocated to strictly pediatric units.¹³ In these populations, immune immaturity transforms bloodstream infections into rapidly fatal events.^{1,6} For patients with liver disease in pre-liver transplant ICUs, the incidence of infections is driven by the inherent deficiency of the immune system resulting from liver failure, making secondary infections a critical barrier to transplant viability.¹²

DISCUSSION

The synthesis of evidence reaffirms that the ICU is not only the place of treatment for the most serious

infections, but also the main cradle for the selection of bacterial resistance mechanisms. The convergence of data demonstrates that prolonged hospital stays and previous exposure to carbapenems are universal variables for the development of sepsis by multidrug-resistant strains, regardless of the geographic location of the study.^{2,3,7,20}

A fundamental aspect raised by the literature is the distinction in the management of primary versus secondary infections. Patients who are admitted to the ICU already colonized by resistant bacteria have an exponentially higher risk of developing active systemic infections during hospitalization, which reinforces the need for surveillance cultures at admission.²⁰ The high mortality observed in cases of ventilator-associated pneumonia underlines the severity of lung inflammation triggered by pathogens such as *A. baumannii*, which often frustrates traditional therapeutic regimens.^{5,19}

The divergences found in the literature refer mainly to the dominant microbial etiology in specific niches. While general ICUs report growing concerns about enterobacteria that produce resistance,^{2,4,7,17} burn units face a continuous challenge with non-fermenting pathogens, which persist in the environment due to protein-rich eschar and constant tissue manipulation.⁹⁻¹¹ This indicates that prophylaxis and empirical treatment protocols cannot be universalized, and must be strictly guided by the local epidemiology of the unit.

To reverse the current scenario of escalating resistance, the analysis points to solutions that go beyond the simple discovery of new antibiotics. Human resource management emerges as a direct health intervention: adjusting the ratio of nurses per bed is vital to ensure that basic measures, such as hand hygiene and care with catheter insertions, are strictly complied with, interrupting the chain of cross-transmission.¹⁴ In addition, the implementation of preventive measures has proven to be a highly effective strategy, resulting in sustained declines in infection rates in hospitals in developing countries.² In the diagnostic and therapeutic realm, the future requires the integration of ultra-rapid microbial identification technologies with institutional antimicrobial stewardship programs. These initiatives allow for early de-escalation of the antibiotic by adjusting the therapy to the narrowest possible spectrum, which saves the life of the critically ill patient and simultaneously protects the ICU ecosystem from selective pressure.⁵ The implications of these findings reinforce the urgent need to implement antimicrobial stewardship protocols and strengthen contact precautionary measures, aiming to reduce morbidity and mortality rates and hospital costs associated with bacterial resistance.

The limitations of this study include the qualitative nature of the review and the temporal and idiomatic constraints in the selection of articles, which may have omitted specific regional epidemiological data from areas with a lower volume of indexed

publications. Despite this, the study offers an updated overview that can guide clinical decisions and the development of infection control policies in critical care units.

CONCLUSION

Healthcare-associated infections caused by multidrug-resistant bacteria pose a threat to the survival of patients in ICUs. The literature review confirms that highly virulent and resistant Gram-negative pathogens are the main responsible for the increase in lethality rates, prolonged hospitalizations, and treatment failures, especially in the context of mechanical ventilation and central vascular accesses. Specific populations, such as large burns and neonates, are disproportionately affected by this phenomenon. In view of the imminent exhaustion of the classical therapeutic arsenal, the clinical implications of this study reinforce that the control of multidrug resistance requires action on multiple fronts. It is imperative that healthcare institutions invest in continuous epidemiological surveillance, the adoption of rapid molecular diagnostic technologies, and the structuring of effective antimicrobial stewardship programs. In addition, the literature demonstrates that the adequacy of nursing team sizing and the rigorous application of prevention packages are not only administrative measures, but vital and scientifically validated interventions to cut the chain of transmission and ensure the safety of critical patients.

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Robotic telesurgery: technological fundamentals, clinical applications and perspective

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TELECIRURGIA ROBÓTICA

Fundamentos tecnológicos, aplicações clínicas e perspectiva

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Central Message

The progressive introduction of highly complex technologies in surgical practice has promoted significant transformations in the current paradigms of patient care, medical training, and translational research. In this context, robotic surgery stands out not as a simple evolution of conventional laparoscopy, but as an integrated technological architecture, which brings together mechanical precision, advanced digital control, real-time data communication, and high-definition imaging systems.

Perspective

More than representing a minimally invasive approach, robot-assisted bariatric surgery is a strategic component of the digitalization of surgical procedures. The future incorporation of these systems into telesurgery platforms has the potential to expand access to specialized care, boost new educational models, and consolidate lines of research in surgery, as long as their adoption occurs in a progressive, judicious, and safety-based manner.

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ABSTRACT

Introduction: Robotic bariatric surgery has established itself as a safe and effective approach for the treatment of severe obesity. At the same time, recent advances in connectivity and digital infrastructure have rekindled interest in telesurgery as a strategy to expand access to specialized surgery, especially in scenarios of inequality in the distribution of centers of excellence.

Objective: To discuss robotic bariatric surgery as a strategic platform for the development of telesurgery, with emphasis on its implications for care, medical education and academic research.

Method: Review of the fundamentals of robotic bariatric surgery, the conceptual evolution of telesurgery and the potential of bariatric surgery as a model applicable to remote interventions, discussing the impacts on the formation and supervision of surgical teams, the main technical challenges in addition to the ethical, legal and regulatory issues involved in the implementation.

Results: Considering only articles that were more related to the theme, the full texts were read and 21 articles were included.

Conclusion: Robotic bariatric surgery goes beyond the role of a minimally invasive technique and is a central element in the digital transformation of surgery. Its progressive integration into telesurgery can contribute to the democratization of access, innovation in teaching, and strengthening of surgical research as long as it is implemented gradually and safely.

KEYWORD: Telesurgery. Robotic surgery. Medical robotics. Innovation in health.

INTRODUCTION

The continued incorporation of advanced technologies into surgical practice has profoundly reshaped contemporary models of patient care, medical education, and translational research. Among these innovations, robotic surgery has emerged, not only as an incremental refinement of laparoscopy, but as a technological platform capable of integrating precision mechanics, digital control systems, real-time data transmission, and advanced imaging.¹⁻⁵

In bariatric and metabolic surgery, robot-assisted procedures have progressively demonstrated safety, feasibility, and reproducibility, especially in technically demanding scenarios, such as revisional surgery, superobese patients, and more complex sutures.^{2,6-9} However, the relevance of robotic platforms goes beyond operational ergonomics or dexterity.

Although telesurgery was conceptually introduced more than two decades ago, its widespread clinical adoption has historically been limited by constraints related to communication latency, network reliability, cybersecurity, and systems costs.^{1,10} Recent advances in high-speed connectivity, low-latency networks, encryption protocols, and reliability of robotic systems have redefined the viability of remote surgical applications.^{4,11} These advances position robotic bariatric surgery as a particularly relevant field for telesurgery within a modern and realistic framework.^{3,4,9,12}

Given the global burden of obesity, the uneven geographic distribution of specialized bariatric surgeons, and the standardized nature of many bariatric procedures, it is reaffirmed that robotic bariatric surgery represents an attractive model to explore the integration of telesurgery into clinical practice, academic training, and research.^{3,7-9,12}

This article aimed to discuss robotic bariatric surgery as a strategic platform for telesurgery, emphasizing its implications for multidisciplinary medical education and scientific research.

METHOD

Integrative review made by collecting information for reading and analysis from online research on virtual platforms. Initially, a search was carried out for DECIs descriptors related to the theme, using the following keywords: "telesurgery, robotic surgery, medical robotics, health innovation" with AND or OR search, considering the title and/or abstract; The chosen ones were read in full. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms. Afterwards, considering only those that were more related to the theme, the full text was read (Table).

RESULTS

The bibliographic search allowed the identification of studies with different approaches, ranging from the historical milestone of telesurgery to contemporary applications of robotics in bariatric surgery, surgical training, advanced connectivity and ethical-regulatory challenges. After reading the titles, abstracts and full texts, 21 articles were selected with greater adherence to the objective proposed in this review (Table).

DISCUSSION

Robotic bariatric surgery: beyond a surgical technique

Robotic bariatric surgery has evolved from an alternative minimally invasive approach to a mature surgical modality with distinct technical and educational attributes. While the core principles of bariatric procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy remain unchanged, robotic systems offer enhanced visualization, articulated instrumentation, tremor filtering, and improved surgeon ergonomics.^{2,6,7}

From an academic point of view, the importance of robotic bariatric surgery lies in its potential for standardization. Robotic platforms enable the consistent execution of critical operational steps, facilitating reproducibility between institutions and

TABLE — Preferred metadata of the review carried out¹⁻²¹

Author (year)	Article Title	Objectives	Conclusion
Marescaux et al. (2001) ¹	Transatlantic robot-assisted telesurgery	To evaluate the technical feasibility and safety of long-range robotic telesurgery, including transoceanic experimental model and clinical application in robot-assisted laparoscopic cholecystectomy.	The study demonstrated that transatlantic robotic telesurgery was technically feasible and safe under controlled conditions, with total latency of about 155 ms, paving the way for expanding remote access to surgical expertise.
Hung et al. (2019) ²	Deep learning on automated performance metrics and clinical features to predict urinary continence recovery after robot-assisted radical prostatectomy	To develop a deep learning model capable of predicting urinary continence recovery after robot-assisted radical prostatectomy, using automated metrics of surgical performance and clinicopathological characteristics, in addition to evaluating the relationship between surgeon technical performance and functional outcomes.	The DeepSurv model was able to predict urinary continence recovery after RARP, and surgeons with more efficient automated performance metrics had better urinary continence rates at 3 and 6 months, reinforcing the usefulness of objective metrics and artificial intelligence in assessing surgical quality.
Dimou et al. (2021) ³	Understanding the Current Role of Robotic-Assisted Bariatric Surgery	To identify temporal trends in the use of robotic bariatric surgery between 2015 and 2018 and to analyze the patient factors associated with the choice of the robotic approach in sleeve gastrectomy and Roux-en-Y gastric bypass.	Robotic bariatric surgery increased in the period studied, but still represented less than 10% of the procedures. The use of the robotic platform was associated with some specific clinical profiles, but the reasons for this selection are not yet fully understood, requiring further studies to better define its indications.
Mohan et al. (2021) ⁴	Telesurgery and Robotics: An Improved and Efficient Era	Review current advances in telesurgery and robotic surgery, highlighting benefits, limitations, and future perspectives related to connectivity, latency, haptic feedback, and new technologies such as 5G and IoT.	Telesurgery is a promising strategy to expand surgical access with greater precision, especially in remote areas, but its expansion still depends on reducing latency, improving haptic feedback, technological safety, reducing costs, and addressing legal and ethical issues.
Rosa et al. (2024) ⁵	Impact of videosurgery training of general surgery residents in a low-fidelity simulator adapted from the Fundamentals of Laparoscopic Surgery (FLS) program	To evaluate the impact of theoretical-practical training in videosurgery, with a low-fidelity simulator adapted from the FLS, on the skill acquisition of first- and second-year general surgery residents, comparing performance before and after training and in relation to a control group of experienced surgeons.	The training promoted a significant improvement in the technical performance of residents in both groups. First-year residents, after training, achieved similar performance to the initial performance of second-year residents, suggesting that sequenced training with a low-fidelity simulator can accelerate the acquisition of skills in videosurgery.
de Barros et al. (2023) ⁶	Robotic versus laparoscopic Roux-en-Y gastric bypass: a retrospective study in a single center	To compare patients undergoing Roux-en-Y gastric bypass by robotic versus laparoscopic approaches, at a single center and by a single surgeon, analyzing surgical time, length of hospital stay, and postoperative complications.	The robotically operated group had a shorter surgical time and a shorter hospital stay, with no differences in stenosis, bleeding or fistula, suggesting that robotic gastric bypass is a safe and potentially advantageous alternative in specialized centers.
Spurzem et al. (2024) ⁷	Robotic bariatric surgery reduces morbidity for revisional gastric bypass when compared to laparoscopic: outcome of 8-year MBSAQIP analysis of over 40,000 cases	To evaluate the use of robotic surgery in revisional bariatric surgery and to compare perioperative outcomes at 30 days between laparoscopic and robotic approaches, especially in revisional sleeve gastrectomy and revisional Roux-en-Y gastric bypass, based on the MBSAQIP database from 2015 to 2022.	The use of the robotic platform has progressively increased in revisional bariatric surgery. In cases of revisional gastric bypass, the robotic approach was associated with lower postoperative morbidity and shorter hospital stay when compared to the laparoscopic approach, although with longer operative time, suggesting a potential benefit of robotics in more complex revisional cases.
Pastrana et al. (2020) ⁸	Outcomes of robotic bariatric surgery in super-obese patients: first report based on MBSAQIP database	To compare the safety and short-term outcomes of robotic versus laparoscopic bariatric surgery in superobese patients, based on the MBSAQIP database from 2015 to 2017.	In superobese patients, the robotic approach had 30-day outcomes similar to those of laparoscopy, with no clear clinical benefit in safety or short-term complications, although both techniques showed worse results in this group when compared to non-superobese obese patients.
Guérios et al. (2021) ⁹	Impact of bariatric surgery on lipid and glycemic profile in obese patients	To evaluate the impacts of bariatric surgery on anthropometric, metabolic and biochemical parameters of obese patients, comparing preoperative data with 3 and 6 months postoperatively.	Bariatric surgery was effective in reducing anthropometric and metabolic parameters, with a significant decrease in total cholesterol, LDL, triglycerides, fasting glucose, glycated hemoglobin and insulin in the postoperative period.
Anvari et al. (2005) ¹⁰	Establishment of the World's First Telerobotic Remote Surgical Service: For Provision of Advanced Laparoscopic Surgery in a Rural Community	To describe the implementation of the first regular hospital service of remote telerobotic surgery between a university hospital and a rural hospital, evaluating its feasibility for offering advanced laparoscopic surgery and collaboration between surgeons at a distance.	The study demonstrated that remote telerobotic surgery can be incorporated into clinical practice safely and effectively, with good collaboration among surgeons, absence of major intraoperative complications, and the potential to expand access to advanced laparoscopic procedures for rural communities.
Fan et al. (2023) ¹¹	Feasibility and Safety of Dual-console Telesurgery with the KangDuo Surgical Robot-01 System Using Fifth-generation and Wired Networks: An Animal Experiment and Clinical Study	To evaluate the feasibility and safety of telesurgery with double console using the KangDuo Surgical Robot-01 system, through animal experiment and clinical study, using 5G and wired networks.	Dual-console telesurgery proved to be feasible and safe both in the animal model and in the clinical study, with acceptable latency, packet loss of less than 1%, and absence of important intraoperative complications, suggesting potential clinical and educational application of this technology.
Vailloux et al. (2020) ¹²	A Review of the Role of Robotics in Bariatric Surgery: Finding Our Future?	To critically review the available literature on the use of robotic surgery in bariatric procedures, evaluating its impact on operative time, clinical outcomes, cost, and possible applications in specific subgroups, such as superobese and revision surgeries.	Most studies suggest that robotic bariatric surgery increases operative time and cost, with no clear generalizable benefit in outcomes. Still, it may play a promising role in more complex cases, such as super-obese patients, revisional procedures, and future applications associated with technological maturation and artificial intelligence.
Patel et al. (2024) ¹³	Technical and ethical considerations in telesurgery	Analyze the main technical, regulatory and ethical aspects involved in the implementation of telesurgery, focusing on network infrastructure, latency, security, data privacy, professional responsibility and doctor-patient relationship.	Telesurgery has great potential to expand access to surgical expertise, but its secure and large-scale adoption depends on robust, low-latency connectivity, cyber protection, technical standardization, and improved ethical and regulatory frameworks.
Dohler et al. (2025) ¹⁴	The crucial role of 5G, 6G, and fiber in robotic telesurgery	Analyze the role of 5G networks, future 6G networks, and fiber optic infrastructure in enabling robotic telesurgery, with a focus on latency, reliability, transmission requirements, network architecture, security, and smart hospital applications.	The study concludes that robotic telesurgery depends on very high-performance connectivity, and that the combination of 5G and fiber backbone represents the most appropriate solution to ensure low latency, high reliability, and scalability. In addition, it points out that 6G, artificial intelligence and smart hospitals tend to further expand the feasibility and clinical reach of telesurgery in the future.
Motiwala et al. (2025) ¹⁵	Telesurgery: current status and strategies for latency reduction	Review the current state of telesurgery, focusing on factors related to latency, its impacts on surgical performance, and proposed technological strategies for its reduction, including 5G/6G, artificial intelligence, edge computing, haptic feedback, and cybersecurity.	Latency remains one of the main barriers to the widespread adoption of telesurgery, and it is ideal to keep it below 200 ms. Advances such as 5G/6G networks, artificial intelligence, edge computing, and improved haptic feedback show potential to reduce this problem, but ethical, legal, regulatory, and safety challenges still need to be overcome to enable its large-scale application.
by Paula Loureiro et al. (2025) ¹⁶	Implementation of Robotic Telesurgery in Brazil: The First Experimental Remote Robot-Assisted Cholecystectomy in a Porcine Model, with High-Performance Fiber Optic Connection and 5G Redundancy between Campo Largo and Cascavel	To report the first telesurgery performed between two Brazilian cities, evaluating the technical feasibility and safety of a remote robotic cholecystectomy in a porcine model, with high-performance fiber optic connection and 5G redundancy between Campo Largo and Cascavel.	The study demonstrated that robotic telesurgery between two Brazilian cities was technically feasible and safe, with low latency, connection stability, and absence of technical-surgical complications, reinforcing the potential of this technology to expand access to specialized surgery in distant regions.
Carmo et al. (2023) ¹⁷	Late post-sleeve gastric fistula	To report a case of late gastric fistula after sleeve gastrectomy and to discuss the diagnosis and therapeutic management of this postoperative complication.	Conservative treatment with an endoscopic approach, including dilation of the narrowing area, proved to be effective in controlling late post-sleeve fistula, suggesting that it is an adequate alternative in selected cases, without the mandatory need for prosthesis or reoperation.
Trute et al. (2022) ¹⁸	Development of a Robotic Surgery Training System	Develop and describe a low-cost robotic surgery training system, with the possibility of local and remote use via the internet, incorporating teleoperation, haptic feedback and 2D/3D vision, aimed at surgical training and experimental research.	The proposed system proved to be viable as an accessible platform for training in robotic surgery and research, allowing remote teleoperation with acceptable latency in good quality networks, in addition to offering visual and haptic feedback. The authors conclude that the platform has the potential to expand access to robotic training, although it still requires future technical improvements.
Saikali et al. (2025) ¹⁹	Society of Robotic Surgery (SRS) special meeting in 2024: insights from the telesurgery consensus meeting	Present the key insights, collaborative proposals, and recommendations discussed at the Society of Robotic Surgery's global meeting on telesurgery, focusing on technical requirements, ethical issues, cybersecurity, regulation, training, and safe implementation of this practice on a global scale.	The meeting highlighted that the safe expansion of telesurgery depends on a multidisciplinary approach, with standardization of training and accreditation, improvement of hospital connectivity, specific regulatory framework and appropriate reimbursement models, reinforcing that the consolidation of telesurgery requires not only technical feasibility, but also ethical, legal and institutional alignment.
Frenkel (2023) ²⁰	Telesurgery's Evolution During the Robotic Surgery Renaissance and a Systematic Review of its Ethical Considerations	To review the recent evolution of telesurgery in the context of the revival of robotic surgery, to discuss its current trends of use, and to systematically analyze the main ethical considerations related to its adoption.	Telesurgery has the potential to expand access to safe, equitable, and high-quality surgical care, but its integration depends on addressing ethical, legal, regulatory, technical, and institutional barriers, with the active participation of surgeons and medical societies in the construction of this process.
Saikali et al. (2024) ²¹	Telesurgery: humanitarian and surgical benefits while navigating technologic and administrative challenges	Discuss the humanitarian and surgical benefits of telesurgery, as well as analyze the key technological, administrative, ethical, regulatory, and safety challenges involved in its implementation.	Telesurgery has the potential to expand equitable access to specialized surgery and favor the dissemination of surgical expertise, especially in remote areas. However, its wide and secure adoption depends on addressing barriers related to latency, connectivity, cybersecurity, regulation, informed consent, and institutional standardization.

operators. This standardization is particularly valuable for research settings and multicenter studies.^{2,7,8}

In addition, robotic systems naturally generate digital data related to instrument movement, operating time, force application, and workflow patterns. These data streams offer a unique opportunity for objective evaluation of surgical performance, skill acquisition, and learning curves in an area of increasing relevance in surgical education research.³

Thus, robotic bariatric surgery should be seen not only as a minimally invasive technique, but as an enabling technology for broader transformations in the delivery of surgical care.^{3,4}

Telesurgery: concept, evolution and current scenario

Telesurgery is defined as the performance of surgical procedures in which surgeon and patient are geographically separated, connected by robotic systems and advanced telecommunications networks.^{1,10} The historical milestone of telesurgery is known as "Operation Lindbergh" (2001), with cholecystectomy performed between New York, USA and Strasbourg, France.

For many years, telesurgery has remained largely experimental, limited by high latency, limited bandwidth, and concerns about safety, reliability, and legal liability.^{4,10}

Contemporary analyses reinforce that these limitations are not only technological, but also ethical and organizational. Recent reviews highlight that overcoming these barriers depends not only on the advancement of communication networks, but also on the adoption of clear regulatory frameworks, cybersecurity protocols, and ethical models adapted to the specificities of telesurgery.¹³

In recent years, however, the rapid expansion of fiber optic infrastructure, fifth-generation (5G) mobile networks, and secure data transmission protocols have substantially altered this scenario.^{4,11}

Dohler et al. in 2025¹⁴ highlighted that the introduction of 5G and 6G networks in telesurgery not only improves latency and reliability, but also offers a robust platform for the necessary advances in telesurgery. 5G networks in particular offer ultra-low latency and high data throughput, which are essential for critical modalities such as kinesthetic, audio-visual and tactile feedback, which are critical for performing precise remote surgical procedures.¹⁴

According to Motiwala et al. in 2025¹⁵, reducing latency is one of the main challenges that limits the feasibility of large-scale telesurgery. The paper reviews emerging strategies to minimize this delay, such as the use of 5G networks, artificial intelligence (AI)-driven latency compensation, and network infrastructure optimization. Such approaches are seen as fundamental to ensure greater precision, dexterity, and patient safety during teleoperated procedures.

Modern telesurgical paradigms now span the spectrum of remote interactions, including: 1) teleproctoring, in which an expert surgeon provides real-time guidance from a remote location; 2)

telementoring, involving structured educational support during in-person procedures; and 3) teleoperation, in which the surgeon directly controls the robotic system from a distant location.^{4,12}

Among them, telesurveillance and telementoring have already demonstrated practical applicability in bariatric surgery, especially for training, accreditation, and dissemination of expertise. Fully remote teleoperation, while technically feasible, remains limited to highly controlled environments and pilot programs.^{1,11}

Recent experimental studies show that this scenario is beginning to become feasible in emerging countries as well. In 2025, the first experimental robotic telesurgery was performed in Brazil, connecting two Brazilian cities separated by approximately 600 km, using dedicated fiber optic infrastructure with mobile network redundancy. The procedure was successfully performed, presenting ultra-low latency and communication stability throughout the surgical act, reinforcing the technical feasibility of robotic teleoperation in highly controlled environments and under strict safety protocols.¹⁶

From an academic point of view, telesurgery represents a convergence of surgery, engineering, informatics, and ethics.⁴ Its integration into bariatric surgery offers a unique opportunity to study not only clinical outcomes,¹⁷ but also educational efficiency, system resilience, and new models of surgical collaboration.^{2,3,12} Thus, robotic bariatric surgery offers an ideal clinical framework to advance telesurgical research and define best practices for future implementation.^{2,4,11}

Robotic bariatric surgery as a strategic model for telesurgery

Bariatric surgery brings together a set of characteristics that make it particularly suitable to serve as a strategic model in the discussion and development of telesurgery. This is an area with a high prevalence of indication, significant impact on public health, and unequal geographic distribution of highly specialized professionals.^{2,7,8} In many countries, centers of excellence are concentrated in large urban areas, while peripheral or remote regions face structural and human limitations in providing adequate surgical treatment for severe obesity.^{2,4}

Robotic surgery enhances this scenario by offering stability of movements, high-definition three-dimensional vision, and articulated instruments, which allow greater precision in digitally controlled environments.^{2,7} These attributes are fundamental for any application of a remote surgical procedure, as they reduce the dependence on fine manual skills directly mediated by physical contact with the patient.^{1,4}

In this context, robotic bariatric surgery can be understood as a clinical and academic proving ground for telesurgery.²⁻⁴

The recent performance of a teleoperated robotic procedure in an experimental model in Brazil reinforces

this concept of clinical and academic proving ground. Although not performed in the bariatric context, the study validated fundamental aspects for telesurgery, such as network stability, secure latency, communication redundancy, and precise remote control of the robotic system, indispensable elements for future more complex clinical applications.¹⁶

Impacts on medical education and academic research

The incorporation of robotic bariatric surgery in the context of telesurgery has direct and profound implications for medical education and scientific research.^{3,4,12} From an educational point of view, the possibility of remote supervision and mentoring redefines the traditional models of surgical training, allowing experienced specialists to monitor, guide and evaluate procedures performed in different centers, without the need for physical displacement.^{4,12}

This approach is especially relevant for medical residency, graduate and advanced training programs, as it expands access to specialized expertise and reduces regional inequalities in surgical training.^{2,4,12} In addition, robotic surgery enables the systematic and standardized recording of operative data, creating a favorable environment for objective performance evaluation, skill acquisition, and learning curve.³

The recent development of robotic surgery training systems with a focus on broad accessibility reinforces this educational and scientific potential. In 2025, the creation of a low-cost robotic training platform, designed for local and remote use, incorporating teleoperation, digital twin environment and real-time monitoring, was described. The system demonstrated high accuracy in instrument control, rigorous maintenance of the remote motion center and very low latency, configuring itself as a robust tool for surgical training, experimental research and validation of educational models in academic environments.¹⁸

In the field of research, robotics associated with telesurgery opens up new fronts of translational investigation.^{3,4} Data generated by robotic systems, such as execution time, instrument trajectory, and movement patterns, can be used for multicenter studies, validation of educational models, and development of tools based on artificial intelligence applied to surgery.³

Finally, the discussion on robotic bariatric surgery and telesurgery also stimulates ethical, regulatory, and pedagogical reflections, which are fundamental for the training of medical researchers who are aware of the responsibilities associated with the use of advanced technologies in clinical practice.^{1,4,10}

In this context, recent initiatives by international scientific societies have reinforced the centrality of structured teaching and professional certification in the evolution of telesurgery. The Society of Robotic Surgery consensus highlights the need for multidimensional training programs, clear proficiency criteria, and accreditation processes specific to telesurgical practice, prioritizing clinical outcomes, patient safety, and ethical responsibility.¹⁹

Current limitations and ethical-regulatory challenges

Despite the significant advances in robotic surgery and the renewed interest in telesurgery, several limitations still restrict its widespread clinical adoption, especially in the context of bariatric surgery.^{2,7,8} The high cost of robotic systems, combined with the need for referral hospitals with adequate technological infrastructure, remains one of the main barriers, particularly in health systems with limited resources.^{2,4}

Frenkel et al. in 2023²⁰ discussed the evolution of telesurgery and the ethical and regulatory hurdles that arise as technology advances. They noted that, in addition to technological limitations, the adoption of telesurgery depends on a robust regulatory framework, including clear regulations on informed consent, professional responsibility, and the creation of legal infrastructure that supports safe practice in different global contexts. The lack of clear guidelines can hinder the growth and universal adoption of telesurgery.

In 2024, Saikali et al.²¹ highlighted that, in addition to technological challenges related to latency and connectivity, telesurgery faces significant administrative and regulatory obstacles. Global implementation of it requires collaboration between governments, academic institutions, and medical societies to overcome issues such as training, certification of surgeons, and the creation of clear international regulations. Addressing these challenges is crucial to ensure that the benefits of telesurgery, such as global access to specialist surgery, can be widely accessed without compromising patient safety.

From a technical point of view, telesurgery requires highly stable connectivity, with minimal latency and system redundancy, to ensure operative safety.^{1,4,11} Signal interruptions, image transmission failures, or delays in command response pose unacceptable risks in complex surgical procedures.^{1,10} Although high-speed networks have reduced these limitations, their availability is still heterogeneous.^{4,11}

Recent reviews have systematically delved into these technical and ethical challenges associated with telesurgery. Aspects such as acceptable latency, network quality of service, cybersecurity, protection of sensitive data, and reliability of robotic systems are pointed out as critical requirements for safe telesurgical practice. In addition, ethical issues related to extended informed consent, shared professional responsibility, and institutional governance are highlighted as central elements for responsible clinical implementation of telesurgery.¹³

Ethical and regulatory challenges are equally relevant. Issues related to professional responsibility, informed consent, interregional or international medical licensing, and patient data protection remain under debate.^{4,10}

Recent studies by the Society of Robotic Surgery (SRS) address these critical points and propose a set of guidelines and recommendations to overcome ethical and regulatory challenges in telesurgery. The article by Patel et al. in 2024¹³ highlights in particular,

the need for shared governance between surgeons, institutions, and regulatory authorities to ensure the safe implementation of telesurgery in different global contexts. The clear definition of responsibilities, the establishment of training and certification standards, and the protection of patient data are pointed out as pillars for the sustainable evolution of this practice.

In telesurgery scenarios, it becomes essential to clearly define the responsibility between the remote surgeon, the local team, and the healthcare institution involved.^{1,12}

These concerns were recently systematized in an international consensus promoted by the Society of Robotic Surgery (SRS), which brought together global experts in surgery, engineering, telecommunications, ethics, and public policy. The meeting resulted in a Delphi-like consensus, establishing recommendations on technological requirements, cybersecurity, training, professional accreditation, legal aspects, and ethical frameworks necessary for the safe and scalable implementation of telesurgery. The document emphasizes the need for standardized guidelines and multidisciplinary governance to enable the responsible adoption of telesurgery in different health systems.¹⁹

In the academic sphere, these limitations reinforce the need for gradual approaches, initially prioritizing hybrid models, such as teleproctoring and telementoring that offer educational and care gains without exposing patients to unnecessary risks.^{4,12} The consolidation of clear regulatory frameworks will be decisive for the safe evolution of bariatric telesurgery.^{4,10}

Perspectives

The future for robotic bariatric surgery in the context of telesurgery is promising.^{2,4,11} The trend of expansion of the robotic platform market, with greater competition and technological diversification, can contribute to cost reduction and increased access.^{2,7,8} At the same time, the continuous advancement of communication networks, with lower latency and greater reliability, brings telesurgery closer to a more feasible clinical scenario.^{4,11} In the field of teaching, hybrid training models, combining simulation, robotics, and remote mentoring, are expected to become progressively more integrated into residency and graduate programs.^{3,4,12} Telesurgery can play a central role in democratizing access to specialized training, especially in countries with large regional inequalities.^{4,12} Recent initiatives point to the practical feasibility of this model. The development of robotic training platforms integrating teleoperation, advanced simulation, and digital twins has allowed expanding access to training in robotic surgery, reducing institutional costs, and creating controlled environments for research and technological validation. These systems represent a concrete step in the consolidation of hybrid educational ecosystems in robotic surgery and telesurgery.¹⁸

From a research perspective, the integration

of robotic surgery, data analysis, and artificial intelligence opens up new possibilities for surgical performance studies, technical standardization, and outcome evaluation.^{3,4} Bariatric surgery, due to its high prevalence and metabolic impact, tends to occupy a prominent position in this process of translational innovation.^{2,7,8}

Thus, more than an isolated technological tool, robotic bariatric surgery must be understood as part of an evolving digital ecosystem, capable of transforming the way surgery is practiced, taught, and investigated.^{3,4,11}

CONCLUSION

Although technical, economic, and regulatory challenges still limit the widespread adoption of telesurgery, the current scenario indicates a progressive transition to more integrated models of care, teaching, and research. In this context, robotic bariatric surgery emerges as a privileged field to test, validate, and consolidate these transformations. It goes beyond the role of a minimally invasive technique and is a central element in the digital transformation of surgery. Its progressive integration into telesurgery can contribute to the democratization of access, innovation in teaching, and strengthening of surgical research as long as it is implemented gradually and safely.

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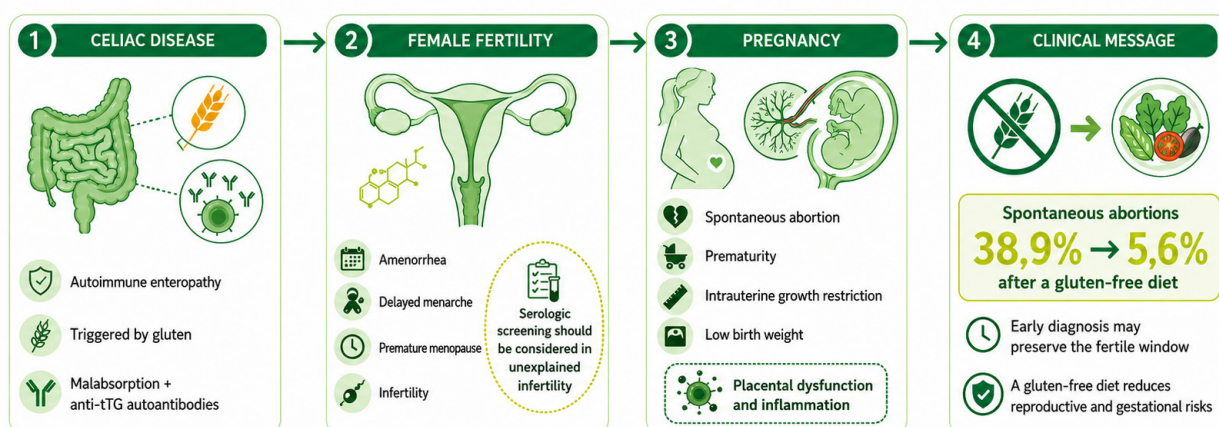
Celiac disease: a hidden cause of infertility and pregnancy complications?

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CELIAIC DISEASE: A HIDDEN CAUSE OF INFERTILITY AND PREGNANCY COMPLICATIONS?

Integrative review | 20 studies included

BioSCIENCE



Celiac disease may be underdiagnosed in women of reproductive age.
Recognizing atypical signs improves reproductive care.



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Central Message

Celiac disease is an autoimmune and genetic enteropathy triggered by gluten ingestion that has significant impacts on the female reproductive cycle and pregnancy. Symptoms such as amenorrhea, late menarche, early menopause, and others due to irregularities in pituitary hormones are found as signs of female fertility. In the gestational period, it can be manifested by impaired placental development, increased risk of prematurity, intrauterine growth restriction, low neonatal weight, and miscarriage. However, adopting a gluten-free diet can avoid the aforementioned manifestations.

Perspective

Celiac disease has an extensive list of symptoms and is commonly associated only with gastrointestinal symptoms. This premise, in the face of a discordant diagnostic technique, can generate several consequences, such as female infertility, with the risk of losing the fertile period, and compromising the health of the mother and fetus during pregnancy. Therefore, based on a greater amount of research and the recognition of these signs, the diagnosis and treatment of atypical cases would be facilitated, reducing or even eradicating the aforementioned adversities.

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ABSTRACT

Introduction: Celiac disease is a chronic and autoimmune enteropathy that manifests itself in individuals who are genetically susceptible to the action of environmental factors, in which the main one is gluten. In addition to symptoms such as chronic diarrhea and abdominal pain, the disease is also associated with extraintestinal symptoms, such as infertility and gestational impacts.

Objectives: To synthesize the main aspects of celiac disease and its implications for female fertility and the gestational period.

Method: Review made with material and analysis selected from searches on the virtual platforms SciELO, Google Scholar and PubMed, through the descriptors: "celiac disease", "gestational period" and "infertility" and their correspondents in English and Spanish, and in the book *Treatise of Gastroenterology from Undergraduate to Graduate Studies* (2nd edition).

Results: A total of 24 articles were included.

Conclusion: Celiac disease has a significant impact on fertility and pregnancy; however, the effects can be reduced or even eradicated with the implementation of a gluten-free diet. However, the greatest challenge persists in the identification and diagnosis of celiac women who are of childbearing age, due to the lack of clinical specificity, genetic variability, and the extent of environmental factors that impact the disease.

KEYWORDS: Celiac disease. Pregnancy. Infertility.

INTRODUCTION

Celiac disease (CD) is a chronic and autoimmune enteropathy triggered by the ingestion of gluten, a protein present in grains such as wheat, rye, and barley. The disease manifests itself in genetically susceptible individuals, carriers of the DQ2 and/or DQ8 haplotype of class II of the human leukocyte antigen (HLA) system, together with the action of environmental factors. The consumption of gluten implies an autoimmune response that inflames and degrades the villi of the mucosa of the small intestine, generating hyperplasia of its cells, and thus affecting the absorption of nutrients.¹⁻³

As a result of nutritional malabsorption and changes in histological structure, it is common for gastrointestinal symptoms such as chronic diarrhea, abdominal pain and bloating, weight loss, among others, to manifest it.¹⁻³ However, CD has a wide spectrum of extraintestinal manifestations, which are often neglected in clinical diagnosis. Among them, female infertility and gestational complications stand out, which can present as amenorrhea, late menarche, early menopause, recurrent miscarriages and intrauterine growth restriction, even in asymptomatic women from a digestive point of view.^{4,5}

The multifactorial etiology of these reproductive alterations ranges from nutritional deficiencies caused by malabsorption to autoantibody-mediated immunological alterations that directly affect endometrial and placental function.⁴⁻⁶ In addition, frequent delay in diagnosis and early interventions can exceed a decade, favoring the loss of the fertile period.^{5,6}

Thus, the objective of this review was to synthesize the main pathophysiological, nutritional, and immunological aspects of CD and its implications for female fertility and the gestational period, reinforcing the need for greater diagnostic attention for atypical cases of the disease.

METHOD

This is an integrative literature review, carried out

from searches in the PubMed, SciELO and Google Scholar databases, in addition to consulting the book *"Treatise on Gastroenterology: From Undergraduate to Postgraduate Studies"* (2nd edition). Articles published between 2002 and 2024, in Portuguese, English, and Spanish, were included. The descriptors used were "celiac disease", "pregnancy" and "infertility", as well as their counterparts in English and Spanish, used alone or combined through Boolean operators (Table 1).

DISCUSSION

The physiopathology of CD results from the combination of the main genetic components (HLA-DQ2 or HLA-DQ8 haplotypes), environmental factors (such as gluten protein and related cereals), and the consequent production of circulating antibodies: tissue antitransglutaminase (TG2) and antiendomysial (EmA).⁷⁻¹³

Genetic factors

CD is a genetic disease of multifactorial and polygenic origin, in which different susceptibility genes act at different stages until the final development of the disease.^{7,8,10} Studies based on molecular genetic methods have allowed the identification of variants associated with predisposition to CD, including loci CELIAC2 (5q33), CELIAC3 (2q33), CELIAC4 (19p13.1) and, mainly, CELIAC1, located in the 6p21 region of chromosome 6.^{8,11-13}

In addition, as with other autoimmune diseases, a strong association was established between CD and the major histocompatibility complex class II (MHC), responsible for the presentation of antigens to the immune system. This genetic component plays a fundamental role in the variability of the disease, estimated at between 40% and 50%.⁸ The main genetic factors of CHM related to CD correspond to HLA haplotypes, also located in the CELIAC1 region.

Approximately 90% of individuals with CD are carriers of a specific variant of HLA-DQ2 (DQA105:01, DQ2.5), while most of the others have HLA-DQ8 (DQA103, DQB103:02) or less frequent variants of

TABLE 1 — Synthesis of the studies incorporated in this review

Author(s) and year	Type of study	Objectives	Method	Conclusion
Lindfors et al. ¹ (2019)	Narrative review	Synthesize the main aspects of celiac disease, including epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment, and impact on quality of life.	Broad review of the scientific literature on celiac disease, with an integrated approach to immunological, genetic, environmental, diagnostic and therapeutic mechanisms.	Celiac disease is immune-mediated enteropathy triggered by gluten in genetically predisposed individuals, with intestinal and extraintestinal manifestations. The diagnosis depends on the association between clinical, serology and histology, with a gluten-free diet being the established treatment.
Lebwohl et al. ² (2018)	Narrative review	Review epidemiology, pathogenesis, clinical presentation, diagnosis, complications, and management of celiac disease.	Critical review of the literature in the format of a clinical update article published in the Lancet.	Celiac disease affects about 1% of the population in many countries, with increasing incidence and varied clinical manifestations. Early recognition and adherence to the gluten-free diet are key to reducing complications.
Fasano and Catassi. ³ (2012)	Clinical review	To present a practical approach to the diagnosis, treatment and follow-up of patients with celiac disease.	Evidence-based clinical review, with discussion of clinical presentation, serology, intestinal biopsy, and dietary management.	Celiac disease has a broad clinical spectrum and may course with gastrointestinal or extraintestinal symptoms. The diagnosis requires adequate investigation even during gluten consumption, and the treatment consists of a gluten-free diet.
Kotze ⁴ (2004)	Descriptive observational study	OBJECTIVE: To evaluate gynecological and obstetric changes in Brazilian patients with celiac disease, relating them to nutritional status and adherence to the gluten-free diet.	Analysis of adult celiac patients according to nutritional status and evaluation of children/adolescents according to adherence to the gluten-free diet.	Patients with celiac disease had gynecological and obstetric alterations, such as late menarche, amenorrhea, and miscarriages. Severity was related to poorer nutritional status and non-adherence to the gluten-free diet.
Di Simone et al. ⁵ (2021)	Narrative review	Update pathogenic mechanisms that relate celiac disease to reproductive failure, infertility, and obstetric complications.	Review of evidence on immunological, inflammatory, nutritional, and placental mechanisms involved in the association between celiac disease and reproductive failure.	Celiac disease can compromise fertility and pregnancy by nutritional and immunological mechanisms, especially by the action of anti-tissue transglutaminase autoantibodies on the endometrium, trophoblast, and placenta.
Casella et al. ⁶ (2016)	Narrative review	To review the contribution of celiac disease to gynecological and obstetric changes.	Review of the literature on celiac disease in women of childbearing age, infertility, miscarriages, fetal growth and gestational outcomes.	Celiac disease is more prevalent in women during the fertile period and should be investigated in cases of infertility, recurrent miscarriages, and unfavorable obstetric outcomes without a defined cause.
Ludvigsson and Murray. ⁷ (2019)	Epidemiological review	Describe the epidemiology of celiac disease, including prevalence, incidence, population factors and geographic distribution, prevalence, incidence, population factors, and geographic distribution.	Review of epidemiological studies on celiac disease in different populations, with analysis of variations by age, sex, region, and diagnostic methods.	Celiac disease is a common chronic inflammatory condition of the small intestine, triggered by gluten in genetically susceptible individuals, with relevant global prevalence and variation according to population and diagnostic strategy.
Marinho et al. ⁸ (2016)	Textbook	Present clinical, pathophysiological, diagnostic and therapeutic foundations of gastroenterological diseases, including celiac disease.	Gastroenterology textbook chapter aimed at undergraduate and graduate studies, with didactic synthesis of consolidated knowledge.	The treatise provides a conceptual basis for understanding celiac disease, including pathophysiology, clinical manifestations, diagnosis by serology and biopsy, and treatment with a gluten-free diet.
Pereira. ⁹ (2020)	Narrative literature review	Analyze the pathophysiology of celiac disease, elucidate its diagnostic methods, and highlight the importance of proper food labeling.	Narrative review prepared between July and December 2020, with a search in MEDLINE, SciELO, PubMed, Virtual Health Library and books, using descriptors related to celiac disease, treatment, signs, symptoms and diagnosis.	Celiac disease results from an inflammatory response to gluten in genetically predisposed individuals, leading to villous atrophy and malabsorption. Diagnosis is based on clinical evaluation, serological markers and endoscopic biopsy, with a gluten-free diet being the only proven treatment.
Iversen and Solild. ¹⁰ (2022/2023)	Narrative review	Describe the immunobiological and pathogenic mechanisms of celiac disease.	Review of evidence on HLA-DQ2/DQ8, gluten peptide presentation, T lymphocytes, transglutaminase 2, and autoantibodies.	Celiac disease has a well-characterized pathophysiology, involving immune response to gluten, HLA predisposition, and production of autoantibodies against transglutaminase 2.
Nieto et al. ¹¹ (2020)	Narrative review	To review causes, pathology, and nutritional assessment of the gluten-free diet in celiac disease.	Literature review on pathophysiology, nutritional deficiencies, and gluten-free diet composition.	Celiac patients may have nutritional deficiencies before and during the gluten-free diet, requiring adequate nutritional monitoring.
Caio et al. ¹² (2019)	Comprehensive narrative review	To update knowledge on the pathophysiology, diagnosis, clinical manifestations, treatment and therapeutic perspectives of celiac disease.	Comprehensive review of the scientific literature on different aspects of celiac disease.	Celiac disease remains a challenging condition, with diverse phenotypes and the need for a better understanding of potential, seronegative, and refractory forms.
Gujral et al. ¹³ (2012)	Narrative review	To review the prevalence, diagnosis, pathogenesis, and treatment of celiac disease.	Review of studies on genetic, environmental, immunological and therapeutic factors.	Celiac disease results from the interaction between gluten, genetic predisposition, and immune response; Its prevalence is estimated to be about 0.5% to 1%, and the treatment is a gluten-free diet.
Husby et al. ¹³ (2020)	Clinical guideline / guideline	Update the ESPGHAN recommendations for diagnosis of celiac disease in children and adolescents.	Evidence review and expert consensus for diagnostic criteria, including serology, biopsy, and biopsy-free approach in selected cases.	Pediatric diagnosis should use specific serology, especially anti-TG2 IgA and total IgA; In specific situations, it can be diagnosed without biopsy according to established criteria.
Rubin and Crowe. ¹⁴ (2020)	Clinical review	Present practical updates on the diagnosis, clinical manifestations, and management of celiac disease.	Clinical review in didactic format, focused on medical practice.	Recognition of intestinal and extraintestinal manifestations is essential for timely diagnosis and for the institution of a gluten-free diet.
Oberhuber et al. ¹⁵ (1999)	Histopathological review / classification proposal	To review histological findings of celiac disease and to propose standardization of the anatomopathological report.	Review of histological changes in celiac disease based on Marsh's classification.	Histopathological standardization allows the classification of lesions of the intestinal mucosa, including increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy.
Harris et al. ¹⁷ (2012)	Narrative review	To review the clinical, endoscopic and histopathological aspects of celiac disease.	Review of the literature on clinical manifestations, endoscopic diagnosis, and histological alterations of CD.	The diagnosis of CD requires integration between clinical, serological, endoscopic and histopathological findings for greater diagnostic accuracy.
Skoracka et al. ¹⁸ (2021)	Narrative review	To assess the influence of nutrition on female fertility.	Review of studies on female fertility and associated nutritional factors.	Nutritional deficiencies can compromise female fertility, and adequate micronutrient intake is essential for reproductive function.
Freeman. ¹⁹ (2010)	Narrative review	To analyze reproductive changes associated with celiac disease.	Review of the literature on fertility, pregnancy and obstetric complications in celiac women.	Untreated CD is associated with infertility, recurrent miscarriages, and adverse pregnancy outcomes, and can be reversed with a gluten-free diet.
Tonai et al. ²⁰ (2020)	Experimental study in animals	To investigate the effects of iron deficiency on female fertility.	Experimental model in mice subjected to iron deficiency, with evaluation of follicular development.	Iron deficiency impairs follicular development and reduces female fertility.
Sóñora et al. ²¹ (2014)	In vitro experimental study	To evaluate the effect of anti-tissue transglutaminase antibodies on human trophoblastic cells.	Culture of human trophoblastic cells exposed to anti-tTG antibodies.	Anti-tTG antibodies reduce proliferation and trophoblastic migration and increase apoptosis, contributing to gestational complications in CD.
Butler et al. ²² (2011)	Narrative review	To review the relationship between celiac disease and pregnancy outcomes.	Review of observational studies on pregnancy in women with CD.	Women with undiagnosed CD are at increased risk of miscarriage, prematurity, and fetal growth restriction.
Boers et al. ²³ (2019)	Case report	OBJECTIVE: To describe the gestational course in a patient with celiac disease.	Clinical report and brief review of the literature.	Early diagnosis and adherence to the gluten-free diet contribute to better maternal and fetal outcomes.
Tack et al. ²⁴ (2010)	Narrative review	To review the epidemiology, clinical manifestations, and treatment of celiac disease.	Comprehensive review of the literature.	CD has a broad clinical spectrum and treatment based on a gluten-free diet remains the main therapeutic strategy.

HLA-DQ2, such as DQ2.² (DQA102:01).^{8,12,13}

However, despite this consistent association, the isolated presence of these haplotypes is not sufficient for the development of the disease. Although they are relatively common in the general population (30% to 40%), only about 2% to 5% of individuals with CD develop CD.⁸ In this context, additional genes related to epithelial function, intestinal mucosal integrity, and metabolism also participate in the triggering of the disease.^{7,8}

Environmental factors

Gluten protein is the main environmental factor that triggers and maintains the changes observed in CD. Gluten is present in wheat, rye and barley, and is composed of two main protein groups: glutenins and prolamins. Prolamins correspond to about 50% of the total gluten content and receive different denominations depending on the cereal of origin, such as gliadin in wheat, hordein in barley and secalin in rye. Oats, although they do not contain gluten in their natural composition, may show traces of this protein, as a result of cross-contamination during cultivation and processing, which can trigger reactions in some celiac patients.^{9,10}

Gliadin, a monomeric gluten protein, represents the main toxic agent involved in the pathogenesis of CD and is classified into four fractions: alpha (α), beta (β), gamma (γ) and omega (ω). Due to its resistance to proteolysis, its digestion is incomplete, resulting in the formation of smaller fragments, such as gliadin-derived oligopeptides. These peptides are rich in proline and glutamine, and are recognized by the immune system, especially in the alpha-gliadin portion, which culminates in the activation of T lymphocytes.⁹⁻¹¹

In addition to gluten, other environmental factors have been implicated in the development of CD, including the potentially protective role of breastfeeding, the occurrence of gastrointestinal infections, the use of antibiotics, and changes in the gut microbiota. The dysbiosis observed in celiac patients is characterized by an increase in *Bacteroides* spp. and a reduction in *Bifidobacterium* spp., including *B. longum*, when compared to healthy individuals, and does not seem to completely normalize even after the adoption of a gluten-free diet.⁸⁻¹⁰

Immunology

In CD, there is production of IgA-type autoantibodies directed against the enzyme tissue transglutaminase (TG2), widely expressed in mucosal cells, smooth muscles, endothelium, fibroblasts, and intestinal epithelium. TG2 plays a central role in catalyzing transamination and deamination reactions, converting glutamine residues into glutamic acid.¹³ When partially digested gluten peptides reach the intestinal lamina propria, genetically predisposed individuals develop adaptive immune response dependent on TG2-mediated deamination of gliadin fragments.¹¹ This process increases the immunogenicity of gliadin by facilitating its binding to HLA-DQ2.²

HLA-DQ2,⁵ and HLA-DQ8 molecules in antigen-presenting cells. The autoantibodies generated may also contribute to extraintestinal manifestations of CD.¹⁰

At the same time, an innate immune response is established in the intestinal epithelium, characterized by intraepithelial lymphocytosis. Intraepithelial lymphocytes express receptors typical of natural killer (NK) cells, such as NKG2D and CD94/NKG2A, which recognize stress-induced surface glycoproteins, including A and B chains of MHC class I and HLA-E molecules, expressed on intestinal epithelial cells. The concomitant activation of adaptive and innate immune pathways contributes to the clinical and pathogenetic picture of CD.^{11,12}

Trypsin-amylase inhibitors, which account for about 2% to 4% of wheat proteins, also participate in the activation of the innate immune response. Certain fractions of these inhibitors are capable of activating Toll-type receptors, such as TLR-4, inducing the release of proinflammatory cytokines by monocytes, macrophages, and dendritic cells, both in celiac and non-celiac individuals.¹⁰⁻¹³

Activation of specific T cells in the lamina propria results in changes in the number, distribution, and activation status of intraepithelial lymphocytes (IELs). These lymphocytes are distributed throughout the intestinal epithelium, with a predominance in the basolateral region of the epithelial cells. Most of them have CD8⁺ $\alpha\beta$ TCR⁺ or $\gamma\delta$ TCR⁺ phenotype, with functional characteristics similar to NK cells, being involved in the death of enterocytes and in the tissue remodeling observed in CD.^{1,7,10-13} There is also a redistribution of ISLs, with an increase in their density at the ends of the villi.¹⁰⁻¹³

Interleukin-15 (IL-15), overexpressed by intestinal epithelial cells of patients with CD, plays a central role in the activation and proliferation of these lymphocytes. In addition, cytokines produced by lamina propria T cells, such as IL-2 and IL-21, additionally contribute to the activation of ISLs.¹⁰⁻¹³

Epithelial changes may also be secondary to CD4⁺ T cell activation. In addition to ISL, other subtypes of innate lymphocytes are particularly abundant in childhood, highlighting a population similar to inborn lymphocytes type 1 (ILC1), interferon-secreting γ (IFN- γ), and a population of ISL highly responsive to IL-15, considered a precursor of the monoclonal expansions observed in refractory CD type 2, a premalignant condition resistant to a gluten-free diet.¹¹⁻¹³

Diagnosis

The diagnosis of CD is based on a combination of clinical findings, serological tests, intestinal mucosal biopsy for morphological evaluation, and response to the gluten-free diet. However, diagnostic confirmation can be challenging due to the possible disagreement between clinical, serological, and histological data.¹²

In 2020, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition

(ESPGHAN) updated its diagnostic guidelines for CD, proposing that, in specific situations, the diagnosis can be made exclusively based on serological tests, dispensing with the need for intestinal biopsy.¹²

Several serological markers have been used over the last decades, and the anti-tissue transglutaminase antibody (anti-tTG) is currently the initial test of choice. The detection of anti-tTG of the IgA type by means of the ELISA method has a sensitivity of approximately 92.5% and a specificity of 98%, constituting the most efficient marker for the diagnosis of CD, in addition to being useful in monitoring adherence to the gluten-free diet.¹³

Prior to serological analysis, serum total IgA is essential, as up to 3% of celiac patients have selective IgA deficiency, which can result in false negatives. In these cases, alternative immunoglobulin G (IgG) tests should be employed, including anti-endomysium (anti-EMA), anti-tTG, and anti-gliadin deaminated peptide (anti-DGP) antibodies.¹³

Small bowel biopsy, currently performed by upper gastrointestinal endoscopy, allows the evaluation of the morphological characteristic changes of CD, particularly in the Kerckring folds of the distal duodenum and proximal jejunum. In these regions, thickening, increased granularity, congestion and, in some cases, atrophy are observed. Additionally, the visibility of blood vessels is increased in approximately 70% of celiac patients.^{14,15}

The histological classification of intestinal lesions follows the Marsh-Oberhuber system (Table 2), which categorizes the findings into four types: Type 1 (infiltrative), Type 2 (hyperplastic), Type 3 (destructive, with subtypes a, b, and c), and Type 4 (hypoplastic). Type 0 or 1 lesions require further investigation before diagnostic confirmation, whereas type 2 or 3 lesions are considered compatible with the definitive diagnosis of CD.¹⁴⁻¹⁶

TABLE 2 — Original Marsh-Oberhuber classification where the presence of subcategories in Type III can be observed.¹⁶

TYPE	FEATURES
TYPE 0	Normal mucosa
TYPE I	Increased number of ISL and infiltrative lesion
TYPE II	Crypt hyperplasia and increase in the number of ILLs with hyperplastic lesions
TYPE III	Villous atrophy and crypt hyperplasia with destructive injury III a - Partial III b - Subtotal III c - Total

Adapted from Harris et al.¹⁷

After the introduction of a gluten-free diet, the regeneration of the intestinal mucosa can take from 6 to 24 months, and this time varies between patients.¹⁴

Infertility in CD

Infertility is defined as the absence of conception after a 12-month period of regular, unprotected sexual activity. It is estimated that approximately 15% of couples around the world face difficulties in getting pregnant. Of these, 15% have idiopathic causes, 20% have combined male and female factors, and 35%

have exclusively female infertility. Currently, about 80 million women are affected by infertility globally, representing a health challenge that demands attention from professionals in the area.¹⁸

In this perspective, female infertility is classified into two clinical forms: primary, when the woman has never had a pregnancy, and secondary, when the woman has already gone through one or more pregnancies, regardless of the outcome - childbirth or abortion - but with current difficulty in conception. In women with untreated CD, both forms of infertility have been observed, despite the variability among studies on the subject.¹⁸

According to a survey conducted in North America, among infertile women (7.4% to 14%), about 15% had infertility without a defined anatomical or hormonal cause. In these cases, the prevalence of CD was estimated to be between 4% and 8%.⁶

In Brazil, a study of 76 adult women with CD showed significant gynecological changes compared to patients with irritable bowel syndrome (control): menarche occurred later (13.7 ± 1.5 years vs. 12.8 ± 1.6 years; $p < 0.0001$), secondary amenorrhea was observed in 28% of patients with CD, and the rate of miscarriages was 24.4% per pregnancy - twice as high as in the control group (11.6%).⁴

In addition, CD is more prevalent among women of reproductive age, and may manifest with gynecological and obstetric symptoms such as amenorrhea, late menarche, early menopause, recurrent miscarriages, and unexplained uterine bleeding.^{5,6,19}

Impact of malabsorption on fertility

Malabsorption, characteristic of CD, contributes significantly to gynecological and obstetric complications, even in nutritionally asymptomatic patients. In this line of care, the most relevant nutrients are: zinc, folic acid and iron.^{5,6,19}

The lack of zinc may be responsible for alterations in the hypothalamic-pituitary-ovarian (HPO) axis, affecting the release of gonadotropin-releasing hormone (GnRH), and, consequently, the secretion of luteinizing hormones (LH) and follicle stimulating hormone (FSH). It is associated with secondary amenorrhea, infertility, miscarriages, congenital malformations, intrauterine growth restriction, prematurity, post-term pregnancy, and perinatal death.^{5,6}

Folic acid is essential for embryonic tissue proliferation, especially in neural development. Its deficiency can increase embryonic apoptosis and be associated with early pregnancy losses.^{5,6,19,20}

Iron is critical for organogenesis and normal follicular development. The lack of this mineral can affect the progression of the follicle secondary to the antral follicle, in addition to compromising endometrial vascularization.²⁰

In addition to specific nutritional deficiencies, the overall degree of malnutrition correlates with the severity of gynecological changes. In the study of Kotze (2004)⁴, patients with severe malnutrition

had the highest rates of secondary amenorrhea (45.5%) and miscarriages (37.2%). Interestingly, even eutrophic patients had anemia (47.6%), suggesting that intestinal malabsorption can occur even in the absence of apparent weight loss.

Shortened fertile window and gynecological complications

Studies indicate that about 50% of women with untreated CD and secondary infertility have experienced miscarriage or other gestational complications. However, the etiology of these losses is identified in only 60% of cases, making the clinical management of the remaining 40% difficult.^{5,6}

CD can compromise female reproductive potential by reducing the fertile window by several mechanisms: high prevalence during the reproductive period, late menarche, early menopause, possibility of infertility as an isolated clinical manifestation, in addition to the often late diagnosis - which can take more than 10 years and is usually established between 40 and 50 years of age.⁶

In view of these factors, it is essential to highlight that CD can lead to the loss of the fertile period due to a combination of elements: late onset of ovarian function, early termination of the reproductive cycle, isolated gynecological manifestations that hinder clinical suspicion, and diagnostic delay that compromises timely interventions.^{5,6}

Considering the strong association between CD and pregnancy losses - especially in women without gastrointestinal symptoms - serological screening for CD is recommended in cases of recurrent miscarriages or unexplained secondary amenorrhea. This recommendation is supported by Brazilian and international evidence and can be decisive for the patient's reproductive rehabilitation.^{5,6,19}

Treatment

Infertility and gynecological-obstetric disorders associated with CD can be, in many cases, reversed or attenuated with the adoption of a gluten-free diet. Although this intervention does not solve all conditions, the benefits are significant. A Brazilian study showed that, after the introduction of the diet, the rate of spontaneous abortions fell from 38.9% to 5.6% ($p = 0.045$), reinforcing the role of gluten as a factor directly involved in pregnancy losses - even in patients without apparent malnutrition.⁴

In addition, correction of nutritional status is often necessary, due to the malabsorption of essential micronutrients such as zinc, iron, folic acid, folate, and selenium, which also play a key role in reproductive health.^{6,19}

Shared immunological mechanisms in infertility and pregnancy

Adequate placentation and gestational success depend on multiple biological events, including trophoblast functional development and endometrial neoangiogenesis. In vitro studies demonstrated that

anti-tissue transglutaminase (anti-tTG) antibodies promote a series of changes that impair placental function.⁵

The process of angiogenesis, together with the action of steroid hormones, is essential to promote endometrial modifications that make the endometrium receptive to the blastocyst and initiate the process of embryonic implantation. In this context, evidence shows that anti-tissue transglutaminase (anti-tTG) antibodies play a detrimental role in human endometrial angiogenesis.⁵

These autoantibodies bind directly to endothelial cells of the endometrium, reducing the formation of new blood vessels, both in vitro and in vivo models. Angiogenesis impairment is attributed to the ability of anti-tTG to inhibit the activation of extracellular matrix metalloproteinase-2 (MMP-2), disrupt cytoskeletal fibers, modify the mechanical properties of cell membranes, and inhibit intracellular phosphorylation of the focal adhesion kinase (FLAG) and ERK (extracellular signal-regulated kinase) signaling pathways).⁵

In addition, anti-tTG antibodies are able to interact directly with human trophoblastic cells in a dose- and time-dependent manner, promoting an increase in the rate of apoptosis and a reduction in trophoblast invasiveness. These effects are attributed to inhibition of the activity of extracellular matrix metalloproteinases (MMPs), which are essential for tissue remodeling during implantation.⁵

In an experimental study, Sónora et al.²¹ evaluated the effects of anti-tTG antibodies on the Swan-71 cell line, derived from human cytotrophoblasts. This lineage mimics the syncytial microvillous surface of the placenta, a region where tTG is strongly expressed, and plays an important role in the regeneration and healing processes during early implantation. The results showed that anti-tTG antibodies significantly reduce trophoblastic proliferation and migration, increase apoptosis, and interfere with the removal of apoptotic bodies, through mechanisms involving the interaction between tTG and the milk fat globulin-EGF factor.²¹

This autoimmune model of placental aggression offers a plausible explanation for the occurrence of infertility, early pregnancy losses, intrauterine growth restriction, and small-for-gestational-age newborns in women with untreated CD. The proposed pathophysiology is comparable to that observed in antiphospholipid antibody syndrome, also characterized by dysfunction at the maternal-fetal interface.^{5,21,22}

In summary, the current evidence supports the existence of a model of placental damage mediated by anti-tTG autoantibodies, which contributes significantly to the reproductive failures associated with active CD in patients who do not adhere to the gluten-free diet. 5:21-23

Gliadin, the main antigenic fraction of gluten, induces an intestinal inflammatory response in CD, with possible systemic repercussions, including in the

uterine environment. Studies have shown that this protein activates peripheral T lymphocytes, promoting the secretion of inflammatory cytokines such as interferon- γ (IFN- γ) and interleukin-2 (IL-2), which can negatively alter endometrial receptivity.^{2,3,5,10}

Dysregulation of the expression of angiogenic, pro-inflammatory, and anti-inflammatory cytokines during the implantation window compromises endometrial development, negatively impacting fertility and increasing the risk of pregnancy losses. In addition, high levels of IL-6 and C-reactive protein (CRP) have been identified in amniotic fluid and cervicovaginal fluid, correlating with spontaneous preterm birth. These findings reinforce the role of systemic and local inflammation as a relevant factor in the pathophysiology of reproductive failures associated with CD.^{5,19}

Gliadin also promotes increased intestinal permeability through activation of the CXCR3–MyD88 pathway, leading to zonulin release and impairment of intestinal epithelial barrier integrity. This condition, known as leaky gut, favors the translocation of bacterial components, such as lipopolysaccharides, into the systemic circulation.^{13,19,22,24} These bacterial products, when they reach the endometrium, activate the NALP-3 inflammasome, a key mechanism of innate immunity. This activation leads to the processing of the cytokines IL-1 β and IL-18, contributing to the inflammatory uterine environment. Studies have demonstrated endometrial overexpression of these cytokines in women with idiopathic recurrent miscarriage, as well as abnormal activation of caspase-1 and AUC, central components of the inflammasome.^{5,10,17,22}

The hypothesis of an intestine-endometrial axis, mediated by intestinal barrier dysfunction and secondary endometrial inflammation, emerges as an explanation for infertility and pregnancy losses in patients with CD. This pathophysiological interrelationship opens new perspectives for the approach of adverse reproductive outcomes in celiac women, even in the absence of classic gastrointestinal symptoms.^{5,19,22}

Gestational outcomes in CD

Numerous studies have revealed an increased risk of preterm births, intrauterine growth restriction, low birth weight, and miscarriage in women diagnosed with CD after delivery. However, those diagnosed and users of a gluten-free diet, did not have a higher risk of pregnancy when compared to undiagnosed women.^{6,19,22,23}

In the placenta, tissue transglutaminase is expressed on another surface of the syncytiotrophoblast microvillus membrane and is accessible to maternal antibodies. Thus, anti-tTG antibodies can affect trophoblast survival by reducing the proliferation rate and promoting apoptosis, impacting the impairment of the functional development of the placenta.¹⁹

Therefore, during pregnancy, the pregnant woman should undergo multidisciplinary prenatal care. A gluten-free diet should be advised, and anti-tTG levels should be

monitored, in addition to regular ultrasound examinations due to the risk of intrauterine growth limitation.¹⁹

CONCLUSION

In summary, CD exerts relevant impacts on female fertility and the course of pregnancy, which can be significantly reduced, and, in many cases, prevented through the early adoption of a gluten-free diet. However, the main challenge remains in the identification and timely diagnosis of celiac women of childbearing age, due to the clinical heterogeneity, genetic variability, and multiplicity of environmental factors involved in the disease.

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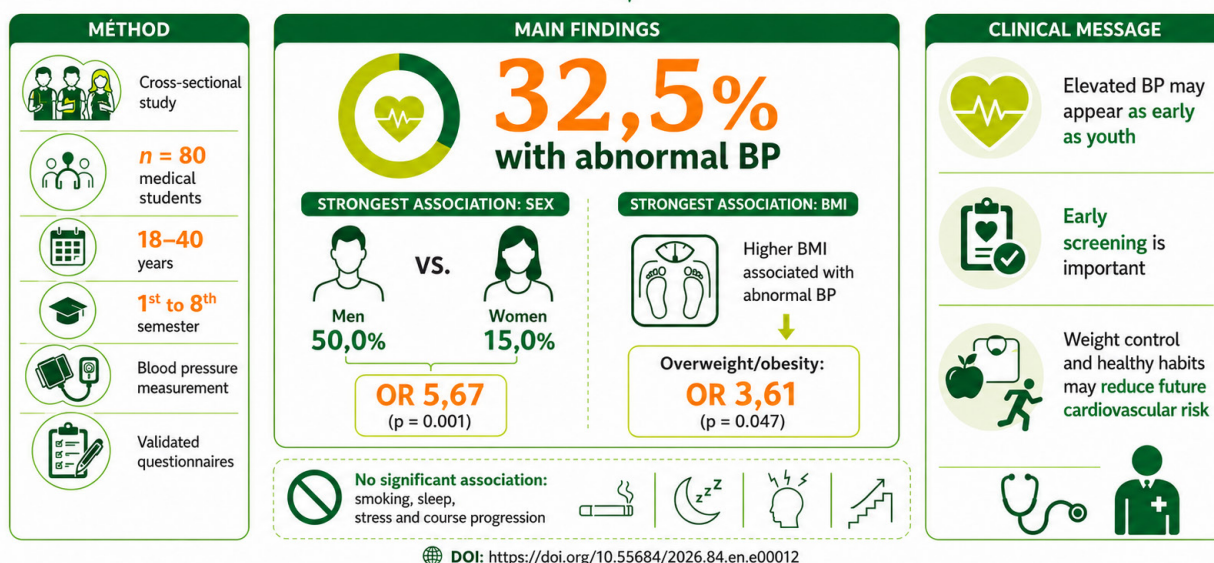
Hypertension in young university students: analysis of risk factors in medical students

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ARTERIAL HYPERTENSION IN YOUNG UNIVERSITY STUDENTS

Analysis of risk factors in medical students

BioSCIENCE



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Central Message

Hypertension is the main modifiable risk factor for global cardiovascular morbidity and mortality, although its investigation in young adults is still limited. In a cross-sectional study with medical students, a high prevalence of altered blood pressure levels (32.5%) was observed, with a significant association with male gender and high body mass index. The findings show that blood pressure changes are already present in a young population, traditionally considered to be at low risk, reinforcing the need for early surveillance.

Perspective

The significant presence of altered blood pressure in medical students suggests that cardiovascular risk factors may be underestimated in young populations. The association with male gender and high BMI reinforces the role of modifiable factors in the genesis of early hypertension. Although variables such as stress, smoking, and sleep quality did not show a significant correlation, the results support the importance of preventive strategies and lifestyle interventions from youth, with a potential impact on the future reduction of the incidence of cardiovascular diseases.

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ABSTRACT

Introduction: Although the harmful impact of hypertension is well known, most studies focus on high-risk populations or older people, leaving the evidence for young adults, traditionally considered low-risk, limited. Awareness and control of hypertension are low among young people, which becomes a significant concern since high blood pressure in youth can increase the risk of cardiovascular disease in adulthood.

Objective: To evaluate the blood pressure of medical students from the first to the eighth semesters.

Method: Cross-sectional observational study, in which 80 students enrolled from the first to the eighth semesters were randomly interviewed.

Results: 32.5% had altered blood pressure, with males being a significant risk factor for hypertension, with men being 5.67 times more likely to develop hypertension compared to women ($p = 0.001$). BMI was also a determining factor, with individuals with a higher index having a higher prevalence of altered blood pressure. There was a negative correlation between stress levels and systolic pressure ($p = 0.019$), indicating a slight reduction in blood pressure in more stressed students. Smoking and poor sleep did not show a significant correlation with blood pressure. In addition, throughout the academic periods, there was stability in the values without significant variations associated with progress in the course, with the exception of diastolic pressure, which decreased in the more advanced periods ($p = 0.025$).

Conclusion: Preventive actions should be adopted to change lifestyle even in younger populations so that, in the long term, these changes result in lower incidence and prevalence of cardiovascular diseases.

KEYWORDS: Hypertension. Risk factors. Cardiovascular diseases. Medical students.

INTRODUCTION

In 2023, the World Health Organization (WHO) published the Global Report on Hypertension: the Race Against a Silent Killer, presenting hypertension in the world or systemic arterial hypertension (SAH)¹. This is a chronic condition that increases the risk of mortality from cardiovascular, renal or cerebral diseases, such as stroke²⁻⁵, infarction, kidney failure, among others, and is characterized by high blood pressure levels ($BP \geq 140 \times 90$ mmHg).⁶

In epidemiological terms, the global prevalence of SAH is estimated at ^{1,28} billion adults, aged 30-79 years, of whom 46% are unaware of having the condition, as some are asymptomatic.^{1,7-9} In Brazil, according to the 2023 Surveillance System of Risk and Protective Factors for Chronic Diseases by Telephone Survey (Vigitel), the percentage of self-reported SAH prevalence between 2006 and 2023 increased from 22.6% to 24.3%.⁷ These data are of concern when one considers that most hypertensive individuals do not have an adequate diagnosis or are not under treatment, increasing the risk of complications.

Risk factors for SAH are divided into modifiable and non-modifiable. Among the non-modifiable, age, sex and genetic predisposition prevail. Hypertension tends to manifest itself more frequently in people over 60 years of age, and this is associated with senility processes such as arterial stiffness, which contributes to the increase in blood pressure.² Regarding gender, males are considered a risk factor until middle age, while after menopause, women have a similar or even higher prevalence of hypertension.¹⁰ Genetic predisposition also plays an important role, influencing individual susceptibility to elevated blood pressure (BP).^{11,12}

Modifiable factors - such as inadequate diet, sedentary lifestyle, smoking, excessive alcohol consumption and stress - are determinants in the prevention and control of SAH.^{1,13-18} For example, a diet rich in sodium and low in potassium, typical

of urban populations, is also related to a higher prevalence of hypertension.

Although SAH is traditionally associated with older individuals, as we have seen, there is a significant increase in cases among young people and young adults. Studies show that the prevalence of hypertension has grown among university students, often associated with academic stress, irregular sleep patterns, inadequate diet and sedentary lifestyle.¹⁹⁻²¹

In view of these data, the present study aims to present the results of the evaluation of BP values in a population of medical students, from the first and eighth periods. We sought to know the relationship with lifestyle habits such as diet, sleep, stress, smoking, alcoholism, physical activity, body mass index (BMI) and progression of values between the academic periods addressed in this study.

METHOD

This was a cross-sectional observational study that included 80 medical students from the Mackenzie Evangelical College of Paraná, Curitiba, PR, Brazil, and randomly selected between the 1st and 8th semesters. Volunteers between 18 and 40 years of age were included, equally distributed between the sexes. Students outside the age group or non-volunteers were excluded. The project was approved by the Research Ethics Committee of the institution (Opinion No. 6,817,896), and all volunteers signed a free and informed consent form.

Validated questionnaires were applied: AUDIT-C (alcohol), DQ-Q (diet), Fagerström test (smoking)²², PSQI (sleep quality)²³, EPS-10 (stress)²⁴ and IPAQ (physical activity).²⁵ These instruments enabled the multidimensional assessment of risk factors.

The interviewees were asked about the practice of physical exercise for 90 minutes, consumption of alcohol, coffee, food or cigarettes in the last 30 minutes, or if they had a full bladder. In case of positive responses to these factors, the students were

evaluated in another session, as these elements could affect BP values.

BP was measured in a reserved room, after a 10-minute rest, with the participants seated and with a calibrated electronic sphygmomanometer (OMRON HEM-7122).^{3,7} The sphygmomanometer cuff was placed about 2-3 cm above the cubital fossa, with the rubber bag centered on the brachial artery. In case of failure in the measurement using an electronic sphygmomanometer, the aneroid could be replaced according to appropriate criteria for its use.

In this case, the sphygmomanometer cuff was placed in the same position, with the rubber bag centered on the brachial artery. Next, the radial pulse was palpated and the cuff inflated until the pulse disappeared, thus estimating systolic blood pressure (SBP); then, it was quickly deflated. The procedure was similar, but after 15-30 s, the stethoscope was placed in the brachial artery and the cuff inflated every 10 mmHg until it exceeded 20-30 mmHg above the estimated SBP. This would be recorded when the first sound manifested (Korotkoff phase I), and diastolic blood pressure (DBP) was recorded when the sound disappeared (Korotkoff phase V) or when there were no more audible sounds (Korotkoff phase IV).

In the evaluation, three BP measurements were taken in alternate arms, with 2-min intervals between them. If and when there was a difference greater than 4 mmHg between the last two SBP and/or DBP measurements, new measurements were taken until smaller differences were obtained. If the mean SBP was equal to or greater than 140 mmHg and/or DBP was equal to or greater than 90 mmHg, two more evaluations were performed at different weeks, following the same procedure. If the values persisted, students would be advised to seek a specialist; and if SBP was less than 140 mmHg and DBP was less than 90 mmHg, BP values would be considered acceptable and a second assessment would not be performed.

Statistical analysis

The data were tabulated in Microsoft Excel and analyzed in IBM SPSS Statistics v.29.0.0. Descriptive statistics, Student's t-test for independent samples (two groups) or the analysis of variance model (ANOVA) with one factor (more than two groups) were used. For the univariate and multivariate analyses, logistic regression models were adjusted. The Wald test was used to analyze the significance of each variable and the estimated measure of association was the Odds Ratio (OR) with 95% confidence intervals (95%CI). Statistical significance was set at < 0.05 .

RESULT

The study evaluated 80 students, and ten volunteers were selected per academic period contemplated in the research (first to eighth periods). The sample had a mean age of 21.6 years ($SD = 3.6$), with equal distribution between genders. The mean BMI was 22.3 kg/m^2 ($SD = 2.5$). The mean systolic pressure

was 119.7 mmHg and the diastolic pressure was 77.8 mmHg .

Of the 80 students, 32.5% had altered blood pressure. Of these, 21.3% were classified as pre-hypertensive, 8.8% as stage 1, and 2.5% as stage 2. Males were significantly associated with altered blood pressure ($OR = 5.7$; $p = 0.001$), as well as high BMI ($OR = 3.61$; $p = 0.047$).

Regarding lifestyle habits, 12.5% reported smoking, with different levels of dependence. Although 50% of the smokers had altered blood pressure, the analysis did not find a statistically significant correlation between smoking and hypertension.

Alcohol consumption was low risk in 56.3% of the sample and increased or high risk in another 22.5%. Students classified as high or very high risk in relation to alcohol consumption had a prevalence of 44.4% linked to altered blood pressure, compared to 29% of students with low or medium increased risk.

Regarding sleep quality, approximately half (48.8%) indicated unsatisfactory sleep. The analysis revealed that students with unsatisfactory sleep had a slightly higher prevalence of altered blood pressure (33.3%) compared to students with satisfactory sleep (31.7%). However, this difference was not statistically significant ($p = 0.877$), which can be explained by the relative homogeneity of blood pressure and sleep results in this sample. In addition, participants who reported poor sleep had slightly higher stress levels, which may indicate an indirect correlation between sleep, stress, and BP.

Regarding physical activity, 92.5% were classified as active or very active. These had a lower prevalence of altered blood pressure values compared to those who were less active.

Regarding the relationship between BP and gender, men were 5.67 times more likely to develop hypertension than women ($p = 0.001$). While 50% of men had altered BP, only 15% of women had altered values, which reflects a significant difference between the sexes.

Based on the scores obtained from the questionnaires applied in the interviews, the stress variable had a mean of 16.3 points, with a standard deviation of 5.9, with a median of 16, with a range between 5-32 points. There was a negative correlation between stress and systolic pressure ($r = -0.26$, $p = 0.019$), indicating that students with higher levels of stress had a slight decrease in systolic pressure. Moderate stress levels were observed in 61.3% of the sample.

Regarding the diet, the mean was 9.5 points with a standard deviation of 2.7, median of 10, and the observed values ranged from 1 to 15 points. About 45% of the participants indicated that they consume a diet below the WHO recommendation. Although no statistically significant association was found between diet and blood pressure, students with inadequate diets were more likely to develop hypertension.

Throughout the academic periods, blood pressure was monitored, and the data showed that systolic

pressure remained stable throughout the periods ($p = 0.583$), and diastolic pressure values decreased in the later periods ($p = 0.025$, Table).

DISCUSSION

The prevalence of 32.5% of altered BP is higher than expected for the age group, indicating the impact of academic and behavioral factors. This result is in line with national and international studies that report rates between 20-35% among university students.^{14,19,26}

The male gender was a significant associated factor¹⁰, corroborating studies that indicate a higher prevalence of SAH in young men due to lower

hormonal protection and greater exposure to risk behaviors, such as alcohol and tobacco. High BMI also showed a strong association^{17,18}, reinforcing evidence that excess weight is a determinant for blood pressure elevation even at early ages.

Limitations of variables such as poor sleep, inadequate diet, and stress^{13,16,27} did not present a statistically significant association in this sample, their high frequency suggests a relevant role in the medium and long term. It is likely that the sample size limited the detection of additional associations. The high proportion of students with poor sleep and moderate or high stress highlights the importance of

Table — Data collected from the 80 students

Variable	Classification	Total	BP				p*	OR (95%CI)
			Unchanged		Changed			
			n	%	n	%		
Course period	1	10	5	50.0%	5	50.0%		
	2	10	7	70.0%	3	30.0%		
	3	10	5	50.0%	5	50.0%		
	4	10	7	70.0%	3	30.0%		
	5	10	5	50.0%	5	50.0%		
	6	10	10	100.0%	0	0.0%		
	7	10	8	80.0%	2	20.0%		
	8	10	7	70.0%	3	30.0%	-	-
Course year (4cl)	1 (ref)	20	12	60.0%	8	40.0%		
	2	20	12	60.0%	8	40.0%	0.999	1.00 (0.28 - 3.54)
	3	20	15	75.0%	5	25.0%	0.315	0.50 (0.13 - 1.93)
	4	20	15	75.0%	5	25.0%	0.315	0.50 (0.13 - 1.93)
Course year (2cl)	1 to 4 (ref)	40	24	60.0%	16	40.0%		
	5 to 8	40	30	75.0%	10	25.0%	0.155	0.50 (0.19 - 1.30)
Age (years)	[average ± SD]		21.7 ± 3.6		21.3 ± 3.5		0.595	0.96 (0.83 - 1.11)
Gender	Female (ref)	40	34	85.0%	6	15.0%		
	Male	40	20	50.0%	20	50.0%	0.001	5.67 (1.95 - 16.5)
BMI (kg/m2)	[average ± SD]		21.9 ± 2.5		23.2 ± 2.3		0.028	1.25 (1.02 - 1.53)
BMI classification	Below normal	1	1		0			
	Normal weight	67	48	71.6%	19	28.4%		
	Overweight	11	4	36.4%	7	63.6%		
	Obesity grade I	1	1	100.0%	0	0.0%	-	-
BMI classification	Below/normal (ref)	68	49	72.10%	19	27.9%		
(agrup)	Overweight/obesity I	12	5	41.70%	7	58.3%	0.047	3.61 (1.02 - 12.8)
Smoking	No (ref)	70	49	70.0%	21	30.0%		
	Yes	10	5	50.0%	5	50.0%	0.216	2.33 (0.61 - 8.92)
Sleep	Unsatisfactory (ref)	39	26	66.7%	13	33.3%		
	Satisfactory	41	28	68.3%	13	31.7%	0.877	1.08 (0.42 - 2.75)
Alcohol	Low risk	45	32	71.1%	13	28.9%		
	Increased risk	17	12	70.6%	5	29.4%		
	High risk	10	5	50.0%	5	50.0%		
	Very high risk	8	5	62.5%	3	37.5%	-	-
Alcohol (group)	Low/Increased Risk (ref)	62	44	71.0%	18	29.0%		
	High/very high risk	18	10	55.6%	8	44.4%	0.223	1.96 (0.67 - 5.76)
Physical activity	Sedentary	2	1	50.0%	1	50.0%		
	Irregularly active A	3	3	100.0%	0	0.0%		
	Irregularly active B	1	1	100.0%	0	0.0%		
	Active	32	25	78.1%	7	21.9%		
	Very active	42	24	57.1%	18	42.9%	-	-
Stress (score)	[median (min-max)]		16 (5 - 32)		15 (5 - 24)		0.248	0.95 (0.88 - 1.04)
Classification	Low level (ref)	27	18	66.7%	9	33.3%		
	Moderate level	49	32	65.3%	17	34.7%		
	High level	4	4	100.0%	0	0.0%	-	-
Stress (group)	Low level (ref)	27	18	66.7%	9	33.3%		
	Moderate/high level	53	36	67.9%	17	32.1%	0.910	0.94 (0.35 - 2.53)
Diet (score)	[median (min-max)]		10 (1 - 14)		9.5 (4 - 15)		0.954	1.01 (0.84 - 1.20)
Diet (classification)	Average recom (ref)	12	11	91.7%	1	8.3%		
	Below average recom	36	23	63.9%	13	36.1%	0.097	6.22 (0.72 - 53.8)
	Above average recom	32	20	62.5%	12	37.5%	0.088	6.60 (0.76 - 57.7)

institutional policies aimed at academic well-being. The literature indicates that interventions in sleep quality, stress reduction, and promotion of physical activity are effective in reducing blood pressure levels in young people.²⁸⁻³¹ Longitudinal studies have shown that high blood pressure levels in young people are associated with a higher risk of future cardiovascular outcomes.^{21,28,30,32}

CONCLUSION

Although most of the variables explored referring to modifiable risk factors did not present statistical significance with the altered BP values, it is concluded that there was also no statistically significant correlation between the progression of academic periods and altered blood pressure among medical students, which suggests that the advancement in the course, between the first and eighth periods, it was not a determining factor for the increase in blood pressure. However, a positive association was evidenced between variables such as BMI and gender and changes in blood pressure values, reinforcing the importance of weight control as a preventive measure for hypertension. In addition, other risk factors, such as alcohol consumption and physical activity, showed relevant trends, highlighting the need for greater attention to cardiovascular health among the young population and their lifestyle habits during academic life and after the training period. These findings highlight the importance of preventive interventions from the beginning of academic life, aiming to reduce the impact of modifiable risk factors and promote healthy lifestyle habits.

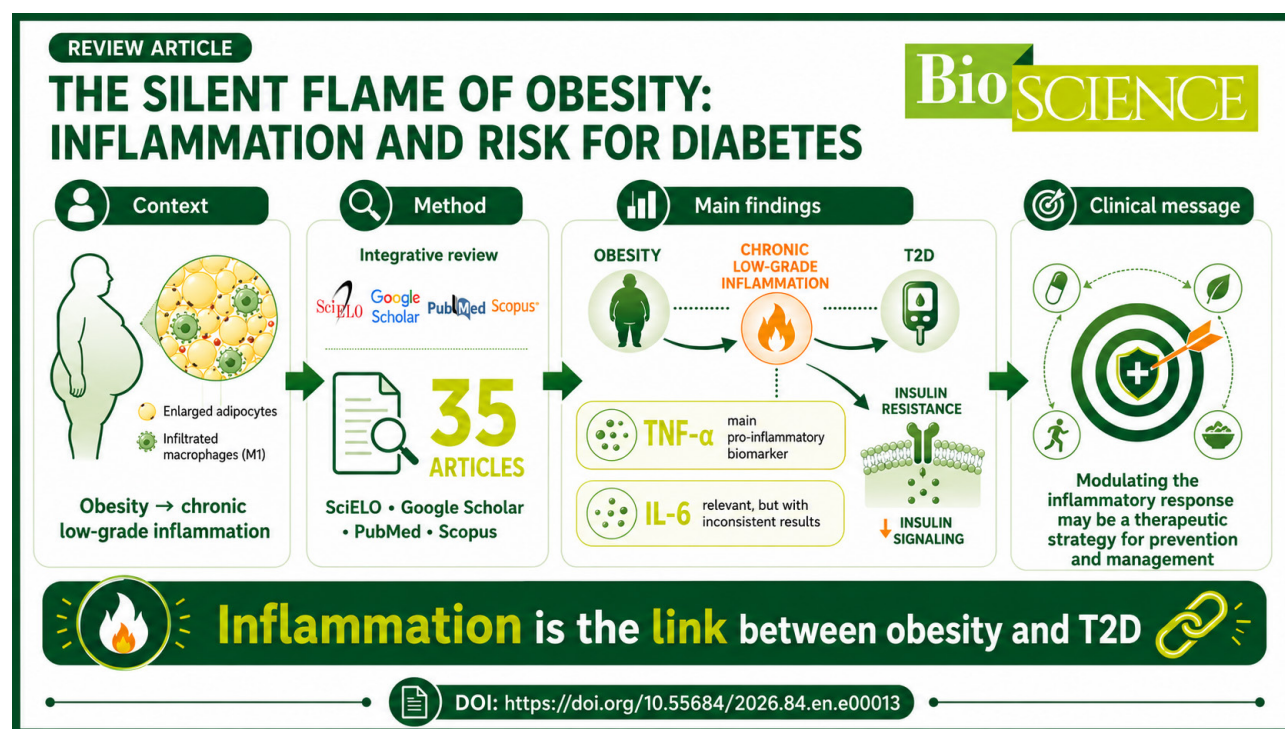
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The silent flame of obesity: inflammation and risk for diabetes

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Central Message

It is important to understand in more depth the inflammatory processes that participate in obesity and type 2 diabetes mellitus. This leads to the development of new therapeutic strategies capable of modulating the inflammatory response associated with these complex metabolic conditions.

Perspective

TNF-α expression is significantly increased in obesity and diabetics, reinforcing the central role of it in inflammation associated with obesity and type 2 diabetes mellitus, validating its usefulness as a more sensitive biomarker.

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ABSTRACT

Introduction: It is important to understand in depth the inflammatory processes that participate in obesity and type 2 diabetes mellitus, aiming to contribute to the development of new therapeutic and control strategies capable of modulating the inflammatory response associated with them.

Objective: To understand in a more in-depth way the inflammatory processes that participate in obesity and type 2 diabetes mellitus.

Method: Integrative literature review was carried out by collecting information published on virtual platforms in Portuguese and English. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for the descriptors "obesity, type 2 diabetes mellitus, TNF- α , IL-6" with AND or OR search, considering the title and/or abstract. Afterwards, considering only those that had a greater relationship with the theme, the full texts were read.

Results: 35 articles that met the inclusion criteria were evaluated.

Conclusion: The integrative review demonstrates that low-grade inflammation plays a central role in the connection between obesity and type 2 diabetes mellitus, highlighting TNF- α as the main pro-inflammatory marker associated with insulin resistance. Although relevant, IL-6 presents results that are still inconsistent, indicating the need for further studies. These findings reinforce the importance of modulation of the inflammatory response as a potential therapeutic strategy in the prevention and management of these metabolic diseases.

KEYWORDS: Obesity. Type 2 diabetes mellitus. TNF- α . IL-6.

INTRODUCTION

The pathophysiology of obesity involves complex interactions between genetic, environmental, neuroendocrine, and immunometabolic factors. One of the main central mechanisms is the dysregulation of the hypothalamic-pituitary axis, especially in the arcuate nucleus of the hypothalamus, where hormones such as leptin, ghrelin, insulin and peptide YY act, responsible for regulating satiety and appetite. In obesity, resistance to leptin is observed, a hormone secreted by adipose tissue that, under normal conditions, inhibits hunger and increases energy expenditure, but loses its effectiveness when levels are chronically high.¹ Obesity poses a global health threat, with rates that have nearly tripled since 1975.²

Middle- and low-income countries concentrate two out of three individuals with obesity, with Brazil being among the five countries with the highest prevalence worldwide. Between 2006 and 2019, obesity in Brazil increased from 11.8% to 20.3% while the percentage of overweight adults rose from 42.6% to 55.4%. This significant growth does not occur only in adults: projections indicate that, by 2044, about 48% of Brazilian adults will live with obesity, bringing the total number of overweight people to approximately 75% of the population.³

This scenario imposes high direct costs on the Unified Health System (SUS) estimated at US\$ 654 million per year only for non-communicable diseases related to excess weight, in addition to representing a significant economic and social burden.⁸ The global prevalence of obesity is expected to reach approximately two billion adults by 2035 and is projected to increase from 14% to 24%.⁵

Thus, it is important to understand in a more in-depth way the inflammatory processes that participate in obesity and type 2 diabetes mellitus, aiming to contribute to the development of new therapeutic strategies capable of modulating the inflammatory response associated with these complex metabolic conditions.

METHOD

This is an integrative review of the literature made by collecting information published on virtual platforms in Portuguese and English. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for descriptors "obesity, type 2 diabetes mellitus, TNF- α , IL-6" with AND or OR search, considering the title and/or abstract. Afterwards, considering only those that were more related to the theme, the texts were read in full and at the end 35 articles that met the inclusion criteria were evaluated.

DISCUSSION

Adipose tissue and inflammation

The pathophysiological mechanism of obesity includes a state of chronic low-grade inflammation, characterized by persistent immune activation and release of systemic inflammatory mediators. This inflammatory cascade is stimulated by the complex interaction existing within adipose tissue. In patients with this condition, adipocytes are hypertrophied, secreting chemokines that recruit and activate immune cells, promoting a microenvironment in favor of inflammation.⁵

In obesity there is intense oxidative stress, caused by the release of reactive oxygen species stimulated by the entry of nutrients existing in obesity, explaining the mechanism of inflammation. In addition, this nutrient overload can promote endoplasmic reticulum stress and unfolded protein response, activating intracellular inflammatory pathways. This inflammation causes the release of inflammatory cytokines such as TNF- α , which can activate several inflammatory signaling molecules, such as JNK (c-Jun N-terminal kinase) and IKK β (Inhibitor of nuclear factor kappa-B kinase subunit beta), causing insulin deficit action on adipocytes and hepatocytes, reducing their sensitivity to it. TNF- α inhibits the expression of PPAR γ (Peroxisome Proliferator-Activated Receptor gamma), which is important for maintaining insulin sensitivity. High levels of TNF- α produced in both the liver and muscle can

induce insulin resistance.⁶

The sustained inflammatory environment causes insulin resistance due to TNF alpha and IL-6 inhibiting the translocation of the GLUT4 transporter in the muscle, favoring hepatic steatosis, stimulating lipid production and, reducing their oxidation, causes beta cell dysfunction, since prolonged exposure to interleukin beta (IL- β) decreases insulin production capacity.⁵

Adipocytes release numerous hormones, inflammatory mediators, and immune system effectors into the bloodstream. In obesity, there is a phenotypic alteration in the cells, creating a chronic low-grade inflammatory environment, characteristic of obesity. Type 1 innate lymphocytes are a type of regulatory cells that make up adipose tissue and are responsible for sustaining homeostasis through the secretion of type 2 interleukins, consequently, preserving adipose tissue macrophages in an anti-inflammatory state. Adipose tissue inflammation in obesity results from a complex interaction between dysfunctional adipocytes and infiltrated immune cells, forming a self-sustaining inflammatory microenvironment, which has a crucial contribution to metabolic dysfunction. As adipose tissue increases in obesity, adipocytes are hypertrophied, subsequently undergo hypoxia and necrosis, releasing molecular patterns related to damage, which are signals that recruit innate and adaptive immune cells.⁵

Adipose tissue expresses high levels of TNF- α , and there is a direct causal relationship between tumor necrosis factor and glucose intolerance. There is an increase in the number of adipose tissue macrophages in obesity in both mice and humans, and macrophages are thought to be the main insulin signals. This is because macrophages in adipose tissue produce factors that act in a paracrine or systemic way and disrupt insulin signaling in target cells. Macrophages produce chemokines and cytokines that stimulate the chemotaxis of circulating monocytes and other immune cells, such as pro-inflammatory M1 macrophages, which make up to 40% of fat cells in obesity.⁶

Macrophage activation occurs through the signaling of the TLR4/NLRP3 (Toll-Like Receptor 4/NOD-Like Receptor Protein 3) inflammasome by SFAs (Saturated Fatty Acids-mediated) as RANTES-Regulated upon Activation, Normal T cell Expressed and Secreted (CCL5). T lymphocytes have altered polarization, characterized by an increase in Th1 cells, which release IFN- α (Interferon alpha) and promote the activation of macrophages, as well as Th17 cells, which produce IL-17, which acts in synergy with TNF- α , intensifying the inflammatory process. In contrast, there is a reduction in regulatory T lymphocytes, decreasing the release of anti-inflammatory cytokines such as interleukin-10 (IL-10) and TGF-beta.⁵

In addition, dendritic cells contribute to the intensification of the immune response by secretariat Interleukin-12 (IL-12) and Interleukin-18 (IL-18), thereby activating T lymphocytes, while B cells produce autoantibodies and IL-6, further stimulating pro-inflammatory T lymphocytes. Concomitantly, stress-stressed adipocytes as well as infiltrated immune cells

release pro-inflammatory cytokines that establish an inflammatory feedback loop, maintaining and aggravating metabolic dysfunction. Excessive weight gain causes hypertrophy and hyperplasia of adipose tissue, which leads to chronic low-grade inflammation of visceral adipose tissue.⁵

Obesity prevention requires a multifactorial approach that involves sustainable lifestyle changes, with an emphasis on healthy eating, regular physical activity, and reducing sedentary behavior. Early interventions, especially in childhood and adolescence, are crucial, considering that inadequate eating habits and low physical activity tend to persist into adulthood. The promotion of school and community environments that favor healthy choices, as well as public policies that encourage clear nutrition labeling, the control of advertising of ultra-processed foods, and the taxation of sugary drinks, have proven to be effective strategies to contain the advance of population obesity.⁷

Diabetes mellitus (DM)

It is a chronic, complicated and non-communicable endocrine disease that has been growing rapidly, which represents a challenge for public health, since it is associated with changes in metabolic development. There are two types, DM1 and DM2. The former presents in children or adolescents, while the latter affects more middle-aged and elderly adults who have had prolonged hyperglycemia due to lifestyle with Western diets and little physical activity. The development of DM2 is related to various polygenic and environmental factors, thus having an important genetic polymorphism, a great diversity of risk factors, and is therefore difficult to cure. Appropriate management includes attention to blood glucose control and attention to risk factors for cardiovascular diseases such as hyperlipidemia, hypertension, and obesity.^{8,9}

MODY, diabetes-onset in the juvenile, is a heterogeneous disease identified by non-insulin-dependent diabetes. It is usually diagnosed at a young age, usually before the age of 25. This version has an autosomal dominant inheritance pattern and does not have autoantibodies like DM1. Several genes are involved in its pathogenesis, including mutations in hepatocyte nuclear factor-1-alpha (HNF1A), which accounts for about 60% of cases, as well as mutations in the glucokinase gene (GCK), present in 15-32% of cases. However, the genetic explanation of MODY is not completely characterized, since in some individuals with mutations they do not develop the disease, while others with clinical symptoms do not have identifiable mutations.¹¹

The current prevalence of T2DM is 10.5% worldwide, equivalent to about 536.6 million adults. The disease has a higher prevalence in high-income countries (11.1%) than in low-income countries (5.5%), due to lifestyle and diets that favor the increase in obesity rates and also due to the fact that low-income countries have underestimated these values due to underdiagnosis.¹⁰

The pathophysiology is not yet completely explained, since it is multifactorial. However, it is known that insulin

resistance, typical of DM2, is associated with excess fatty acids and the presence of inflammatory cytokines, which compromise glucose transport, in addition to stimulating lipolysis. Due to this insufficient insulin response, there is a stimulus to increase glucagon production, further contributing to hyperglycemia.¹¹

Genomic studies have identified genetic variants that influence insulin secretion and action, such as TCF7L2 (Transcription Factor 7 Like 2), PPARG (Peroxisome Proliferator-Activated Receptor Gamma) and FTO (Fat Mass and Obesity- Associated gene). In addition, epigenetic modifications, such as DNA methylation and histone acetylation modulated by factors such as diet and physical activity, have a great influence on the expression of genes involved in glucose regulation.⁹

The gut microbiota also plays an important role in the pathogenesis of DM2, since gut dysbiosis affects glucose metabolism through inflammation, which increases intestinal permeability, leading to changes in the production of short-chain fatty acids. Such microbial changes directly influence insulin sensitivity.⁹

Chronic hyperglycemia is responsible for the non-enzymatic glycation of proteins and lipids, which is monitored by the glycated hemoglobin (HbA1c) test. This glycative process causes damage to small vessels, such as those of the retina, kidneys, and peripheral nerves, conferring the typical clinical condition of the complication of hyperglycemia, which includes retinopathy, nephropathy, and neuropathy. If left unchecked, these complications can progress to blindness, dialysis, and amputations, all of which are potentially preventable with appropriate treatment.¹²

Chronic low-grade inflammation

This inflammation with pro-inflammatory cytokines impairs insulin signaling. Immune cells such as macrophages and T lymphocytes also participate actively, especially in adipose tissue, promoting a pro-inflammatory environment, aggravating insulin resistance.⁹ This chronic low-grade inflammation plays a central role in the pathophysiology of DM2, being strongly associated with insulin resistance and β pancreatic cell dysfunction. Hypertrophied adipocytes and macrophages infiltrated in adipose tissue secrete pro-inflammatory cytokines, such as TNF- α , IL-6, and C-reactive protein (CRP), which interfere with insulin signaling pathways through the phosphorylation of insulin substrates in serine residues, impairing their action on target tissues. In addition, these cytokines contribute to oxidative stress and activation of the innate immune system, perpetuating the inflammatory state and worsening glycemic control. Interventions aimed at reducing this inflammatory process have shown therapeutic potential in the prevention and management of T2DM.^{11,13}

Treatment of diabetes

The therapeutic pattern of T2DM has been changing its trend, focusing on the pathophysiology and its metabolic comorbidities and long-term complications, focusing on the management of obesity to prevent the

condition. This is because weight reduction has been reported to be the most responsible for better glycemic control, including remission of the disease.¹⁰

It is important that there is attention directed to patient education and lifestyle habits. Support of community health agents has shown benefits in the education and self-management of DM, especially in vulnerable populations. Regular physical activity should be encouraged, with realistic goals indicated on an individual basis and based on the assessment of the patient's initial level. The practice of aerobic exercises, resistance, flexibility and balance help in physical fitness, in addition to reducing HbA1c levels. For people who are overweight or obese, weight loss must combine several approaches, including calorie restriction, increased energy expenditure, drug review that induces weight gain, use of weight loss drugs and, in specific cases, bariatric surgery.¹⁰

Drug therapy for T2DM includes injection of insulin-like agents and administration of hypoglycemic agents. In the case of DM1, insulin is crucial for treatment since there is a lack of beta cells.⁸

The initial treatment of T2DM usually starts with metformin, which reduces glucose, has a low risk of hypoglycemia, does not cause weight gain, is safe and easy to use. However, risks such as atherosclerotic cardiovascular disease, heart failure, and kidney disease should be evaluated. The choice of drugs should be made in a shared way with the patient, prioritizing drugs that reduce cardiovascular and renal risks.¹⁰

Lowering glucose to achieve glycemic goals should also be taken into account when choosing medication. A GRADE (Grading of Recommendations, Assessment, Development and Evaluation) study showed that insulin and GLP-1 receptor agonists (Glucagon-Like Peptide-1) are more effective in reducing HbA1c than sulfonylureas or DPP4 inhibitors (Dipeptidyl peptidase-4). There is a tendency to start combined treatment early, instead of following the slow progression between medications, aiming at better long-term control. In cases of marked hyperglycemia (HbA1c > 10%), it is recommended to start insulin or insulin combined with GLP1RA (Glucagon-Like Peptide-1 Receptor Agonist).¹⁰

New studies are being directed to gene therapy with the incorporation of the exogenous normal gene, being an option for the cure of DM1, being responsible for modulation and gene editing. Another therapeutic option would be with stem cells, which aims to replace dysfunctional pancreatic cells, using pluripotent or multipotent stem cells.⁸

Experimental obesity in animals

The litter reduction model is an experimental approach widely used in studies with rodents, such as rats and mice, for the early induction of obesity and metabolic programming. This method is based on a simple principle: by reducing the number of puppies per litter soon after birth, the availability of breast milk per puppy is increased during the lactation period. As consequence the remaining puppies consume a greater amount of milk, which leads to high energy intake in the

first weeks of life, favoring accelerated weight gain and the early accumulation of adipose tissue.¹⁴

The procedure usually consists of standardizing litters to a reduced number of puppies, usually between 3-4 animals per mother, in the first 24-48 h after birth. In contrast, control litters maintain the usual physiological number, which can vary from 8-12 puppies, depending on the species and lineage used. Early overfeeding provided by less competition for breastfeeding results in persistent metabolic alterations, such as hyperphagia (increased food intake), insulin resistance, dyslipidemia, and adipocyte hypertrophy, typical characteristics of obesity.¹⁵

From a physiological point of view, the effects of litter reduction are not limited to the neonatal period. Studies show that the offspring overfed in this model present, throughout their lives, alterations in the hypothalamic-pituitary-adrenal axis, greater expression of genes related to lipid metabolism and inflammation, in addition to a predisposition to the development of metabolic syndromes when exposed to high-calorie diets in adulthood. This makes the model highly relevant for investigations into early metabolic programming, i.e., how nutritional stimuli in the early stages of life affect long-term metabolic health.¹⁶

This model is particularly advantageous because it is non-invasive, low-cost, and mimics real clinical conditions, such as excessive early nutrition in human neonates, either by excessive breastfeeding or artificial feeding. In addition, it allows for a more accurate analysis of the influence of the neonatal nutritional environment on the regulation of appetite, body composition, and endocrine function. For these reasons, litter reduction is considered a robust and reliable experimental model for the study of obesity and its comorbidities, such as T2DM, metabolic syndrome, and chronic low-grade inflammation.¹⁷

The Lee index is a morphometric parameter used mainly in studies with rodents, such as rats and mice, to indirectly assess relative body obesity, especially in experimental models involving metabolic disorders, such as diabetes or induced obesity. It is a formula that relates the animal's body weight to its nasoanal length (from the snout to the base of the tail), providing a standardized measure of body size as a function of mass. This index is considered an adaptation of the body mass index (BMI) used in humans, allowing the identification of excessive body fat accumulation in a simple and non-invasive way. Under normal conditions, the Lee Index presents relatively constant values, and significant increases are indicative of body fat gain, even in situations where the total weight of the animal does not seem to change. It is worth mentioning that the index should be interpreted in conjunction with other parameters, such as visceral fat analysis, blood glucose and lipid profile, for a more complete assessment of the animal's nutritional and metabolic status.¹⁸

Whitten effect for obtaining litter

The Whitten effect is a physiological and behavioral phenomenon observed in rodents, especially in mice

and rats, in which exposure of females to pheromones present in the urine of sexually mature males induces or synchronizes the estrous cycle. Discovered by researcher Wesley K. Whitten in the 1950s, this effect is based on the ability of male pheromones to act as potent chemical signals, which, when detected by the olfactory system of females, especially by the vomeronasal organ, cause neuroendocrine modulation in the hypothalamic-pituitary-gonad axis. As a result, there is a pulsatile release of gonadotrophic hormones (LH and FSH), promoting the entry or synchronization of estrus in exposed females. This effect is especially relevant in situations where females are in anestrus or in less fertile phases of the cycle. In experimental practice, it can be induced by putting females in indirect contact with males, for example, by exposing them to the bull impregnated with urine and other odors of the male, without the need for direct physical contact. The Whitten effect highlights the importance of sensory and social stimuli in the reproductive physiology of rodents.¹⁹

Experimental models of DM

There are different experimental approaches for the induction of DM in animal models, varying according to the type of diabetes to be simulated and the objectives of the research. Among these strategies are: the destruction of β cells of the pancreas by chemical means, partial or total surgical removal of the pancreas (pancreatectomy), induced lesions in the ventromedial hypothalamus, diets high in fat or sugar, malnutrition during pregnancy (intrauterine nutritional restriction) and the administration of high doses of hormones that antagonize the action of insulin, such as glucocorticoids. Despite this variety of methods, the most widely used model today is chemical induction performed through the application of cytotoxic substances that act selectively on pancreatic β cells. The two main drugs used in this context are alloxan (AL) and streptozotocin (STZ), both of which are capable of causing persistent hyperglycemia by compromising endogenous insulin production.²⁰

Induction through STZ administration has been widely used in studies with rodents, due to its ability to promote gradual progression of the disease, with mild clinical manifestations in the early stages. STZ, a glucosamine-derived nitrosourea, has a high affinity for β -pancreatic cells, being taken up by the GLUT2 transporter. Its cytotoxic action results in selective destruction of these cells, leading to deficiency in insulin production and consequent persistent hyperglycemia.^{21,30} The systemic toxicity of STZ is a known and reported factor in several studies, especially when there is variability in the dose, weight of the animals, or inconsistency in the handling and preparation of the substance. In addition to pancreatic toxicity, STZ can induce nephrotoxicity and hepatotoxicity, which contributes to increased lethality, especially when adequate tampons are not used for its preparation or when strict monitoring of the animals is not carried out in the post-induction period.^{31,32} STZ can be administered by different routes, such as subcutaneous, intramuscular, or intracardiac; however,

the most frequently used routes are the intraperitoneal (IP) and intravenous (IV) routes, as they provide greater reproducibility and efficiency in the experimental model.²¹⁻²³

The installation of the diabetic condition occurs in a triphasic and acute way. Initially, in the first 2-4 h after administration, an episode of early hyperglycemia is observed, resulting from the mobilization of hepatic glycogen, without concomitant elevation of serum insulin levels. Between 6-10 h, there is a phase of hypoglycemia, due to the transient increase in insulin secretion. Finally, persistent hyperglycemia is established approximately 24 h after application, characterizing the condition of induced diabetes.

It is important to emphasize that, although there are other strategies for inducing diabetes in animal models, such as partial pancreatectomy, LA administration, or the combination of a high-calorie diet with low doses of STZ to simulate DM2, the use of intraperitoneal STZ is motivated by its speed, low cost, and specificity for β cells, in addition to allowing the achievement of an acute hyperglycemic condition with high predictability in the metabolic parameters evaluated.

It is interesting to mention that the intraperitoneal STZ model warns of the need for technical refinements in the management of the substance and in post-induction care. Strategies such as the use of freshly prepared pH 4.5 citrate buffer, administration in fasting conditions, and intensive follow-up in the first hours after injection can contribute to the reduction of mortality and greater homogeneity of the experimental groups.³³

Serum inflammatory markers

TNF- α is a central inflammatory cytokine in the development of insulin resistance, being secreted predominantly by macrophages in white adipose tissue in obese individuals and animal models. It acts through the activation of MAPK and NF- κ B pathways, reducing IRS-1 phosphorylation and thus directly impairing insulin signaling and promoting lipolysis, decreased adipogenesis, and reduced adiponectin, aggravating metabolic imbalance.²⁴

IL-6 is a pleiotropic cytokine synthesized by several cell types, such as adipocytes, macrophages, endothelial cells, hepatocytes, and muscle fibers. It plays essential roles in the regulation of the acute inflammatory response, the synthesis of phase proteins (CRP, fibrinogen), and the control of hematopoiesis.²⁵ Approximately 1/3 of circulating IL-6 in the absence of inflammation is produced by adipose tissue, contributing to the proinflammatory state observed in obesity.²⁶ Through classical signaling and trans-signaling via the sIL-6R and gp130 receptor, IL-6 influences metabolic processes, such as insulin resistance, and may also act as muscle-derived myokine, stimulating lipid oxidation and glucose uptake in response to exercise.²⁷ IL-6, secreted by adipocytes, macrophages, hepatocytes, and muscle fibers, is positively correlated with insulin resistance, central adiposity, and CRP elevation, reinforcing its role as a clinical marker of systemic inflammation.

The Markers inflammatory TNF- α and IL-6 are recognized as reliable indicators of chronic inflammation associated with metabolic diseases. The TNF- α , produced predominantly by macrophages in adipose tissue, promotes insulin resistance by inhibiting signaling via IRS-1 and favor lipolysis and metabolic dysfunction.²⁸

Population studies have shown that high levels of these cytokines increase the risk of developing metabolic syndrome and T2DM, which suggests their potential as useful biomarkers in the prevention, diagnosis, and monitoring of therapeutic interventions.^{14,24}

Previous studies have shown that excess nutrition in the neonatal period can have a lasting impact on energy regulation mechanisms, mainly due to changes in the hypothalamic-pituitary-adrenal axis and in leptin and insulin sensitivity, which favors the development of metabolic syndrome in adulthood.¹⁶ A study using the experimental model of obesity induction with sucrose diluted in water proved to be effective with increased body weight, but without statistical difference, when comparing the Lee index of the obese group with the control group.¹⁸

The investigation of the inflammatory response through the analysis of serum levels of TNF- α and IL-6 in experimental models of obesity and T2DM represents a fundamental approach to understand the immunometabolic mechanisms underlying these chronic diseases. Both conditions are associated with the state of chronic low-grade inflammation, characterized by the persistent production of pro-inflammatory cytokines, which contribute to insulin resistance, endothelial dysfunction, and the development of metabolic complications.³⁴

In 2013, studies stated that animal models, particularly rodents with obesity and induced DM2, offer a standardized and controlled system to validate inflammatory biomarkers, such as TNF- α and IL-6, allowing not only the characterization of the inflammatory profile, but also the evaluation of possible therapeutic interventions.³⁵

The validation of these markers is especially relevant in the context of the development of new drugs aimed at controlling the inflammatory process and preventing associated complications, such as nephropathy, neuropathies, and cardiovascular diseases.

CONCLUSION

The present integrative review shows that subclinical inflammation is a determining link between obesity and type 2 diabetes mellitus, revealing TNF- α as a more consistent and metabolically disruptive pro-inflammatory mediator, whose high expression in obese and diabetic models reinforces its central role in insulin resistance. In contrast, the contribution of IL-6 remains ambiguous and methodologically heterogeneous, requiring further investigations to elucidate its relevance at the interface between adipose tissue and glycemic homeostasis. Thus, the findings not only deepen the understanding of the inflammatory mechanisms that

fuel the progression of these chronic diseases, but also signal the need for therapeutic strategies aimed at the selective modulation of this inflammatory response.

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Behind the white coat: depression and anxiety among medical students

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Behind the white coat

Depression and anxiety among medical students

Cross-sectional study with 162 students | HADS scale

Method

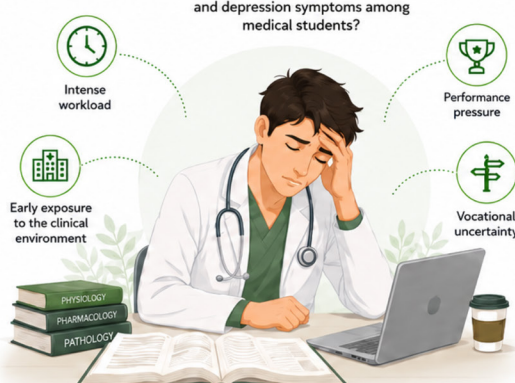
- Prospective, observational and cross-sectional
- Questionnaire via Google Forms
- Instrument: Hospital Anxiety and Depression Scale (HADS)
- n = 162 medical students

Sample

- 70% women
- 87% pre-internship
- Highest concentration in the 8th semester

Central question

What is the prevalence of anxiety and depression symptoms among medical students?



Main message

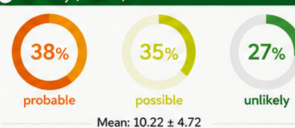
Anxiety and depression are frequent among medical students, especially in the early phases. These findings reinforce the need for continuous institutional strategies to support mental health throughout medical training.

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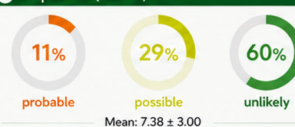
BioSCIENCE

Main findings

A Anxiety (HAD-A)



B Depression (HAD-D)



C Additional findings

- Men showed significantly higher anxiety and depression scores
- No statistical difference between pre-internship and internship
- Trend toward lower scores during internship

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Author's contribution

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Central Message

Evidence shows that the prevalence of mental disorders is higher among medical students compared to the general population, potentially impairing academic performance, relationships, and professional training. Factors such as demanding workloads, performance pressure, early exposure to clinical situations, and vocational insecurity contribute to psychological symptoms

Perspective

Although no statistically significant differences were observed between pre-internship and internship groups, a trend toward reduced Hospital Anxiety and Depression Scale scores was noted during the internship. These results highlight the importance of institutional strategies to promote mental health and continuous support throughout medical training.

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ABSTRACT

Introduction: Depression and anxiety are major mental health concerns, particularly among medical students exposed to intense academic and emotional stress. Factors such as demanding workloads, performance pressure, early exposure to clinical situations, and vocational insecurity contribute to psychological symptoms. Evidence shows that the prevalence of these disorders is higher among medical students compared to the general population, potentially impairing academic performance, relationships, and professional training.

Objective: This study investigated the prevalence of depression and anxiety symptoms among medical students and identified the main factors associated with these disorders.

Method: A prospective, observational, and cross-sectional design was employed. Data collection used a questionnaire via Google Forms, applying the Hospital Anxiety and Depression Scale (HADS) as the assessment instrument.

Results: The sample included 162 medical students, predominantly women (70%). Most participants (87%) were enrolled between the first and eighth semesters, with the highest concentration in the eighth semester (19%). Anxiety results (HAD-A) indicated that 38% were classified as "probable anxiety", 35% as "possible anxiety", and 27% as "unlikely anxiety". For depression (HAD-D), 60% were classified as "unlikely", 29% as "possible", and 11% as "probable depression".

Conclusion: Anxiety and depression are significant among medical students, particularly in the early stages with greater impact among men. Although no statistically significant differences were observed between pre-internship and internship groups, a trend toward reduced HADS scores was noted during the internship. These results highlight the importance of institutional strategies to promote mental health and continuous support throughout medical training.

KEYWORDS: Depression. Anxiety. Medical students.

INTRODUCTION

The prevalence of depression and anxiety among medical students has become an increasingly relevant topic, as these individuals are frequently exposed to intense workloads, high academic pressure, and the responsibilities inherent in medical training.^{1,2} This context fosters the emergence of significant psychological symptoms, making this group particularly vulnerable to the development of mental disorders.

Depression is characterized by feelings of emptiness or irritability, accompanied by somatic and cognitive changes that significantly affect the quality of life of an individual.³ It is considered one of the most common and affecting psychiatric disorders today, affecting approximately 300 million people worldwide.⁴ In Brazil, lifetime prevalence has been estimated at 15.5% with a substantial impact on primary care, where about 10.4% of patients presented depression alone or associated with other clinical conditions.⁵ Anxiety, in turn, is often a response to academic stress and the high expectations imposed on medical students. Its symptoms include excessive worry, insomnia, difficulty in concentration, and physical manifestations such as tachycardia and sweating. In 2019, it was estimated that around 301 million people worldwide suffered from anxiety disorders⁶, and in 2024 its prevalence ranged between 3.8% and 7.3% of the global population.⁷ Brazil shows even more alarming rates, leading the world ranking, with 26.8% of the population affected by some degree of anxiety, corresponding to approximately 56 million people.⁸

Given this scenario, the urgency to investigate the magnitude and associated factors of depression and anxiety among medical students becomes evident.

This study is justified by the importance of mapping such phenomena in this specific group in

order to support institutional policies and strategies for prevention and early intervention, contributing to the promotion of mental health throughout medical training.

METHOD

The study was previously approved by the Research Ethics Committee of the Mackenzie Evangelical University Hospital of Curitiba, according to the substantiated opinion No. 7,272,636 and CAAE: 85002424.7.0000.0103, issued on December 6, 2024. This research complied with all ethical principles established by Resolution No. 466/2012 of the National Health Council, ensuring confidentiality, privacy, and respect for the autonomy of the participants.

This is a prospective, observational, and cross-sectional study with a descriptive approach, emphasizing the analysis of both quantitative and qualitative data. It was conducted with the aim of identifying the prevalence of depressive and anxiety symptoms among medical students through the application of a questionnaire administered via Google Forms, using the Hospital Anxiety and Depression Scale (HADS) as the assessment instrument.

RESULTS

Profile of the participants

As presented in Table 1, the sample of 162 students was predominantly composed of female participants, representing 70% of the total, while males represented 30%, and one person identified as non-binary (1%). The distribution of students in the stages of the medical program showed the highest concentration in the eighth semester, with 19% of the participants. The vast majority of the respondents, 87%, had not yet entered the internship.

TABLE 1 — Sociodemographic and academic characterization of the sample

Variables	Count
Gender	n (%)
Female	113 (70%)
Male	48 (29%)
Non-binary	1 (1%)
Semester	n (%)
1st semester	13 (8%)
2nd semester	28 (18%)
3rd semester	22 (14%)
4th semester	19 (12%)
5th semester	22 (14%)
6th semester	4 (3%)
7th semester	8 (5%)
8th semester	30 (19%)
9th semester	15 (9%)
10th semester	2 (1%)
11th semester	3 (2%)
12th semester	1 (1%)
Internship	n (%)
Before internship	141 (87%)
During internship	21 (13%)

Evaluation of symptoms

In the evaluation of anxiety symptoms (Table 2) using the Hospital Anxiety and Depression Scale (HAD-A), the mean score of the sample was 10.22 ± 4.72 . The analysis of the results indicated that 38% of the students were classified as having “probable anxiety,” 35% as “possible anxiety” and 27% as “unlikely anxiety.” For depression symptoms (HAD-D), the mean score was 7.38 ± 3.00 . The majority the participants (60%) were classified as “unlikely depression,” while 29% presented “possible depression” and 11% “probable depression.”

TABLE 2 — Descriptive analysis of anxiety and depression scores and classification

Variables	Count
HAD-A, Mean $\pm$ Standard Deviation	10.22 ± 4.72
Anxiety	Result, n (%)
Unlikely anxiety	44 (27%)
Possible anxiety	58 (36%)
Probable anxiety	62 (38%)
HAD-D, Mean $\pm$ Standard Deviation	7.38 ± 3.00
Depression	Result, n (%)
Unlikely depression	97 (60%)
Possible depression	47 (29%)
Probable depression	18 (11%)

HAD-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; HAD-D=Hospital Anxiety and Depression Scale – Depression Subscale.

Comparison between sexes

When comparing mental health scores by sex (Table 3), statistically significant differences were found both for anxiety symptoms ($p = 0.001$) and for depression symptoms ($p = 0.018$) in the numerical difference between the scores. For anxiety (HAD-A), the mean score for males was 11.14 ± 4.60 , a value higher than the mean for females, which was 7.92 ± 4.18 . This difference was shown to be statistically significant in the multiple comparison test ($p = 0.001$) between males and females. The categorical

classification analysis confirms this finding, showing that 45.1% of the male participants fell into the category of “probable anxiety”, compared to 20.8% of the females ($p = 0.001$). With respect to depression (HAD-D), the mean score for the males (7.73 ± 3.02) was also higher than that for the females (6.44 ± 2.77). This difference was also statistically significant in the multiple comparison test ($p = 0.022$) between males and females.

Similarly, the prevalence of “probable depression” was higher among males (14.2%) compared to females (4.2%), with statistical significance ($p = 0.028$).

Comparison between course phases

When comparing medical students according to their progression in the program (Table 3), no statistically significant differences were found in anxiety or depression levels. For anxiety symptoms (HAD-A), the mean score of the students before the internship was 10.48 ± 4.83 , while for those in the internship it was 8.48 ± 3.59 . Although the mean was numerically lower in the internship group, the difference did not reach statistical significance ($p = 0.076$). Similarly, the distribution among the categories of “unlikely,” “possible,” and “probable” anxiety did not differ significantly between the two groups ($p = 0.588$). Regarding depression symptoms (HAD-D), the results were similar. The mean score for the pre-internship group was 7.44 ± 3.06 , and for the internship group it was 6.81 ± 2.48 , without statistically significant difference ($p = 0.395$). The categorical classification of depression outcomes also showed no significant variation between the groups ($p = 0.738$).

TABLE 3 — Distribution of anxiety and depression classification according to sex and course phase

Course Phase	Before Internship	During Internship
Anxiety Result – Female		
Unlikely	15 (9%)	5 (3%)
Possible	34 (21%)	8 (5%)
Probable	47 (29%)	4 (2%)
Anxiety Result – Male		
Unlikely	22 (14%)	2 (1%)
Possible	13 (8%)	1 (1%)
Probable	9 (6%)	1 (1%)
Anxiety Result – Non-binary		
Unlikely	0 (0%)	0 (0%)
Possible	0 (0%)	0 (0%)
Probable	1 (1%)	0 (0%)
Depression Result – Female		
Unlikely	49 (30%)	12 (7%)
Possible	32 (20%)	4 (2%)
Probable	15 (9%)	1 (1%)
Depression Result – Male		
Unlikely	34 (21%)	2 (1%)
Possible	8 (5%)	1 (1%)
Probable	2 (1%)	0 (0%)
Depression Result – Non-binary		
Unlikely	0 (0%)	0 (0%)
Possible	1 (1%)	0 (0%)
Probable	0 (0%)	0 (0%)

Comparison between course phases by sex

A stratified descriptive analysis was also conducted to explore the classification of anxiety and depression by sex, considering the course phase (before or during the internship), as shown in Table 3. In anxiety analysis, it was observed that the highest concentration of “probable anxiety” cases occurred in the female group before the internship, with 29% of the total related to anxiety; however, during the internship, this number decreased to 2%. In the male group, 6% were classified as having “probable anxiety” before the internship and one student during the internship. The non-binary participant was classified as having “probable anxiety” in the pre-internship phase. Regarding depression, among females, 9% of the total of students were classified as having “probable depression” before the internship, a number that decreased to one student during the internship. In the male group, two students (1%) had “probable depression” before the internship, with no cases in this category during the internship phase. The non-binary participant was classified as having “possible depression” in the pre-internship phase.

DISCUSSION

General interpretation of results

The analysis of the results obtained in this study reveals that anxiety showed a higher prevalence than depression among the evaluated medical students. This difference can be explained, in part, by the fact that anxiety tends to manifest more immediately in contexts of pressure and intense academic demands, which are defining characteristics of medical training. Early exposure to situations of high responsibility, such as patient care and practical evaluations, combined with extensive workload, may intensify anxious symptoms even before depressive conditions develop. Furthermore, the perfectionist profile often observed in this group of students, coupled with self-demand and fear of failure, acts as an important risk factor for the increase in anxiety levels.

Comparisons with the literature

The findings of the present study, which identified 38% of students with “probable anxiety” and 11% with “probable depression,” are consistent with both national and international literature, although they present distinct prevalence rates. In Uberlândia, MG, Brazil⁹, for example, a prevalence of depressive symptoms of 79% among medical students was reported, with varying degrees of intensity. Systematic reviews have also high-lighted high prevalence rates, such as one that included 77 studies and found 28% of depressive symptoms among medical students, with greater concentration in the early years of the program¹⁰, a finding similar to that observed in our sample, in which pre-internship students showed higher levels of anxiety and depression compared to those in the internship. Comparable results were described in a study conducted at CEUMA University¹¹, which

identified 54% of students with depressive symptoms, with females being more affected and internship students less symptomatic, corroborating the trend of reduced mean scores observed in our study during this phase. On a global scale, analyses involving more than 160 studies estimated a combined prevalence of depression at 27.2%¹², while a Brazilian meta-analysis reported a prevalence of 30.6%¹¹, both higher than those found in our sample. Regarding anxiety, our results (38% probable anxiety) align with studies describing high rates, such as the one conducted at the ABC Medical School¹³, which found a prevalence of up to 79.9% and research in Dubai, which identified 28.7% of anxiety symptoms among medical students.¹⁴ Similarly, a systematic review with Chinese students reported an average prevalence of 27.22% for anxiety and 32.74% for depression¹⁵, reinforcing that, although percent-ages vary across contexts, the presence of these disorders is consistent and concerning. Furthermore, the literature emphasizes that academic, emotional, and social factors such as workload overload and initial adaptation to the program are among the main determinants of depression and anxiety in medical students^{2,16}, which helps explain the higher concentration of symptoms in the early phases identified in our research.

Study limitations

Among the strengths of this study, the use of the HADS stands out, a validated and widely used instrument for assessing anxiety and depression, which allows efficient screening and comparability with data from different studies.^{17,18} Another relevant aspect is the specificity of the sample, composed exclusively of medical students, which ensures greater homogeneity of the group and relevance to the field. However, some limitations must be acknowledged. This is a cross-sectional study, which makes it impossible to establish causal relationships between academic factors and the presence of symptoms.¹⁹ In addition, the use of a self-report questionnaire may be subject to social desirability bias and underreporting of symptoms by participants. Direct comparison between the data obtained in this study and the results of other research on mental health in medical students presents important limitations, especially regarding the instruments used for symptom screening. This study employed the Hospital Anxiety and Depression Scale (HADS), an instrument developed to identify subclinical symptoms of anxiety and depression in hospital settings, with a focus on psychological manifestations and the exclusion of somatic symptoms. The HADS classifies results into ranges of normality, possible, and probable presence of disorders, which differs from scales such as the Beck Depression Inventory (BDI), PHQ-9, or STAI, which categorize symptoms into levels of clinical severity (mild, moderate, severe). Therefore, the findings of this study 38.27% probable anxiety and 11.11% probable depression should be interpreted with caution. Although they fall within the range observed

in the literature, the nature of the instrument used may influence the sensitivity and specificity of the results.

Perspectives

Finally, it is recommended that future research consider the standardization of instruments or comparative analysis between different scales to allow greater consistency in data and facilitate the development of more effective intervention strategies. Moreover, the results reinforce the need for institutional policies that prioritize mental health in the academic context, especially in medical education. The implementation of continuous psychological support programs, stress management workshops, and well-being promotion strategies may contribute to reducing the prevalence of anxiety and depression, preventing negative impacts on academic performance and future professional practice.^{2,20,21}

CONCLUSION

The results showed that the prevalence of "probable anxiety" was higher than that of "unlikely anxiety", while, in the case of depression, the values for "unlikely" were higher than those for "probable." A statistically significant difference was observed between sexes in the comparison of anxiety and depression scores, with a higher prevalence of "probable anxiety" and "probable depression" among male students. In the analysis of academic progression, considering all semesters of the medical program, no statistically significant differences were identified in anxiety and depression levels. However, there was a trend towards an increase in cases classified as "probable anxiety" and "probable depression" among students from the first to the eighth semester compared to those from the ninth to the 12th semester (internship). Among female students, a significant decrease in rates of "probable anxiety" was observed during the internship. Regarding depression, both in the female and male groups, a relevant reduction was found in cases classified as "unlikely depression" throughout this phase of the program, suggesting changes in the symptom pattern as academic progression advances.

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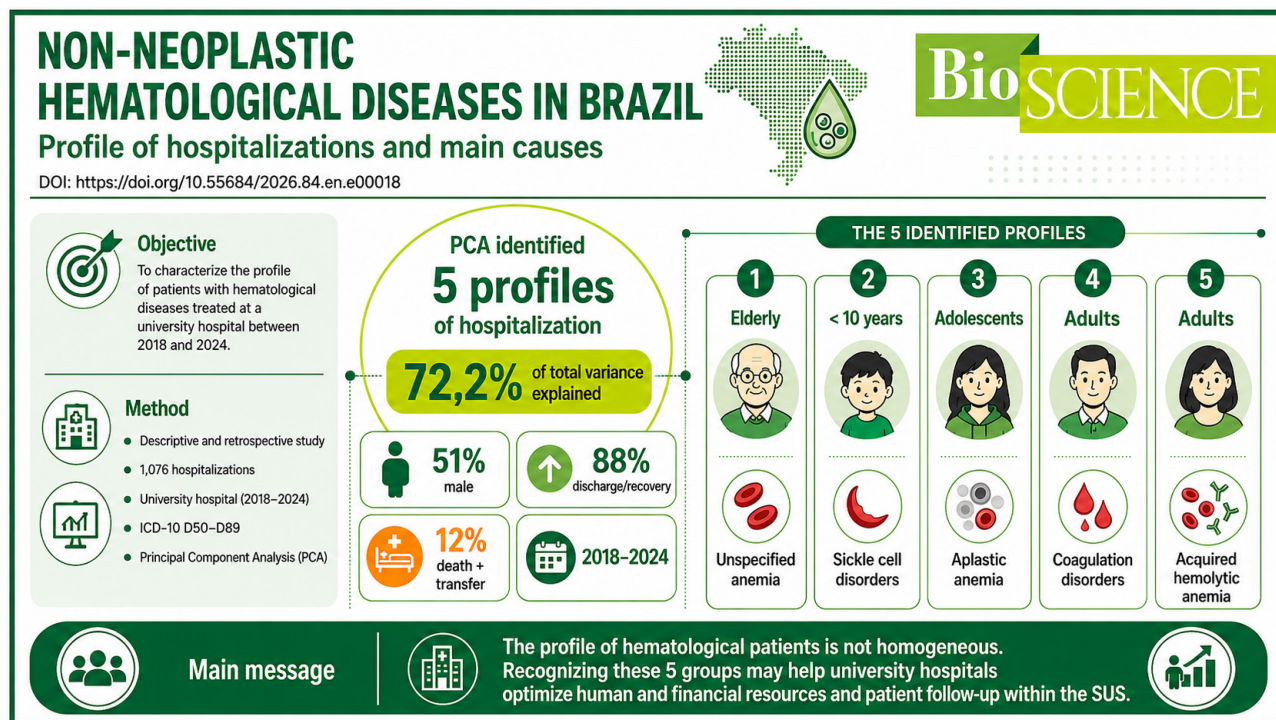
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Non-neoplastic hematological diseases in Brazil: profile of hospitalizations and main causes

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Central Message

Hematological diseases are disorders that affect the blood, bone marrow, and lymphatic system, impairing the production or functioning of blood cells. They contribute to the morbidity and mortality of populations, negatively influencing the growth and development, especially of countries with few resources, and overloading health systems due to the need for continuous treatment.

Perspective

The profile of hematological patients is not homogeneous, and five groups can be identified, namely: Component 1 - Elderly with unspecified anemia; Component 2 - children under 10 years of age with sickle cell disorders; Component 3 - adolescents with aplastic anemia; Component 4 - adults with coagulation defects; and Component 5 - adults with acquired hemolytic anemia. This characterization is important for university hospitals to optimize human and financial resources, as well as the follow-up of patients at the outpatient level and high complexity in the SUS.

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ABSTRACT

Introduction: Hematological diseases are disorders that affect the blood, bone marrow and lymphatic system, impairing the production or functioning of blood cells. They contribute negatively to morbidity and mortality, overloading health systems due to the need for continuous treatment

Objective: To characterize the profile of patients with hematological diseases treated at a university hospital between 2018 and 2024, through principal component analysis.

Method: This is a descriptive and retrospective study based on secondary data of hospitalized patients with hospitalization diagnoses classified in groups D50 to D89 of the 10th Revision of the International Classification of Diseases.

Results: A total of 1,076 hospitalizations for non-neoplastic hematological diseases were recorded. There was a predominance of men (51%). Recovery was high (88%), while deaths and transfers added up to 12%. In the principal component analysis, five groups were identified that together explain 72.2% of the total variance.

Conclusion: The profile of hematological patients is not homogeneous and the classification into five groups is important for university hospitals to optimize human and financial resources, as well as outpatient and high-complexity follow-up in the SUS.

Keywords: Hematological diseases. Medical records. Public health surveillance. University hospitals

INTRODUCTION

Hematological diseases are disorders that affect the blood, bone marrow, and lymphatic system, impairing the production or functioning of blood cells. They can be inherited (e.g., sickle cell anemia, thalassemia), acquired (due to environmental, infectious, or immunological factors, such as leukemia and lymphomas), or due to other health problems (e.g., anemia due to chronic renal failure). These diseases contribute to the morbidity and mortality of populations, negatively influencing the growth and development, especially of countries with few resources, and overloading health systems due to the need for continuous treatment.¹

The prevalence of hematological diseases, both globally and in Brazil, is conditioned by a multiplicity of interrelated factors, among which the limited access to early diagnosis, population aging (considering that hematological neoplasms have a higher incidence among the elderly), genetic elements (such as the occurrence of specific diseases in certain populations, exemplified by sickle cell disease), socioeconomic inequalities (including obstacles in accessing health services and differentiated exposure to environmental risk factors), and the insufficiency of quality epidemiological data in several nations. These aspects, taken together, impose significant barriers to the formulation and implementation of effective programs for the prevention and control of these conditions.¹⁻⁴

In Brazil, according to data from the Department of Information and Informatics of the Unified Health System (DATASUS), there was a significant growth in the number of hospitalizations for hematological diseases between 2018 and 2024: from 6,620 to 130,093, with Paraná accounting for 6.7% of these hospitalizations. Thus, there was a significant increase in hospitalizations in Brazil (20%) and even greater in Paraná (22.2%) in the period analyzed. Despite the increase in the number of cases, the mortality rate in Paraná (3.16%) was lower than the national average (4.92%), which may indicate improvements in treatment or access to health care in the state.⁵

In Brazil and worldwide, the prevalence of

hematological diseases varies widely, depending on the type of disease. Anemia represents the greatest challenge in terms of prevalence among hematological diseases, with a great impact on global public health, especially in low- and middle-income countries.^{1,4,6,7} Among the factors that contribute to the higher prevalence of anemia, poor nutrition, iron deficiency, chronic diseases, and frequent blood loss (hemorrhages) stand out. According to the World Health Organization (WHO), anemia affects 30% of the global population², and is most frequently observed in children under five years of age, women, and the elderly.³ Some conditions, such as onco-hematological neoplasms and genetic diseases, are rarer and, although of low prevalence, have a high economic and clinical impact because they require complex treatment, often of high cost.

Thus, morbidity and mortality and the clinical-epidemiological characteristics of hematological diseases vary according to the type of disease, gender, age group, geographic region, and access to health services. The detailed analysis of these profiles is essential for the formulation of more effective strategies aimed at prevention and early diagnosis.

The present study aimed to perform an exploratory analysis of hospitalizations for non-neoplastic hematological diseases in a university hospital, covering the period from 2018 to 2024. Principal component analysis was used to identify and establish correlations between events or implicit characteristics in patients affected by these conditions.

METHOD

This is a descriptive, retrospective, and quantitative study, based on the analysis of specific reports of patients hospitalized for non-neoplastic hematological conditions at the University Hospital of Western Paraná, State University of Western Paraná, and Epidemiological Surveillance Center, Cascavel, PR, Brazil, covering a period of seven years (2018 to 2024). The study was approved by the Human Research Ethics Committee – CAAE 60158922.5.0000.0107.

Hospitalizations with diagnoses corresponding to codes D50 to D89 of the 10th revision of the International Classification of Diseases (ICD-10), including hematological diseases, were included.⁸ Hospitalizations with ICD codes different from this interval were disregarded.

In the present study, the information was obtained from reports extracted from the Tasy hospital management system and collected in 2025. The variables analyzed were: year of hospitalization, age group of the patients, sex (female and male), clinical outcome (hospital discharge, transfer to another hospital unit or death), municipality of origin (Cascavel or other municipalities) and diagnosis related to hospitalization. The diagnoses were categorized into six subgroups, according to the classifications established in Chapter III (D50 – D89) of the ICD-108, namely: 1) other anemias and aplastic anemias; 2) coagulation defects, purpura and other bleeding conditions; 3) hemolytic anemias; 4) nutritional anemia; 5) other diseases of the blood and hematopoietic organs; and 6) disorders related to the impairment of the immune mechanism. For inclusion in the analysis, only patients whose information was complete in relation to the variables of interest of the study were considered.

Statistical analysis

The data obtained were transcribed into Microsoft Excel spreadsheets. When analyzing the quantitative variables, classical statistical methods were used to calculate frequencies and percentages. To evaluate possible relationships between the variables, Principal Component Analysis (PCA)⁹ was used, which allows patients to be grouped into distinct profiles based on sociodemographic and clinical variables. The PCA aims to reduce the dimensionality of the data (e.g., age, sex, disease type) to identify components that explain most of the variation. To this end, the database was structured as a matrix with 30 variable columns (gender, age group, among others). Each variable column contained 84 elements, corresponding to the number of months between 2018 and 2024. To avoid statistical distortions in the universe of variables, the data were adjusted to the distribution of values of a normal distribution pattern. In view of parameterized variables, the total variance was obtained, and presented in principal components. The Jamovi software was used in the ACP statistical option and Varimax rotation, for the analysis of the data matrix.¹⁰

RESULTS

In the seven-year period (2018-2024), 1,076 hospitalizations for non-neoplastic hematological diseases were recorded. There was a significant increase in hospitalizations (130% in seven years), especially in the last three years, from 125 (2018) to 288 (2024), which may be related to increased detection or worsening of hematological conditions (Figure 1). Regarding biological sex, males (51%) predominated over females (49%). Regarding the

predominant age group (Figure 2), young men (20 to 29 years) had a higher prevalence and among women, cases in advanced age groups (60+) predominated, suggesting a relationship with comorbidities or physiological states (e.g., postmenopause).

The origin of the patients covered 77 cities. More than half of the hospitalizations (59.3%) were from Cascavel, suggesting a greater supply of specialized services (tertiary care) and centralization of hospital referrals. In 40.7% of hospitalizations came from other cities in Paraná, highlighting the relevance of Cascavel as a regional health center. It is essential to highlight that the municipalities of Quedas do Iguaçu, Cafelândia and Toledo also recorded a high frequency of hospitalizations. However, these values were lower than those observed in the municipality of Cascavel.

The clinical profile, consisting of "Other anemias", was the most frequent group (37.2%), indicating the importance of various non-nutritional causes, followed by "coagulation defects and purpura", which represented almost 1/3 of the cases (Figure 3).

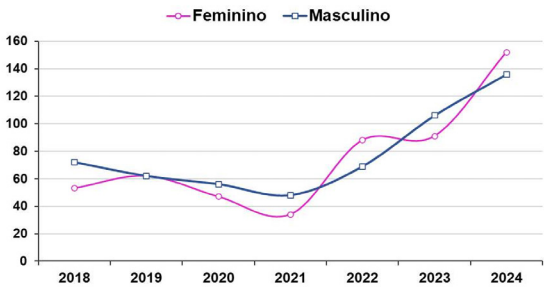


FIGURE 1 — Number of hospitalizations by sex and year of hospitalization

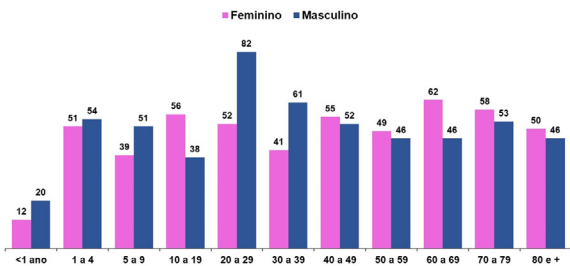


FIGURE 2 — Number of hospitalizations by sex and age group

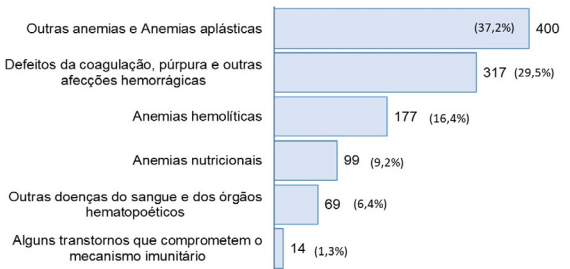


FIGURE 3 — Number and percentage of hospitalizations for hematological diseases grouped according to ICD-10.

In a more detailed analysis, the group called “other anemias and plastic anemias” (n = 400) was composed of 88% of unspecified anemias, 5% of acute post-hemorrhagic anemias, and 7% of aplastic anemia. In the group referring to coagulation defects, purpura and other hemorrhagic disorders (n = 317), 82.3% were related to purpura and other hemorrhagic conditions, 13.9% to other coagulation defects and 3.8% to hereditary deficiency of factor VIII. Regarding hemolytic anemias (n = 177), 84.7% resulted from hereditary hemolytic anemias, mainly associated with sickle cell disorders, while 15.3% were attributed to acquired hemolytic anemias. Among the cases of nutritional anemias (99), 87% had iron deficiency as the main cause, followed, to a lesser prevalence, by anemias caused by vitamin B12 or folate deficiency. In the group of “other diseases of the blood and hematopoietic organs” (n = 69), 63% were classified as other diseases miscellaneous, while 13% involved other disorders of the white blood cells and 9% referred to diseases of the spleen. Finally, the group of disorders affecting the immune mechanism was composed of conditions associated with immunodeficiencies.

Regarding the clinical outcome, there was a high recovery rate (88%), indicating the effectiveness of hospital management, while death (6%) and transfers added up to 12%, representing cases of greater severity.

In the Principal Component Analysis (PCA), five principal components were identified, which explain 72.2% of the total variance, as illustrated in Figure 4. The first component explained 28.2% of the variance, the second contributed with 14.6% and the third with 13.1%. The other components presented smaller contributions, but still relevant. To determine the number of principal components, the eigenvalues greater than one were adopted as a criterion, following Kaiser’s proposal.¹¹ The Table presents the variables and their respective contribution weights to the formation of the five main components.

TABLE — Analysis of principal components according to hospitalizations for hematological diseases. HUOP, 2018 to 2024

Variables	Weight of components				
	1	2	3	4	5
Aged 60 and over	0.913				
Unspecified anaemia	0.899				
Rattlesnake	0.749	0.511			
Death	0.722				
Women	0.715	0.322	0.403		
Iron deficiency anemia	0.711				
High	0.695	0.517	0.433		
Male	0.619	0.434			0.370
Other municipality	0.564		0.546		0.405
Under 10 years old		0.735		-0.371	
Hereditary hemolytic anemia		0.677			
Other blood disorders		0.636			
From 20 to 59 years old	0.418	0.434		0.372	0.408
Aplastic anemias			0.852		
Purple		0.371	0.679		
From 10- 19 years old			0.581		
Other coagulation defects				0.756	
Immune Disorders				-0.729	
Acquired hemolytic anemia					0.864

Note: The varimax rotation was used

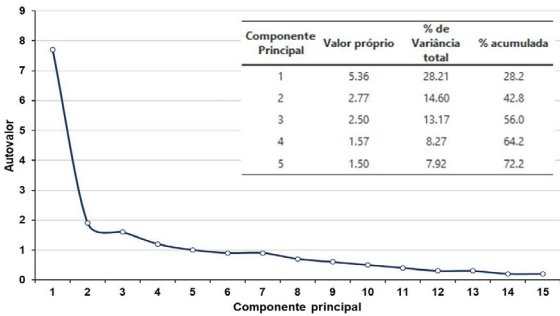


FIGURE 4 — Number and percentage of hospitalizations for hematological diseases grouped according to ICD-10

DISCUSSION

The objective of this study was to identify and interpret linear relationships between a set of variables of patients with non-oncological hematological diseases admitted to a teaching hospital, using PCA over seven years. In the analysis performed, the total variance was distributed in five main components, which, together, explain 72.2% of the total variation of the data (as illustrated in Figure 4). The Table details the contribution of each original variable to the formation of these five main components.

Component 1

Elderly with unspecified anemia.

The first main component, with an eigenvalue of 5.36 and responsible for 28.2% of the variability in the data, highlighted that hospitalizations of patients diagnosed with unspecified anemia and iron deficiency anemia were mostly recorded among people aged 60 years or older. This behavior was consistent regardless of gender, municipality of origin, or hospitalization outcome (discharge or death).

Anemia stands out as a health problem, the incidence of which progressively increases with advancing age. Estimates indicate that this condition affects about 10% of people aged 65, affecting approximately 20% of adults aged 85 and over.¹² However, in hospital contexts, the prevalence of anemia in the elderly varies significantly between studies, ranging from 40% to 84%, suggesting that such variations may be related to the different criteria adopted to characterize anemia.^{7,12-15}

To determine the appropriate treatment of anemia, it is essential to identify its underlying cause, which, in the elderly, may be due to chronic diseases, idiopathic anemia, or nutritional deficiencies.¹³

Anemia associated with chronic diseases is linked to several pathological conditions and, during hospitalization, is related to worse outcomes, including higher mortality, worsening of comorbidities, prolonged hospitalization, and reduced quality of life.^{12,13,16}

Among the elderly, the prevalence of unexplained or idiopathic anemia stands out, affecting approximately 20% to 30% of individuals living in communities, 17% of hospitalized patients, and more than half of residents in long-term care

facilities. Studies indicate that between 5% and 15% of the elderly with this diagnosis can progress to myelodysplastic syndrome.¹⁷

In the geriatric environment, anemia is also recorded due to nutritional deficiencies, especially iron, vitamin B12 and folate.^{17,18} Iron deficiency accounts for almost half of the cases of anemia associated with nutritional deficits in this population, and its etiology is predominantly due to chronic blood loss in the gastrointestinal tract.^{16,19} An analysis based on data from the Hospital Information System (SIH), conducted between 2017 and 2021 in five municipalities of the 4th regional health district of the state of Paraná, identified that hospitalizations for anemia caused by iron deficiency accounted for 8% of the total, while other forms of anemia accounted for 82.1% of the identified cases.²⁰

In this study, the predominance of unspecified anemia among the elderly was verified, a relevant finding, considering that the care took place in a university hospital with infrastructure, specialized staff and adequate laboratory resources for diagnostic elucidation. This fact may indicate difficulty in establishing a more accurate etiological diagnosis, possibly influenced by the presence of other conditions, as described in the literature. The possibility of outdated final diagnoses or inadequate completion of the International Classification of Diseases (ICD) should also be considered, which can lead to underestimation of cases classified by specific cause. Such aspects reinforce the importance of the quality of the information recorded in the system, which is fundamental for care, teaching and research. Finally, it was observed that iron deficiency anemia was the least frequent, in line with the profile described in the literature.

Component 2

Children under 10 years of age with sickle cell disorders.

The second main component, with an eigenvalue of 2.77 and responsible for 14.6% of the variance, indicated that the hospitalization of children under 10 years of age, originally from Cascavel, had as its main reason hereditary hemolytic anemia, often associated with discharge outcome with improvement. In this context, sickle cell disease stood out as the most prevalent condition among the conditions.

Sickle cell disorders affect millions of people worldwide. The absence of early diagnosis, the lack of guidance to families, limited access to preventive measures, the lack of effective government programs for the distribution of medicines, and inadequate care for complications contribute to the reduction of patients' life expectancy.²¹ According to a global analysis carried out on the burden of sickle cell disease between 2000 and 2021, the number of carriers increased by 41.4% and continues to be the 12th leading cause of mortality in children under five years of age.¹⁹ In addition, there has been a significant reduction in the life expectancy of individuals affected

by the disease, especially in the age group between 25 and 30 years.²¹

In Brazil, sickle cell disease is one of the most prevalent genetic conditions, especially among the black population, with unequal distribution among different regions of the country.¹⁹ A survey conducted with 9,349 hospitalized patients in the regions of Bahia, Rio de Janeiro and São Paulo, between 2000 and 2002, indicated that 70% were young people under 20 years of age and that 90.8% of hospitalizations occurred in emergencies.²¹ A recent study in Rio de Janeiro, carried out between 2015 and 2020, analyzed 254 deaths of children and adolescents, finding that 23% of these deaths were caused by sickle cell disorders, predominantly in individuals with brown and black skin and in the age group of 15 to 19 years.²²

In this study, a higher prevalence of sickle cell disease was found in relation to other hereditary diseases. Although most patients identified themselves as white, cases were also recorded among brown people from other states and among immigrants from Haiti and Venezuela. The region has health services capable of offering rapid diagnosis and appropriate treatment, especially at the university hospital, whose efficient care has favored the recovery and discharge of these patients.

Component 3

Adolescents with aplastic anemia

The third main component, with an eigenvalue of 2.50 and explaining 13.1% of the variance, refers to hospitalizations for aplastic anemia and purpura in individuals aged 10 to 19 years, originating from municipalities in Paraná other than Cascavel.

Aplastic anemia is a rare and potentially fatal pathological condition that can affect individuals of any age. Adequate diagnosis, combined with effective therapeutic interventions, is a central element for the clinical management of the disease. An investigation conducted in five regions of Brazil revealed an annual incidence of 2.7 cases per million inhabitants.²³ Another study conducted in the state of Rio de Janeiro recorded a mortality rate from aplastic anemia of 19% among children and adolescents.²² In addition, a comprehensive analysis conducted in Brazil between 2000 and 2019 examined ^{15,157} deaths due to bone marrow aplasia, based on the causes of death declared on death certificates. Of the total, 83.3% of the cases referred to individuals aged between 30 and 40 years, 50.6% of whom were men and mostly residents of the state of São Paulo. In 85.8% of the occurrences, the underlying cause of death was unspecified aplastic anemia, whereas the most frequent immediate causes were septicemia and acute respiratory failure.²⁴

In this study, aplastic anemia was highlighted as a condition of significant relevance among adolescents, reinforcing the need for specific attention to this age group. However, available studies investigating aplastic anemia in hospitalized children and young

adults remain scarce, since most analyses address broader age groups or focus on the overall incidence of the disease.²³

Component 4

Adults with coagulation defects

The fourth main component, characterized by an eigenvalue of 1.57 and accounting for 8.2% of the explained variance, revealed that hospitalizations associated with the diagnosis of other coagulation defects were predominantly associated with individuals in the 20-59 age group.

In Brazil, hospitalizations for coagulation defects include both hemorrhagic and thrombotic disorders, and can have a hereditary origin - such as hemophilia and von Willebrand's disease - or be acquired due to conditions such as liver disease, vitamin K deficiency or the use of certain medications. Hospitalizations for inherited disorders are less frequent, while those related to thrombotic conditions are more common among adults.

There is no specific information on the prevalence of hospitalizations exclusively for coagulation defects in adults. The available data generally address the prevalence of diseases more comprehensively or relate to associated conditions, such as thrombosis. This absence of precise numbers reflects the complexity in compiling public health data, often categorized by broad age groups or by more prevalent diseases.

Regarding hereditary coagulopathies, a survey carried out in 2016 identified 24,228 cases in Brazil. Of these, 41.78% referred to hemophilia A, 8.24% to hemophilia B, 32.24% to von Willebrand's disease, and 7.54% to rare coagulopathies. Most cases occurred in males (67.41%) and were concentrated in the Southeast region, followed by the Northeast, South, Midwest, and North regions of the country.²⁵ A study in Brazil on patients hospitalized for hemophilia in the period from 2020 to 2025 pointed to 2,864 hospitalizations, 84.6% of which were urgent, with a mortality rate in the period of 2.27, with higher rates in the Southeast region.²⁶

Component 5

Adults with acquired hemolytic anemia

The fifth main component, characterized by an eigenvalue of 1.50 and representing 7.9% of the variance, indicated that hospitalizations for acquired hemolytic anemia occurred predominantly among individuals aged 20 to 59 years, from municipalities in the state of Paraná, other than Cascavel.

Autoimmune acquired hemolytic anemia (AIHA) is considered a rare condition; however, hospitalizations occur because it is an urgent condition. The disease can be caused by both immune and non-immune factors. It is most often diagnosed in women in their 40s, with an incidence rate of one case per 100,000 people. Among individuals under 20 years of age, the incidence is 0.2 per million, with a peak in the preschool age group.^{27,28} A study conducted in Brazil, covering a period of nine years (2010 to 2019),

recorded an annual increase of 7% in deaths from hemolytic anemia. This growth was observed, for the most part, among white women over 55 years of age, in addition to standing out for the high mortality rates in the Southeast and Northeast regions.²⁹

The results obtained are consistent with the literature regarding the age profile of the patients. However, other aspects identified require further investigation.

Limitations

This study has limitations that should be considered. The data used were extracted from a secondary database (Tasy), which makes it impossible to completely ensure the absence of underreporting or typing errors. In addition, the information reflects exclusively the population served by the university hospital, which prevents the generalization of the results. Under certain conditions, the scarcity of studies in the literature reinforces the need for more research in the area. The findings of this study are valid and relevant, offering important subsidies for the formulation of public policies in the field of health. They highlight the importance of identifying and understanding the most prevalent hematological conditions, with the aim of not only developing therapeutic approaches that prioritize the efficacy and well-being of affected individuals, but also promoting improvements in the quality of care provided and implementing measures that minimize long-term complications.

CONCLUSION

Hematological diseases encompass a wide range of conditions, some more common than others. The PCA allowed us to identify that the profile of hematological patients is not homogeneous, being divided into elderly patients with unspecified anemia, children under 10 years of age with sickle cell disorders, adolescents with aplastic anemia, adults with coagulation defects, and adults with acquired hemolytic anemia. This characterization is important for university hospitals to optimize human and financial resources. The exploratory analysis performed in this study has the potential to be extended to other hospitals, enabling a more comprehensive overview of the prevalence of hematological diseases in local, regional, or even national populations. This type of approach can support public policies, considering the different realities of human development in each region. The results obtained can also contribute to the formulation of policies aimed at improving the quality of health care for these patients at the various levels of care in the SUS, from outpatient care to high complexity.

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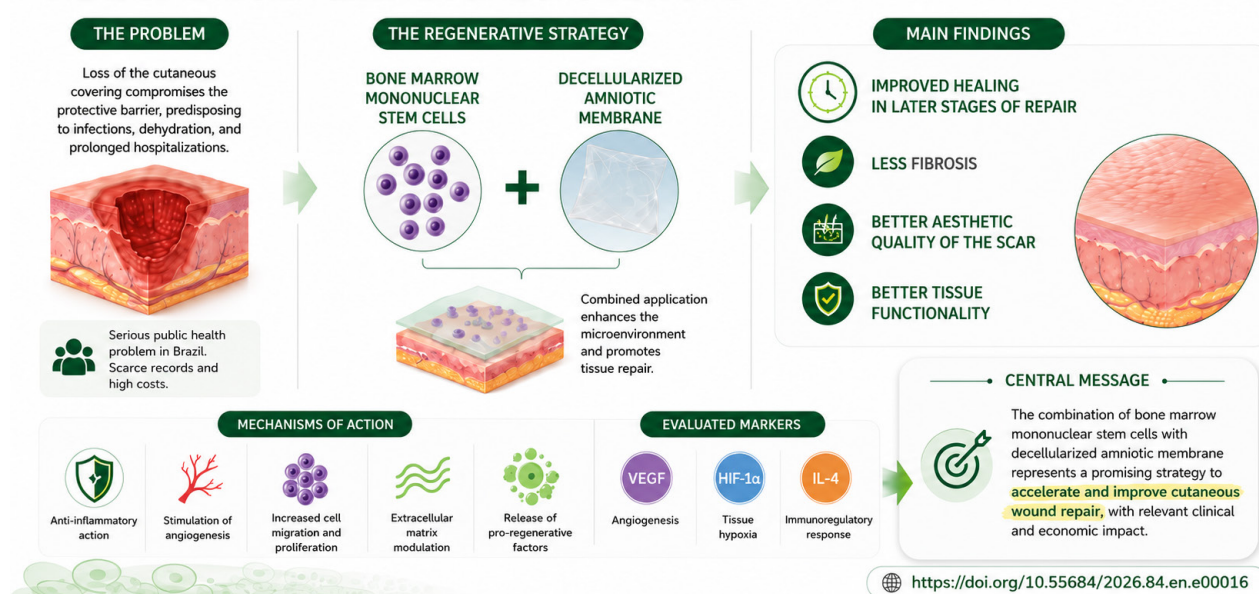
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How to speed up the repair of skin wounds? Evidence with stem cells and amniotic membrane

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REVIEW ARTICLE

HOW TO ACCELERATE CUTANEOUS WOUND REPAIR? EVIDENCE WITH STEM CELLS AND AMNIOTIC MEMBRANE



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Central Message

The skin plays a fundamental role as a biological barrier, acting to protect the body against physical, chemical and microbiological agents from the external environment. In this context, approaches based on tissue engineering have been widely investigated, especially those that combine the use of stem cells and biomaterials, such as the amniotic membrane

Perspective

Future research should focus on the detailed characterization of the underlying molecular and cellular mechanisms, as well as on the evaluation of the sustained effectiveness and safety of this approach in experimental models of greater complexity, especially in the presence of comorbidities that interfere with the dynamics of tissue repair.

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ABSTRACT

Introduction: The skin plays a fundamental role as a biological barrier, acting in the protection of the body against physical, chemical and microbiological agents of the external environment. In this context, approaches based on tissue engineering have been widely investigated, especially those that combine the use of stem cells and biomaterials, such as the amniotic membrane.

Objective: This review aimed to critically analyze the evidence available in the literature on the effects of the application of bone marrow-derived mononuclear stem cells, alone or in association with the decellularized amniotic membrane.

Method: Integrative review conducted with methodological rigor, gathering evidence for clinical practice. It was performed in the PubMed and Medline databases, using the Boolean operator "AND" to associate relevant descriptors.

Results: 97 articles were included that were related to the descriptors mentioned.

Conclusion: The findings demonstrate that mononuclear stem cells associated with the amniotic membrane improve healing in later stages of repair, and may generate less fibrosis, better aesthetic and functional quality of the scar.

KEYWORDS: Wound healing. Mononuclear stem cells. Amniotic membrane. Regenerative medicine.

INTRODUCTION

The skin is a complex organ that performs multiple functions, such as protection, temperature regulation, sensory perception, excretion and synthesis of vitamin D and melanin.¹ Several clinical situations, including burns, trauma, infections, autoimmune diseases, result in the loss of the skin lining, predispose to infections, increase insensible water losses and hypothermia, generating prolonged hospitalizations with high cost and even death.² In Brazil, wounds are a serious public health problem, due to the large number of patients with alterations in the integrity of the skin, although there are few records of these treatments.³

Skin healing is a dynamic process that involves a series of coordinated events with multiple levels of complexity and aims to restore local tissue integrity, resulting in scarring as the final product.⁴ Several studies have been developed seeking new therapeutic strategies for extensive skin lesions,^{5,6} with the objective of improving the quality of healing and reducing treatment time, factors that interfere not only in the quality of life of patients, but also in costs.

Studies with stem cells (SC) in acute or chronic wounds demonstrate acceleration in the healing process, due to the beneficial impact they bring to all phases of healing (inflammatory, proliferative, and remodeling).⁷ An increase in epithelial migration, angiogenesis, and healing rate is observed, in addition to less evident scar formation.^{8,9} The therapeutic possibilities offered by SC isolation and expansion techniques with the potential to regenerate and restore the function of injured organs and tissues represent an important step for the health area.⁴

The amniotic membrane (AM) is a biocompatible tissue and its mechanical properties such as stability, flexibility and permeability, make it a potential scaffold, which improves cell growth, adhesion and migration.¹⁰ It acts to promote re-epithelialization, with anti-inflammatory, antifibrotic, and antiangiogenic actions. Its physical properties, particularly its thin thickness, smoothness and transparency also favor its use.¹¹

Thus, recent studies in tissue engineering have been seeking the association of different cell types

with biomaterials, accelerating the repair process by reducing the time required for cells to occupy the implanted matrix.^{12,13} In this context, it has been demonstrated that the use of AM associated with SC can accelerate and improve the quality of tissue regeneration.^{14,15}

Thus, the objective of this review was to update what the literature has been researching regarding the effect of mononuclear SC therapy associated or not with decellularized MA on the healing process of cutaneous wounds regarding immunohistochemical responses on the 28th postoperative day of the following markers: Vascular Endothelial Growth Factor (VEGF), Hypoxia-Induced Factor (HIF-1 α) and Interleukin 4 (IL-4)

METHOD

Integrative review made by collecting information for reading and analysis from online research on virtual platforms. Initially, a search was carried out for DEC descriptors related to the theme, using the following terms: "Wound healing, mononuclear stem cells, amniotic membrane, regenerative medicine" with AND or OR search, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms, considering only those that were more related to the theme. The full texts were read, including 97 articles in this review.

DISCUSSION

Healing

When the skin is injured, the healing process initiates a series of dynamic events that trigger the coordinated interaction of blood cells, proteins, proteases, growth factors, and extracellular matrix components.¹⁶ The objectives of this repair involve adequate and rapid wound closure, immediate improvement of pain, and the development of an aesthetically acceptable scar.¹⁷ Some internal or external factors such as type 2 diabetes mellitus, radiotherapy and infections can cause delayed or impaired healing.¹⁸

The healing process is a complex multicellular process¹⁹ that can be divided into three overlapping phases: inflammatory, proliferative, and remodeling.¹⁶

Inflammatory phase

Soon after the injury occurs, coagulation and hemostasis begin, which reduce blood loss. This protects the vascular system and maintains the function of vital organs despite injury. There is rapid vasoconstriction through the contraction of smooth muscle cells in the circular muscle layer of the injured vessels. This constriction is strong enough to stop bleeding in arteriole 0.5 cm in diameter. Associated with hemostasis, the coagulation cascade is activated by intrinsic and extrinsic pathways, promoting platelet aggregation and clot formation.²⁰

Once blood loss is reduced, the priority is the removal of dead tissue and the prevention of infections. In the first five days, neutrophils reach a fibrin-rich region and perform phagocytosis and protease secretion. In course of this process, neutrophils destroy local bacteria and degrade devitalized tissues. On the third day of injury, macrophages penetrate the injury area and assist in pathogen phagocytosis and tissue debridement. In addition, macrophages also secrete large amounts of growth factors, chemokines, and cytokines, which are important molecules in the next stage of healing.²¹ Tumor necrosis factor- α (TNF- α) promotes fibroblasts and angiogenesis; transforming β growth factor (TGF- β) stimulates keratinocytes, and vascular endothelial growth factor (VEGF), which is also produced by macrophages, initiates the production of granulation tissue in the transition to the next phase of healing.¹⁶ Mast cells are also active and release granules with active enzymes, histamines, and other amines. These mediators are important for triggering the characteristic signs of inflammation at the wound site: flushing, warmth, pain, and edema.²²

Lymphocytes produce lymphokines such as migration inhibition factor (MIF), interleukin-2 (IL-2), macrophage-activating factor (MAF), and chemotactic factors. They amplify the initial stage of healing through the stimulation of macrophages, endothelial cells, and fibroblasts.²³

Phase proliferated

The proliferative phase is marked by epithelialization, angiogenesis, granulation tissue formation, and collagen deposition.¹⁶

In epithelialization, the keratinocytes of the wound edges and appendages of the dermis form a barrier that prevents bacterial invasion and continuous loss of fluids. Epithelialization is mediated by epidermal growth factors, fibroblast growth factors, and transforming growth factor beta.²⁴ Epithelialization occurs within hours of injury.¹⁶ Epithelial cells migrate upward following standard epithelialization and the epidermis is restored in two to three days if the basement membrane remains intact. If this membrane is damaged, then the epithelial cells at the edges of the skin begin to proliferate and send projections to reestablish the protective barrier.²⁵

Neovascularization is critical to provide nutrients and to maintain granulation tissue. Molecules responsible for angiogenesis include fibroblast growth

factor, vascular endothelial growth factor, transforming growth factor beta, angiogenin, angiotropin, angiopoietin-1, tumor necrosis factor-alpha (TNF α -), and thrombospondin.¹⁶ TNF- α promotes angiogenesis and is characterized by endothelial cell migration and capillary formation.²⁶

Angiogenesis is a complex process that involves the migration and proliferation of endothelial cells, capillary creation, and neovascular remodeling.²⁷

Several other growth factors have also been proven to stimulate angiogenesis, including fibroblast growth factor (FGF), transforming growth factor alpha (TGF- α), and vascular endothelial growth factor (VEGF).²⁷ VEGF also acts on lymphogenesis during tissue healing. The lymphatic vessels drain the lymph from the interstitial space, allowing the arrival of immune response cells. The reduction in lymphatic development can promote the perpetuation of edema and delay in the removal of debris and inflammatory cells.²⁸

The final stage of proliferation is the elaboration of extracellular matrix (ECM) granulation tissue and collagen deposit. Fibroblasts from neighboring tissues migrate to the wound site, become active, and initiate collagen synthesis. Platelet-derived growth factors (PDGF) and epidermal growth factor (EGF) are the main signals for fibroblasts and are sourced from platelets and macrophages. Contraction of the wound occurs through the transformation of fibroblasts into myofibroblasts. Provisional matrix composed of type III collagen, glycosaminoglycans, and fibronectin is synthesized by fibroblasts in response to PDGF.²⁵

Refurbishment phase

The last phase of healing is characterized by the transition of granulation tissue to scar tissue formation.¹⁶ This stage can last 1-2 years or more.²² Initially, the collagen produced is thinner than that of uninjured skin and is deposited parallel to it. Over time, this initial collagen is reabsorbed, and denser and more organized fibers are deposited in the skin's tension lines. However, even after a year of maturation, the collagen in the scar will never reorganize itself as in unharmed skin. The tensile strength of the wound will also not fully return, reaching 30% in the first three weeks and at three months (or more) approximately 80% of the strength of healthy skin.²⁵

Collagen deposition is initially done in a highly disordered way, but over time the new collagen matrix becomes more organized. The underlying connective tissue contracts and brings the wound margins closer together. Several factors, mainly PDGF, TGF- β and FGFs promote this process. Finally, there is a decrease in the density of fibroblasts and macrophages by apoptosis. The rate of capillary growth and blood flow to the area is reduced, as is metabolic activity, resulting in a healed wound.²²

Immunohistochemical markers

Vascular endothelial growth factor (VEGF)

VEGF is one of the most important growth signaling factors in vasculogenesis and angiogenesis.²⁹ It binds

to Flt-1 (VEGFR-1) and KDR (VEGFR-2) receptors that are located on the endothelial surface of developing and mature blood vessels.³¹

Three to five days after tissue injury, new capillaries become visible in the wound bed as granulation tissue, which acts as a matrix for blood vessel proliferation, fibroblast migration, and new collagen.³⁰ Subsequently, the formation of the capillary tube occurs, followed by the anastomosis of the capillary buds and finally, the formation of a new basement membrane.³¹

Progression to the remodeling phase results in a significant decrease in the metabolic needs of the new tissue. In this phase, there is a decrease in angiogenic molecules and an increase in angiostatic molecules, promoting vascular regression. The exact mechanism for vessel regression is not well understood, but it may be associated with upregulation of CXCL10 (IP-10) and secretion of CXCL11 (IP-9, ITAC). The neovasculature regresses to vascular density, similar to that of pre-wounding.³²

Recent studies have indicated extra-angiogenic effects related to VEGF on tissue repair, contributing to the production of scar tissue. Johnson et al 33 showed that VEGF levels correlate with the amount of scar tissue produced in murine models of fetal and adult wound healing. The researchers also reported that VEGF can directly affect a variety of non-endothelial cells known to play an important role in the wound healing response, including keratinocytes and macrophages. Mogili et al 34 found increases in serum VEGF levels as well as increases in VEGF mRNA and protein in keloid vs. normal tissue. WILGUS et al 35 reported in a study that the mechanisms for VEGF-induced scarring in fetal wounds include an increase in the number of fibroblasts or an increased presence of myofibroblasts, a type of cell known to correlate with scars in fetal wounds. The study also demonstrated that injections with anti-VEGF antibodies resulted in a reduction of almost 75% in scar width compared to control.

Hypoxia-induced factor (HIF)

Relative hypoxia is essential in wound healing, as it plays a key role in regulating all critical processes involved in tissue repair. Hypoxia-induced factor (HIF) is a critical transcription agent that regulates adaptive responses to hypoxia.³⁶

At the molecular level, HIF-1 transcriptional target products have been shown to regulate the process of survival, migration, and proliferation of endothelial cells (VEGF, ANGPT-1, ANGPT-2, ANGPT-4, FGF-2, PIGF, PDGF-B, RGC-32), vascular smooth muscle cell migration and proliferation (FGF-2, EGF, PDGF, thrombospondin), and mobilization of circulating angiogenic cells to the periphery (SDF-1/CXCR4).³⁷

The regulation of angiogenesis by HIF-1 is critical for reintegrating oxygen and nutrient delivery to the healing site and improving cell survival. Without HIF-1 activation, continuous vascular disruption can lead to cessation of blood flow, ischemia, hypoxia, and tissue necrosis. In addition, HIF-1 also transcriptionally regulates the expression of many wound repair genes

such as metabolic proteins, adhesion proteins, soluble growth factors, and MEC components (type 1 collagen and fibronectin). For these reasons, HIF-1 α is generally seen as a positive regulator of wound healing and a potential regulator of tissue fibrosis.³⁸

Interleukin 4 (IL-4)

Excessive inflammation is synonymous with tissue repair failure and its control is one of the first essential steps to move from initial containment to the construction of the provisional matrix. IL-4 has traditionally been associated with its anti-inflammatory properties and also for being one of the most important means by which type 2 immunity contributes to tissue repair.³⁹ IL-4 is mainly produced by T-Helper 2 (Th2) and other immune cells. It activates endogenous lymphocytes and promotes the polarization of M2 macrophages, both of which are crucial for tissue repair, playing a critical role in the regulation of immune responses. Recent research has revealed an important connection between immune function and tissue regeneration.⁴⁰

According to Kucukcelebi et al 41, IL-4 has been shown to have several effects in vitro e in vivo which may be useful in the wound repair process, including monocyte stimulation to produce granulocyte and macrophage stimulating factors; neutrophil activation, improved fibroblast proliferation, and increased synthesis and secretion of ECM proteins by fibroblasts. Nguyen et al 42 showed that IL-4 is an essential profibrotic agent with an important role in mediating ECM synthesis to maintain tissue integrity. While IL-4 promotes collagen production to maintain normal physiological processes, its dysregulation can result in abnormal wound healing and fibrotic disease.

Tissue engineering

Tissue engineering comprises therapeutic strategies with materials that stimulate cell and tissue adhesion and proliferation. It also acts on cell-associated products and bioactive molecules or biophysical processes that promote cell proliferation and differentiation in the material.⁴³

Regenerative medicine uses tissue engineering to develop biological substitutes to treat patients with changes in skin integrity. Through use of the body's own stem cells and growth factors, a therapeutic alternative capable of repairing these damaged tissues emerges.⁴⁴

The combination of different cell types with biomaterials can help the repair process by reducing the time required for the patient's cells to occupy the implanted matrix.^{12,13} Some studies have shown that the use of matrices, such as the amniotic membrane, associated with CT accelerates and improves the quality of tissue regeneration.^{14,15}

Stem cells

Stem cell therapy (CT) has It has been shown to be an important artifice in tissue regeneration due to its capacity for differentiation and self-renewal. The CTs they can originate multiple cell lines and have low immunogenicity, a characteristic that favors

them for autografting; In addition, they exert an immunoregulatory effect, which brings new hope for the treatment of various diseases.⁴⁵

Classification

The CTs can be classified according to their cellular plasticity, and can be totipotent, pluripotent and multipotent.⁴⁶ Totipotent cells can originate any cell type in the body, including the entire central and peripheral nervous system.⁴⁷ They correspond to the cells of the newly formed embryo and have the potential to originate even the cells of the extra-embryonic leaflet that will form the placenta.⁴⁸ Multipotent cells are a little more differentiated, present in the adult individual, with the ability to originate only a limited number of tissue types.⁴⁶ Pluripotent cells, on the other hand, can differentiate into all tissues and cells of the three germinal leaflets (endoderm, mesoderm and ectoderm), without gametes and embryonic appendages, these being the CTs embryonic arteries.^{49,50}

As for the place of origin, CTs are divided into two large groups: embryonic cells, which come from the inner cell mass of the embryonic blastocyst; and adults, mainly from umbilical cord blood, bone marrow and peripheral blood. Research indicates that there are also resident CTs, which are for specific tissues or organs throughout the adult organism.^{51,52} and that contribute to tissue homeostasis.

Studies have suggested that adult CTs or somatic cells would not be restricted to the production of tissue-specific cells from which they originate, and would be able to exhibit a wider spectrum of differentiation, characterizing the plasticity of CTs somatic.⁵³ These adult cells develop from ectoderm (epidermal cells, neurons, pigment cells), mesoderm (cardiac muscle, striated muscle, smooth muscle, kidney tubular, blood, adipose tissue), endoderm (pancreatic, thyroid, and lung cells), and germ cells.⁵⁴

Bone marrow CTs are pluripotent and can undergo two differentiation processes: mononuclear cells, which are undifferentiated, and multinuclear cells. From the mononuclear cells, the hematopoietic lineage will originate blood cells (lymphocytes, eosinophils, basophils, neutrophils, red cells and platelets) and mesenchymal, which may originate muscle cells, hepatocytes, osteocytes, adipose tissue, chondrocytes and stroma.⁵⁵

Studies have indicated that adult CTs present in the tissues themselves are reservoirs of reparative cells, being mobilized and differentiated in response to signs of wounds or diseases, thus contributing to the regeneration process of various tissues, such as the skin.^{56,57}

Thus, it is possible to find adult CTs both in the skin and in other various organs. According to Rehen et al.⁵⁸ they are present in the deepest layer of the skin, the hypodermis, where it matures with subsequent migration to the other layers, giving rise to the cells of the epidermis and cutaneous attachments. Alonso et al.⁵⁹ mention that the location of the CTs in the skin is in the basal layer of the epidermis, a membrane rich

in extracellular matrix and growth factors. Alonso et al.⁵⁹ reported that, generally, the proliferation and differentiation of adult epidermal CTs can repair minor skin injuries; however, the low number of these cells does not allow the repair of larger lesions, which can lead to the formation of scars.

Biological properties

Regarding the functionality of CTs, the maintenance of skin integrity occurs through epidermals, which are faster, but less potent. Small repairs can be performed by the CT bulbs, which can be differentiated into different types of tissue. In the case of extensive lesions, adults present in the bone marrow could be recruited; However, it takes longer for them to be able to move from the site of origin to the wound, through circulation. This time can be reduced with the use of cell therapy, through the isolation of large number of cells from donor sites, which can be cultured if necessary and then returned to the patient.⁵⁷

The main sources of CTs extraction are bone marrow and adipose tissue. Other sources of collection have been studied, such as hair follicles as a promising alternative for obtaining CT.⁶⁰

Bone marrow is one of the most studied sources of adult CT, providing hematopoietic and mesenchymal sources (MSC). Among the mesenchymal cells, those of medullary origin are among the best described in the literature and originate from the marrow support stroma. These cells have already been differentiated into adipocytes in vitro, hepatocytes, osteoblasts, endothelial cells, chondrocytes, cardiac myocytes, neural cells, skeletal myocytes, myofibroblasts and renal tubular cells.⁶¹

Studies show that there are at least two pathways through which CTs aid healing: by paracrine signaling and by differentiation. The first shows that they have the property of secreting various growth factors and cytokines that are important for tissue repair or regeneration. When they migrate to the wound, they are activated when they come into contact with the environment of pro-inflammatory substances. The activation of CTs could potentiate the action as small "bioreactors" in the wound microenvironment and secrete growth factors and cytokines. Mesenchymal CTs also facilitate revascularization by paracrine action by secreting FGF and VEGF-A, which promote the proliferation, migration, and differentiation of endothelial cells from the vessels. In addition, the MSCs facilitate revascularization through differentiation into pericytes (vascular endothelial cells).²²

The second pathway of action of CTs is related to the plasticity and the ability of these cells to differentiate into various cell types and to integrate into tissues. Thus, they would help the healing of lesions by differentiating into multiple cells that reside in the skin (keratinocytes, pericytes and endothelial cells).^{9,62,63} However, the contribution of each of these mechanisms of action of CTs is not yet fully known, and is still an element of studies.⁶⁴

The use of CT in acute or chronic wounds results

in acceleration in the healing process, due to the beneficial impact they bring to all phases of healing (inflammatory, proliferative and remodeling).⁷

In the inflammatory phase, CTs coordinate the effects of inflammatory cells and reduce the deleterious effects of inflammatory cytokines, such as TNF and IFN- γ .²² Thus, the inflammatory process of the wound activates the CTs to initiate their immunomodulatory functions, including increased activation of cyclooxygenase-2 (COX-2) and activation of prostaglandin E2 (PGE2) expression, which have multiple fibroregulatory effects on the lesion.⁸ In addition, CTs aid in the elimination of infections through the direct secretion of antimicrobial factors and stimulate phagocytosis by immune cells.²²

The ability of CTs to promote the transition from the inflammatory to the proliferative phase is of utmost importance for the treatment of chronic wounds where high levels of inflammation prevent healing.²²

Finally, they regulate the remodeling of the healed wound, promoting the organized deposition of the extracellular matrix (ECM). Several mechanisms are involved in TC-mediated wound healing, including anti-inflammatory and antimicrobial, immunomodulatory, and tissue repair activities.²²

The usual routes of application of mesenchymal CTs (MSCs) in wound healing, they are intravenous and local, the latter being the most indicated.^{62,63,65} Phalanga et al.⁶⁶ report that it is essential that the CTs remain in contact with the wound bed and remain viable in the environment for them to be effective. Methods of local application of cells include: injection around the wound, topical fibrin spray, and incorporation into a scaffold,^{67,68} that is, matrices that are structures that keep cells adhered to the target site.⁶⁹ When CTs are applied directly to the lesion or its periphery, they adhere and differentiate into various types of skin cells (keratinocytes, endothelial cells, and pericytes), enhancing the healing process.⁶⁴

Studies suggest that CTs injected alone with the defect do not respond satisfactorily. One strategy would be to combine cells with some components, known as a matrix or scaffold.⁷⁰ Thus, the development of strategies in tissue engineering, associating CTs with matrices, such as the amniotic membrane, becomes promising to achieve better results.

Amniotic membrane

The amniotic membrane (AM) has a range of specific and important properties for tissue engineering, such as reduced inflammation and scarring, cell proliferation and differentiation capacity, and the presence of growth factors, collagen, fibronectin, laminin, and proteoglycans in its extracellular matrix.⁷¹

Structure

MA is smooth, resistant, translucent, flexible and slender structure with a thickness of 0.02 to 0.05 mm.⁷² It consists of three microscopically distinct layers: the epithelial, the basal and the mesenchymal layer.⁷³

The epithelial layer, adjacent to the amniotic fluid and the amniotic cavity, is made up of a monolayer

of cuboid epithelial cells, rich in immunomodulatory cytokines and epithelial growth factors. It joins through interdigitations to the second layer - basement membrane - which is thin and resistant, basically formed by reticular fibers, collagen and laminin.⁷⁴

The basement membrane is responsible for the tension and elastic resistance that allows MA distend during the gestational period and resist the intense movements of the embryo/fetus.⁷⁵

The outer layer of the amniotic membrane, known as the mesenchymal or stromal, can be subdivided into three avascular leaflets: compact, fibroblastic, and spongy. Compact leaflet forms the main fibrous skeleton of AM, while fibroblast is rich in fetal hyaluronic tissue, which suppresses cell proliferation by altering the regulation of TGF- β and decreases fibrosis by inhibiting the proliferation and differentiation of myofibroblasts.^{76,77} The spongy leaflet, rich in mucin, is the most external from MA and the closest to the chorion. It has a high abundance of proteoglycans, glycoproteins and collagen, particularly type 3.^{75,78}

Biological properties

The amniotic membrane assists in the epithelialization process by facilitating the adhesion and migration of basal epithelial cells, in addition to preventing apoptosis and restoring the epithelial phenotype. It reduces inflammatory, angiogenic and scarring processes and has antimicrobial action.^{76,79-81}

Due to the structural integrity, transparency, and elasticity of the basement membrane, MA renders as ideal product for the growth of stem cells, as it increases cell life and prevents apoptosis of epithelial cells, facilitating re-epithelialization.^{77,82}

MA presents several growth factors, which makes its use as a biological dressing, especially due to KGF, FGF, PDGF, EGF and VEGF. Of these, FGF stimulates the synthesis and deposition of ECM proteins. It also has some components also present in ECM, such as collagen types 1-7, elastin, laminin and fibronectin. Growth factors and ECM components give AM characteristics of re-epithelialization, reduction of fibrosis, inhibition of pain, infection and inflammation.⁸³

A unique characteristic of AM is that it does not induce immune rejection, as it does not express histocompatibility antigens HLA-A, B or DR 5. Its use has covered several areas of medicine, such as the treatment of burns, prevention of tissue adhesion in surgical procedures of the head, vagina, abdomen, among others.⁸⁴

MA It has metabolic functions such as the transport of water and soluble materials, production of bioactive factors such as vasoactive peptides, growth factors and cytokines.^{75,85} It has a fundamental structural property in clinical application, as a support as a substrate for epithelial cell organization, acting as a biological support.⁸⁶ In addition, it reduces the contraction of the scar in its maturation phase and leaves the final area with macroscopic characteristics more similar to that of the local skin.⁸⁷

The anti-inflammatory property of MA is related

to the high amounts of hyaluronic acid present in the basement membrane, which bind to the trypsin alpha inhibitor, forming an active complex.⁸⁸ Antiangiogenic activities, on the other hand, may be associated with large amounts of extracellular proteins such as type 4 and 7 collagen, laminins 1 and 5, fibronectin, angiostatin, and endostatin⁸², which are involved in the neovascularization process.

MA adheres to the surface of wounds and burns and prevents the formation of space that allows serous secretion to accumulate, reducing bacterial infiltration. This natural barrier function of it, and also its ability to express numerous molecules - such as cystatin - provides antimicrobial and antiviral actions to this tissue.^{81,89,90}

The patient's pain during wound care is an important factor and the use of MA It reduces this symptom by adhering to the wound surface, covering nerve endings, reducing bacterial contamination, and decreasing local inflammation.^{80,91} Its antifibrotic effect may be associated with the inhibitory action of this tissue on TGF- β , responsible for activating the fibroblasts that participate in the healing process.⁹²

Decellularization of the amniotic membrane

An important part of the use of MA is its preparation, which is done through decellularization; There is no change in the strength and elasticity of the fabric, nor in the barrier properties such as antimicrobial and antiviral action. During this process, the basement membrane remains intact due to the presence of collagen, fibronectin, and laminin. Decellularized MA promotes better cell proliferation and differentiation, adequate structural integrity, and also, a more uniform pattern of cell growth when compared to non-decellularized MA.⁹³ Wilshaw et al 94, compared the use of acellular human MA with the use of in natura. The study demonstrated that the decellularized amniotic membrane was able to support adhesion, viability, and proliferation of fibroblasts and keratinocytes, concluding that the acellular membrane has the potential to treat several conditions, such as diabetic foot ulcers, corneal defects, and severe burns.⁹⁵

Due to its characteristics, it is possible that MA can be used as a bio-scaffold macromolecular, and can replace common dressings.⁹⁶ It acts by reducing healing time and/or complications of extensive wounds, acting in a way that allows more physiological wound repair, with better aesthetic and functional results in the final appearance of the scar. In addition, its low cost, as it is a disposal material, makes it advantageous due to the availability and ease of acceptance of donation by pregnant women.⁹⁷

CONCLUSION

Among the therapeutic strategies investigated, the use of mononuclear CTs in association with MA has shown a more evident impact on the advanced stages of tissue repair, with signs of more organized remodeling, less fibrotic deposition, and superior

scarring results from an aesthetic and functional point of view. However, it is still essential to deepen the understanding of the biological processes involved in this cellular and matrix interaction throughout all phases of skin healing. Future research should focus on the detailed characterization of the underlying molecular and cellular mechanisms, as well as on the evaluation of the sustained effectiveness and safety of this approach in experimental models of greater complexity, especially in the presence of comorbidities that interfere with the dynamics of tissue repair.

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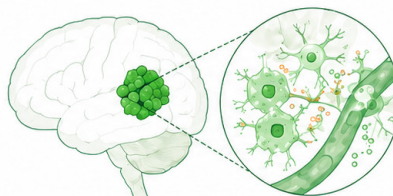
CSF3R/CD114: a predictor related to worse survival in gliomas

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REVIEW ARTICLE

CSF3R/CD114: a predictor related to worse survival in gliomas

High CSF3R/CD114 expression is associated with reduced global survival in different types of glial tumors.



BioSCIENCE

1 LITERATURE REVIEW



Search in databases: BVS, Medline, PubMed and SciELO
Descriptors: CSF3R, CD114, granulocyte colony-stimulating factor, glioma, glioblastoma, brain tumor (AND)



95 articles analyzed

Types of gliomas included



Astrocytoma



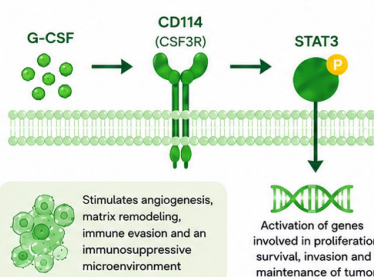
Oligodendroglioma



Glioblastoma (GBM)

2 PROPOSED MECHANISM

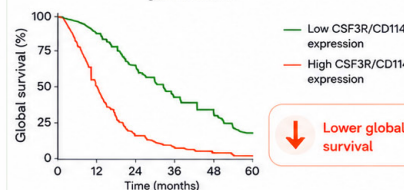
G-CSF/CD114 axis promotes tumor progression



3 PROGNOSTIC IMPACT



High CSF3R/CD114 expression = worse prognosis
Significant reduction in global survival



Association observed in gliomas and glioblastoma (GBM) (P < 0.05)



CENTRAL MESSAGE

High CSF3R/CD114 expression is associated with worse prognosis in gliomas, suggesting its potential as a prognostic biomarker and a promising therapeutic target.

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PERSPECTIVE

More experimental studies are needed to validate CD114 as a therapeutic target and improve the management of patients with gliomas.

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Central Message

Gliomas are neoplasms derived from glial cells, such as astrocytes, oligodendrocytes, and ependymal cells. These tumors are classified into different histological subtypes, the main ones being astrocytoma, oligodendroglioma and glioblastoma, which, among them, stands out as the most common, aggressive subtype, with a reserved prognosis even in the face of multimodal therapeutic approaches.

Perspective

Despite the evidence, the role of CSF3R/CD114 as a possible prognostic biomarker in gliomas is not yet well elucidated and, if, its role in pathogenesis is confirmed, CD114 could be used as a therapeutic target in the development of new drugs or even as a diagnostic and prognostic marker of the disease.

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ABSTRACT

Introduction: Gliomas are the most frequent primary brain tumors, accounting for more than 80% of all primary neoplasms of the central nervous system. These tumors are classified into different histological subtypes, the main ones being astrocytoma, oligodendroglioma, and glioblastoma. Among them, glioblastoma stands out as the most common and aggressive subtype, associated with a poor prognosis, even in the face of multimodal therapeutic approaches that combine surgical resection, radiotherapy, and chemotherapy with temozolomide.

Objective: To analyze the association of CD114 expression with survival in patients with glioma.

Method: The articles were selected by searching the following databases: Virtual Health Library (VHL), Medline, PubMed, and SciELO. The descriptors used were "CSF3R, CD114, colony-stimulating factor of granulocytes, glioma, glioblastoma, brain tumor", performing advanced search by combining them with the Boolean operator AND.

Result: A total of 95 articles were analyzed.

Conclusion: There is an association between high expression of CSF3R/CD114 with worst prognosis of patients, reflected by the reduction in overall survival in different types of glial tumors.

KEYWORDS: CSF3R. CD114. Granulocyte colony-stimulating factor. Glioma. Glioblastoma. Braintumor.

INTRODUCTION

Gliomas are the most frequent primary brain tumors, accounting for more than 80% of all primary central nervous system (CNS) neoplasms. These are histologically heterogeneous neoplasms and classified by the World Health Organization in different degrees, according to their cellular characteristics and their capacity for tissue invasion. Gliomas are neoplasms derived from glial cells, including astrocytes, oligodendrocytes, and ependymal cells. These tumors are classified into different histological subtypes, the main ones being astrocytoma, oligodendroglioma, and glioblastoma (GBM), which, among them, stands out as the most common, aggressive subtype, with a poor prognosis even in the face of multimodal therapeutic approaches that combine surgical resection, radiotherapy, and chemotherapy with temozolomide. The presence or absence of mutation of the enzyme isocitrate dehydrogenase (IDH) allows GBM to be subdivided into three categories: 1) GBM wild-type IDH, which corresponds to about 90% of cases; 2) GBM with mutated IDH; 3) unspecified GBM (NOS), when the IDH mutation is not evaluated.¹⁻⁵

The cell surface protein CD114 (Cluster of Differentiation 114), encoded by the CSF3R gene, acts as a receptor for granulocyte colony-stimulating factor (G-CSF).^{6,7} When stimulated by G-CSF, CD114 activation triggers the transcription activator-mediated signaling pathway 3 (STAT3), which regulates cellular processes such as cell proliferation, differentiation, and survival, and in abnormal situations can promote a cancer stem cell phenotype.⁸

CD114 has been proposed as a marker of cancer stem cells in tumors derived from the neural crest, such as neuroblastoma and melanoma.^{7,9,10} CD114 expression has also been identified in several other solid tumors, such as ovarian, cervical, bladder, and skin tumors.^{7,10-18} In addition, mutations in the CSF3R gene have been found in rare forms of leukemia.^{19,20}

CD114-positive cancer cells demonstrated the ability to self-renew and generate offspring.⁹ Malignant brain neoplasms are capable of

confiscating molecular and cellular mechanisms involved in neuronal plasticity.²¹⁻²⁶ In this context, G-CSF acts as a growth factor, stimulating the survival and plasticity of neurons and neural stem cells²⁷ and, in addition to stimulating neurogenesis,⁶ G-CSF acts synergistically with stem cell factor to induce the growth of cell projections, dendrites and axons, in cortical neurons.²⁸

The combination of G-CSF and stem cell factor also protects against neurodegeneration and promotes the reorganization of the neurostructural network in a murine model of traumatic brain injury.²⁹

In human gliomas, generalized expression of RNA and G-CSF protein was demonstrated, with increased proliferation and migration in CD114+ cells after exposure to the factor. Neutralization of G-CSF, in turn, inhibited tumor growth and cellular migratory capacity.¹¹

Despite the existence of evidence, the role of CSF3R/CD114 as a possible prognostic biomarker in gliomas is not yet well elucidated and, if its role in pathogenesis is confirmed, CD114 could be used as a therapeutic target in the development of new drugs or even as a diagnostic and prognostic marker of the disease.³⁰

This study aims to analyze the levels of CSF3R transcription in gliomas and its possible association with clinical prognosis, evaluated by means of overall survival, and to analyze the association of CD114 expression with survival in patients with glioma.

METHOD

The articles were selected through a search in the following databases: Virtual Health Library (VHL), International Literature in Health Sciences (Medline), PubMed and SciELO. The descriptors used were "CSF3R, CD114, colony-stimulating factor of granulocytes, glioma, glioblastoma, brain tumor", performing an advanced search combining the descriptors with the Boolean operator AND. The inclusion criteria included freely available publications in full in English and Portuguese, specifically addressing glioma and its subtypes.

Incomplete or repetitive articles, preliminary clinical trials in animals, or those involving other diseases unrelated to the tumors mentioned were excluded, totaling 95 articles.

DISCUSSION

Gliomas are the most common and lethal group of brain neoplasms, accounting for about 80% of malignant brain tumors. In addition, they, including low-grade ones, have highly variable clinical behavior and their survival cannot be adequately predicted by histological classification.³¹

The highly aggressive and invasive nature of gliomas poses significant challenges to their complete elimination using current therapeutic strategies, including surgery, radiotherapy, and chemotherapy. Residual tumour cells often lead to malignant recurrence and progression, with some gliomas tending to progress to glioblastoma (WHO grade IV glioma) in a short period of a few months, resulting in a poor prognosis.³¹

These tumors are classified into different types, according to the type of cell from which they originate or with which they share histological characteristics. Thus, gliomas are classified into ependymomas, astrocytomas, and oligodendrogliomas. Of these, astrocytoma is the most common type of glial tumors.³²

Glioblastoma, classified as grade IV glioma by the World Health Organization, is the most common and aggressive type of glioma.^{1,4,33} In this sense, it presents excessive malignancy, being almost always lethal and leading to the death of the patient usually within 12-18 months after diagnosis,³² regardless of the treatment, and in cases of recurrence, it is quickly fatal.³⁴ It differs from low-grade gliomas in that it presents necrosis and microvascular proliferation, with infiltrative behavior and rapid growth as characteristics. In addition, glioblastoma can arise as a primary or secondary tumor, and the secondary tumor is a malignant transformation of a low-grade brain tumor and/or with a mutation in the isocitrate dehydrogenase (IDH) gene³⁵ and codeletion of chromosome 1p/19q.³²

One of the most striking and challenging biological characteristics of gliomas, which are diffuse, is the extreme infiltration capacity of their tumor cells. These cells can spread over extensive regions beyond the primary focus, following structures of the neuropilus, which deals with the network of nerve fibers and glial cells of the brain, even crossing to the contralateral hemisphere and, in some cases, originating additional tumor foci, as observed in multiple glioblastoma. And it is this biological behavior that is one of the greatest challenges of treatment, considering that complete microscopic resection can never be achieved.³⁴

Extracranial metastases are very rare events in glioblastoma, as it is the communication between neoplastic cells and the adjacent tumor stroma that has been shown to be a crucial factor for the invasive growth and dissemination of this type of glioma. Thus,

the processes of invasion and migration by brain tissue represent the main mechanisms of disease propagation.³⁶

In this context, three fundamental routes of dissemination are considered: 1) the collective invasive potential, in which tumor cells advance through the adjacent tissue through interstices of the extracellular matrix, expanding from the primary tumor without completely detaching; 2) the invasion mediated by inflammatory cells, characterized by the action of pro-tumor immune cells that secrete metalloproteinases and degrade the extracellular matrix, creating an imbalance with their physiological inhibitors and facilitating the advancement of malignant cells and it is, in this scenario, that tumor hypoxia stimulates the production of pro-inflammatory proteins and favors the activation of cancer stem cells, promoting gliomagenesis; and 3) via epithelial-mesenchymal transition, described in heterogeneous subpopulations of glioblastoma, where intercellular adhesion and senescence are compromised, which favor epigenetic alterations that culminate in cell dedifferentiation and acquisition of phenotypes similar to those of stem cells, expanding the invasive and adaptive capacity of the tumor.³⁵

The epithelial-mesenchymal transition is a biological process in which cells with epithelial characteristics, that is, those with high adhesion to each other and little mobility, start to acquire characteristics of mesenchymal cells, with less adhesiveness and greater migratory and invasion capacity. This mechanism decisively confers the aggressiveness, plasticity and therapeutic resistance of glioblastomas. In them, there are subpopulations of heterogeneous cells with different phenotypes, so that they pass through similar pathways to the epithelial-mesenchymal transition, even though it is not a classic epithelium; This concept is expanded to tumors of the central nervous system.

Under natural conditions, cell adhesion limits proliferation. However, when it begins the process of senescence, this adhesion is impaired, this "natural brake" is lost, favoring tumor proliferation.

Thus, this pathway gives glioblastoma an infiltrative and adaptive phenotype, making surgical and pharmacological treatments difficult, and in clinical terms it is one of the reasons why glioblastoma has a high recurrence rate and poor prognosis.

The current standard treatment of glioblastomas consists of multimodal therapy involving surgical resection - which should be as broad and safe as possible - radiotherapy and chemotherapy. However, even with adequate treatment results, median survival is 12-15 months.³⁷⁻³⁹ In this core, even with aggressive treatment, in 75-90% of cases, recurrence occurs within 7-10 months after surgery.³²

Pharmacological treatment options for these patients are very limited, making the development of new alternatives one of the greatest unmet demands of current medicine.⁴⁰⁻⁴³ There is also an urgent need to identify and validate new appropriate molecular

biomarkers to improve diagnosis, as well as to guide treatment choices.⁴⁴⁻⁴⁶

Glioblastoma in the current classification of central nervous system tumors

The classification of central nervous system (CNS) tumors is traditionally based on histological characteristics and supported by immunohistochemical analyses.

Glioblastoma multiforme, which was named by Percival Bailey and Harvey Cushing in 1926⁴⁷, based on the histological appearance where it was evident that the tumor tissue would originate from precursors of glial cells and, in addition, because its configuration is very varied due to the presence of necrosis, hemorrhages and cysts, it was called "multiforme".⁴⁸ Currently, glioblastoma multiforme is called glioblastoma. Thus, it is considered an extremely heterogeneous disease, and this tumor heterogeneity is translated by histological patterns, genetic alterations and gene expression profiles.³⁴

The status of the gene encoding the enzyme isocitrate dehydrogenase (IDH) determines the classification of glioblastomas into three types: 1) wild-type HDI, which represents about 90% of cases; 2) mutated HDI; and 3) unspecified.

IDH is an enzyme that stimulates the expression of proteins involved in cellular metabolism and energy production. It performs oxidative decarboxylation of isocitrate to form alpha-ketoglutarate, a crucial step in the Krebs cycle.⁴⁹

In glioblastoma classified as IDH wild-type, the gene is normal, that is, it does not present a mutation and consequently produces the protein in its normal chemical structure. When the mutation occurs in the IDH1 or IDH2 genes, the enzyme gains a new function and starts to produce 2-hydroxyglutarate (2-HG), which is an oncometabolite that alters the methylation of DNA and chromatin, promoting epigenetic changes that affect cell differentiation and proliferation.⁵⁰

In adults, primary glioblastomas are also defined as wild-type HDI, while secondary glioblastomas can be mutated HDI and intact 1p/19q, or mutated HDI and 1p/19q codeletion.³² Mutations in the IDH gene appear to be early events in gliomagenesis, followed by acquisition of mutations in the TP53 gene, and are markers of secondary glioblastoma.³⁴

IDH-wild tumors typically occur in older patients, while those with IDH mutations, which correspond to about 10% of cases, affect younger people and originate from gliomas of lower grade in addition to presenting a better prognosis.^{2,4}

More recently, molecular markers have been validated and incorporated, acquiring increasing importance, and are already represented in the most recent classification of the World Health Organization (WHO). The fifth edition of the international standard classification for brain and spinal cord tumors, established by the WHO and published in 2021⁴ represents an update of the previous classification

from 2016, incorporating advances in the molecular and genetic understanding of CNS tumors.

Thus, this classification determines that glioblastoma (wild-type HDI) must include molecular criteria, such as: mutation in the telomerase reverse transcriptase promoter (TERT), amplification of the gene encoding the epidermal growth factor receptor (EGFR), gain of chromosome 7, and loss of chromosome 10 [+7/-10].⁴

Current treatment of glioblastoma

The current standard treatment of glioblastoma in newly diagnosed patients consists of extensive surgical resection followed by radiotherapy and adjuvant chemotherapy with temozolomide.^{39,51-54} The fruitful work of Stupp et al. in 2005³⁹ established the multimodal treatment protocol for glioblastoma.³⁹

Neurosurgical management

The current consensus indicates that maximal surgical resection correlates significantly with better prognosis as measured by survival in patients with glioblastoma.

Harvey Cushing, known as the father of modern neurosurgery, pioneered craniotomy for the resection of hundreds of glioblastomas from the beginning of the twentieth century.

In the 1950s and 1960s, the development of pneumoencephalography and angiography allowed important advances in the localization of tumors. The ability to visualize tumors underwent a revolution in the 1970s with the invention of computed tomography and, later, functional magnetic resonance imaging (MRI), allowing better surgical planning.^{5,55}

In addition, MRI tractography is a complementary imaging method that allows visualizing, mapping, and reconstructing the direction of nerve fibers, i.e., the tracts, in their path in the white matter.⁵⁶

Glioblastoma is a highly aggressive and invasive tumor. Early attempts at extensive resections, including removal of the entire affected cerebral hemisphere, often resulted in significant neurological deficits, without, however, preventing disease recurrence.

The trend from the following decades onwards became the search for a balance between the maximum increase in survival and the preservation of neurological function. In the 1980s and 1990s, there was an advance in the concept of "maximum safe surgical resection", aiming at the removal of the largest possible volume of tumor mass with minimal functional impairment.

The introduction of craniotomies performed in awake patients allowed intraoperative functional mapping, with the identification and preservation of eloquent cortical areas involved in motor functions and language during surgery. Surgical precision has been constantly improved, with the inclusion, since the 2000s, of ultrasonic aspiration instruments, intraoperative electrophysiological monitoring, and neuronavigation systems using information obtained with CT or MRI in real time.⁵⁷⁻⁵⁹

Radiotherapy management

Radiotherapy protocols in the treatment of glioblastoma have advanced notably in terms of the establishment, fractionation, spacing and staggering of the doses used, in order to adjust the treatment to each patient individually. From a technological point of view, advances are made in the use of MRI-based techniques and positron emission tomography (PET), including MRI-based linear accelerators. These new strategies aim to reduce treatment toxicity by refining the selectivity of exposure on tumor tissue, preserving healthy ones. Other areas of progress include particle, photon, and proton therapy techniques.⁵²

Chemotherapy management

Temozolomide is an atypical alkylating agent for oral use that has emerged as the cytotoxic chemotherapy agent of choice for patients with glioblastoma. The addition of adjuvant temozolomide to treatment leads to significant prognostic improvements, with an increase in median overall survival compared with radiotherapy-based treatment.^{53,60} In addition, the introduction of temozolomide in multimodal therapy does not lead to significant increases in toxicity.⁶¹

The effectiveness of temozolomide treatment is influenced and importantly by the methylation status of the O⁶-methylguanine-DNA methyltransferase (MGMT) promoter. Methylation is associated with better response to temozolomide and can be used as a predictive biomarker, while unmethylated MGMT is related to temozolomide resistance, which is currently one of the biggest challenges in terms of limiting treatment efficacy.^{53,62}

Molecular changes in glioblastoma

Tyrosine kinase receptors

Glioblastoma presents high biological heterogeneity among tumors, with significant variations in molecular and cellular abnormalities. Molecular and genetic alterations common to several tumors are observed in cell signaling pathways involved in proliferation, growth, survival, resistance to apoptosis, and invasion capacity in glioblastoma cells.⁶³⁻⁶⁵

Oncogenes are genes that, when activated by mutations, promote the development of cancer, transforming normal cells into cancerous ones. The amplification and activation by gain-of-function mutations of these oncogenes, including genes encoding receptor tyrosine kinase (receptor tyrosine kinases, RTKs), such as the epidermal growth factor receptor (EGFR), which is a protein present on the surface of cells and plays a fundamental role in cell growth and development. Mutations in this protein can trigger uncontrolled cell growth. Also called ErbB1 or HER1, EGFR is the prototypical member of the ErbB/EGFR family, which also includes ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4).

EGFR is one of the most frequently altered oncogenes in glioblastoma, being observed in 57% of tumors that present modified amplification, mutation,

rearrangement, or splicing.^{66,67} The increase in copy number and gain-of-function mutations of the EGFR gene or other RTKs, such as platelet-derived growth receptor (PDGFR) and HER2/neu and MET, which are two important receptors involved in cell growth and development and that determine the increased activation of intracellular signaling pathways mediated by protein kinases, such as phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK). Activation of the PI3K pathway also occurs frequently in glioblastoma due to loss of function of the tumor suppressor gene PTEN.^{64,68-70}

Apoptosis and cell cycle regulatory genes

Loss-of-function mutations in tumor suppressor genes that regulate the cell cycle and apoptosis are also commonly found in glioblastoma, e.g. loss of function of the p53 protein due to mutations in the TP53 gene or aberrant expression of MDM2 (Murine Double Minute 2), negative p53 inhibitor, and loss of function of p16INK4a and p14ARF due to deletion of the CDKN2A gene.⁷¹ The loss of p16INK4a leads to activation of cyclin-dependent kinase (CDK), resulting in phosphorylation of the retinoblastoma protein, which then releases the transcription factor E2F, allowing cell cycle progression. The p14ARF protein downregulates MDM2 and thus acts as a stabilizer of p53. The loss of these regulatory proteins promotes cell cycle progression and evasion of apoptosis, contributing to glioma tumorigenesis.^{64,69-72}

Epigenetic mechanisms

Mutations that affect the process of DNA organization and compaction, within the cell nucleus and epigenetic regulation are also central features of gliomas.

Alterations in components of the epigenetic regulatory system include mutations and modified expression of histone deacetylases (HDACs), which regulate chromatin structure.^{67,73} Mutations in the IDH1 and IDH2 genes are common in low-grade and secondary gliomas, leading to the production of oncometalyte 2-hydroxyglutarate (2-HG), which inhibits α -ketoglutarate-dependent enzymes, such as histone demethylases and DNA demethylases of the TET (ten-eleven translocation) family. This results in alteration in the epigenome that contributes to cell dedifferentiation and malignant transformation.^{73,74}

Tumor microenvironment

The tumor microenvironment is a concept that refers to the cellular and extracellular environment that permeates a tumor, which directly influences growth, progression, and response to treatment. The understanding is that the tumor microenvironment is a complex and dynamic ecosystem, where tumor cells interact with normal cells, blood vessels, stromal cells, extracellular matrix, and immune system cells.⁷⁵

This concept evidences heterogeneous collection of infiltrating and resident host cells, secreted factors,

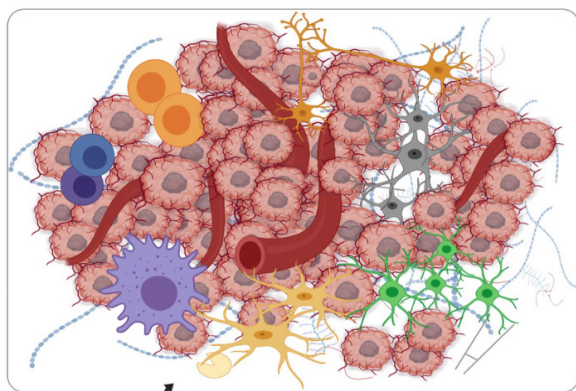
and extracellular matrix, where tumor cells stimulate significant molecular, cellular, and physical changes in host tissues to sustain tumor growth and progression. The "tumor microenvironment is believed to be not just a silent bystander, but rather an active promoter of cancer progression."^{75,76}

From the beginning of tumor growth, a dynamic and reciprocal relationship is established between cancer cells and the components of the tumor microenvironment, which favors survival, local invasion, and locoregional or metastatic dissemination of tumor cells.

In the face of a tumor microenvironment, cell proliferation determines a tissue state of hypoxia and acidity, causing the promotion of angiogenesis with the objective of restoring the supply of oxygen and nutrients, in addition to the removal of metabolic waste.

In the analysis of tumors, it is observed that they are infiltrated by several adaptive immune cells. The role of these cells in the tumor microenvironment (TME) can be both to suppress tumor formation (antitumor microenvironment) and to promote tumorigenesis (immunosuppressive microenvironment). Depending on the context and tumor type, immune cells can perform both pro-tumor and anti-tumor functions.⁷⁵

In this context, additional alterations that contribute to tumor progression include those that affect the tumor microenvironment. In the case of glioblastoma, this involves activation of angiogenesis, through overexpression of vascular endothelial growth factor (VEGF), and remodeling of the extracellular matrix (ECM) through the regulation of matrix metalloproteinases (MMPs), facilitating invasion. Gliomas also exhibit remarkable ability to evade the host immune response by expressing immunoinhibitory ligands such as PD-L1, recruiting immunosuppressive immune cells such as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), and releasing immunosuppressive cytokines such as TGF- β and IL-10.^{77,78} (Figure 1)



Source: Tonan [2025]

FIGURE 1 — Tumor microenvironment

Tumor stem cells

The scientific conceptualization of tumor stem cells is based on their ability to differentiate and self-renew, having the same characteristics as normal stem cells, but

also being able to initiate tumor proliferation composed of more heterogeneous cellularity of normal tissue.

It is believed that tumor stem cells promote tumorigenesis from the mechanism of differentiation, i.e., cNeural stem cells turning into glioma stem cells and driving gliomagenesis.⁷⁹

It is identified that neural stem cells, which transform into glioma stem cells and are the purported precursors of glioma stem cells, are commonly found in the toothed swivel of the hippocampus, subcortical white matter, and subventricular zone.⁷⁹

Intratumoral heterogeneity is a hallmark of glioblastoma, with genetic, epigenetic, phenotypic diversity, and distinct subpopulations of cells coexisting within the same tumor. Glioma tumor stem cells represent a subpopulation of cells with a high capacity for self-renewal, resistance to therapy, and potential to initiate tumors. Glioma tumor stem cells reside in specific niches, such as perivascular and hypoxic zones, and are regulated by signaling pathways such as Notch, Hedgehog, and Wnt, which are characteristic of the regulation of embryonic development.^{80,81}

The Notch, Hedgehog and Wnt signaling pathways are the main signaling pathways involved in embryonic development, being essential for the transformation of the single-celled zygote into a highly specialized multicellular organism. These same pathways also regulate fundamental cellular processes such as cell proliferation, differentiation, and migration. It is important to highlight that its action is not limited to differentiated somatic cells, but also extends to adult stem cells.⁸²

Given their central participation in essential biological processes, alterations or dysregulations in these pathways are often associated with several diseases, including cancer.

Molecular targets and experimental pharmacological therapies in glioblastoma

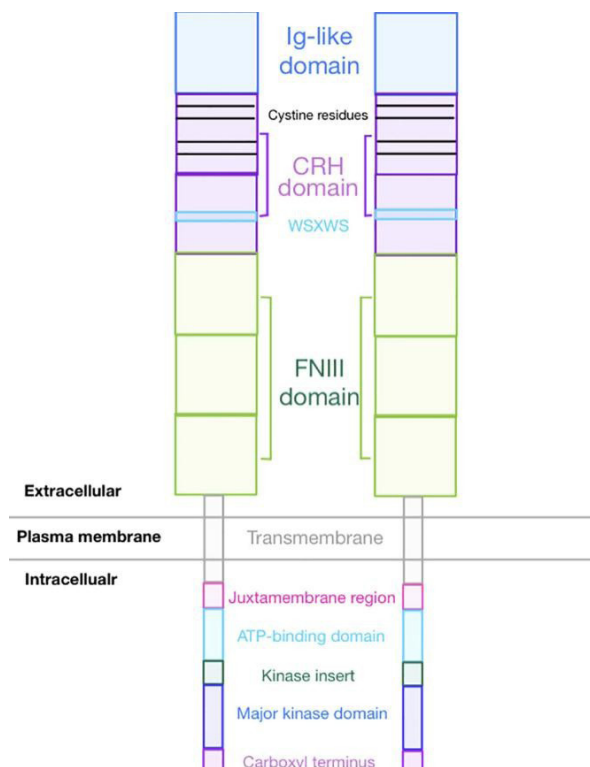
Examples of experimental targeted therapies already evaluated in clinical studies, some focusing on tumor angiogenesis, are studies of antiangiogenic inhibitors such as cediranib (Recentin®), vatalanib, sunitinib (Sutent®), sorafenib (Nexavar®, and vandetanib (Zactima®). Phase I/II studies of these agents administered as monotherapy or combined with cytotoxic chemotherapy and radiotherapy have demonstrated some promising initial results. The PDGFR inhibitor, imatinib mesylate (Gleevec®) has shown limited activity in patients with relapsed glioblastoma. Rapamycin analogues such as sirolimus (Rapamune®) have been tested as monotherapy or in combination with EGFR inhibitors. More recently, epigenetic modulators and immunotherapy are among the most promising candidate therapies.^{43, 64,65}

CD114 granulocyte colony-stimulating receptor and glioblastoma

CD114 as a regulator of brain development and neural plasticity

Brain tumors utilize the cellular and molecular processes of healthy CNS development and

synaptic plasticity, hijacking and modifying these mechanisms.^{21,22,25,26} The CD114 cell surface protein, also called GCSFR or CSFR and encoded by the CSF3R gene, acts as a receptor for granulocyte colony stimulating factor (GCSF).^{6,7} Granulocyte colony-stimulating factor (GCSF) is a pleiotropic cytokine encoded by the CSF3 gene.⁸³ The GCSF receptor, GCSFR, is an 813-amino acid protein encoded by the CSF3R gene and is a member of the cytokine receptor family. Its structure corresponds to the single transmembrane protein composed of several extracellular and intracellular domains CSF3 (Figure 2).⁸³



Source: Park et al.⁸³

FIGURE 2 — General structure of the GCSFR

By binding GCSF to the receptor, CD114 activation stimulates signal transducer and activator of transcription 3 (STAT3). GCSF/CD114 signaling promotes neuronal and neural stem cell survival and plasticity,²⁷ in addition to stimulating neurogenesis⁶ and, together with stem cell factor (SCF), induces the growth of neurites in cortical neurons.²⁸ The combination of GCSF and SCF has neuroprotective action and promotes the reorganization of neural networks in experimental models of neurodegeneration and brain trauma.²⁹ Systemic administration of GCSF attenuates learning and memory impairments and dendritic spine density in the hippocampus in rats submitted to a model of cerebral ischemia.⁸⁴ GCSF treatment also recovers synaptic plasticity as measured by long-term depression in hippocampal slices obtained from the APP/PS1 transgenic model of Alzheimer's disease.⁸⁵

CD114 in malignant neoplasms

Activation of STAT3 by GCSF/CD114 promotes a tumor stem cell phenotype, and CD114 is proposed as

a biomarker of tumor stem cells in neural crest-derived cancers such as neuroblastoma and melanoma.⁷⁻¹⁰

CD114-positive cells isolated from neuroblastoma tumors were highly tumorigenic and capable of self-renewal and differentiation.⁷

Later studies have also demonstrated that CD114 expression is limited to a subpopulation of melanoma tumor cells that demonstrate altered growth and resistance to treatment, suggesting that CD114 expression may be a marker for identifying melanoma tumor cells that contribute to disease relapse and poor patient outcomes.¹⁰

CD114 expression is found in adult solid tumor types including ovarian, cervical, bladder, and skin cancers, although most previous studies have found no significant associations between CSF3R/CD114 expression and survival prognosis.^{7,10-18} In addition, mutations in the CSF3R gene have been described in an atypical type of chronic leukemia.^{19,20} In brain tumors, CD114 expression occurs in medulloblastoma, the most common type of malignant pediatric brain tumor, both in cell lines, mouse grafts, and primary tumor samples. The presence of CD114 appears to confer resistance to cytotoxic chemotherapy.¹⁷ In medulloblastoma samples obtained from patients, there is a difference in CSF3R gene expression between tumors of the Group 3 molecular subgroup compared to the other subgroups, as well as between the SHH molecular subtypes γ , Group 3 α , and Group 3 β .

However, no significant associations were found between CSF3R expression levels and overall survival of patients.¹⁸

A previous study in glioma described the widespread expression of GCSF, both at the mRNA and protein level, in tumor samples. Cell proliferation and migration were stimulated by GCSF treatment in CD114-expressing glioblastoma cells, and an antibody against GCSF produced opposite effects.¹¹

Binding of GCSF to its CD114 receptor (CSF3R) activates the JAK-STAT signaling pathway, culminating in the phosphorylation and activation of signal transducer and transcription activator 3 (STAT3), which acts as a transcriptional regulator of genes involved in the proliferation, survival, invasion, and maintenance of tumor stem cells in glioblastoma.⁸⁶

STAT3 regulates several cellular processes including cell growth, differentiation and apoptosis, and is often activated during tumor genesis. Thus, STAT3 signaling was considered important for the maintenance of tumor stem cell-like subpopulations, including glioblastoma.⁸⁷

Specific STAT3 inhibitors are currently being developed and represent a new class of stimulant therapeutic agents likely to be effective against tumor stem cell subpopulations in these tumors.⁷

Thus, the volume of evidence regarding the possible role of CSF3R/CD114 as prognostic biomarkers or therapeutic targets in glioblastoma or other types of glioma is very limited. In this context, this study aimed to evaluate the expression of the CSF3R gene and its

correlation with overall survival in tumors of patients with different subtypes of glioma, with a special focus on glioblastoma.

Conceptual aspects

Gliomas constitute the most frequent group of primary malignant tumors of the central nervous system in adults.⁸⁸ the clinical course is heterogeneous, with median survival of 14-16 months in IDH-wildtype glioblastoma,⁸⁹ and may exceed 8-10 years in diffuse IDH-mutant gliomas of lesser degree.⁹⁰

These tumors are classified into different types, according to the type of cell from which they originate or with which they share histological characteristics, and are then classified into ependymomas, astrocytomas, and oligodendrogliomas. Of these, astrocytomas are the most common type of glial tumors.³²

In gliomas, residual tumor cells often lead to malignant recurrence and progression, with some gliomas tending to progress to glioblastoma,³¹ a very aggressive neoplasm.

Although morphological classification based on histopathology provides important information for the diagnosis of glioblastoma, it has limitations, as it cannot reflect the heterogeneity of these tumors and, therefore, ends up being insufficient for patient management.⁷⁰

The 2016 WHO classification of CNS tumors, therefore, restructured the classification of glioblastoma by incorporating molecular features into histopathological appearances and was recently updated, in 2021, by advances in the molecular and genetic understanding of CNS tumors,⁴ so that there was progress in the role of molecular diagnostics in the subclassification of glioblastoma.

In fact, glioblastoma is one of the first tumor types that have been systematically investigated by large international cancer projects, e.g., TCGA, due to its high incidence and in cohort, glioblastoma corresponded to 57.51% (n = 153) of the sample.

The CSF3R gene encodes the GCSFR protein. GCSFR presents differentiation giving rise to CD114, which is the granulocyte colony-stimulating factor (GCSF) receptor.

Granulocytic colony-stimulating factor (GCSF) was first identified in bone marrow cells and derivatives, and is a cytokine, i.e., a small protein that acts as a messenger of the immune system, encoded by the CSF3 gene that acts as a hematopoietic growth factor regulating the function of granulocytic precursors and neutrophils.^{6,7}

The actions of the GCSF are mediated by the activation of its receptor, called GCSFR or CD114. Recombinant human GCSF is clinically used to prevent neutropenia, due to its effects on neutrophil mobilization and maturation.⁸³ GCSF/CD114 signaling has also been investigated as a modulator of neuronal survival, synaptic plasticity^{6,28,29,84,85}, and cancer.^{7,10-20}

Specifically, CD114 has been proposed as a

marker to identify cancer stem cell subpopulations associated with tumorigenicity, metastasis, and treatment resistance.^{7,9,10}

In epithelial skin tumors, the presence of CD114 is significantly higher compared to normal skin, Bowen's disease, or actinic keratosis, and has been associated with carcinogenesis. However, no association between CD114 protein expression and patient mortality was found.¹³

Similarly, different levels of CSF3R transcriptions occur between different tumor subgroups and medulloblastoma subtypes, but no significant association with patient survival has been established.¹⁸

A previous study in glioma looked at GCSF and CD114 RNA and protein expression in a set of 22 human gliomas (WHO grade II, III, and IV) and cell cultures derived from these tumors.

Although GCSF and CD114 expression, as well as that of granulocyte-macrophage colony-stimulating factor (GM-CSF) and its receptor, has been found in all gliomas and cell cultures, joint expression of both factors and their receptors has been selectively observed in grade IV tumors (GBMs), and thus expression correlates with advanced tumor stage.¹¹ This makes understanding CSF3R gene expression important to know the oncogenesis of each tumor type and, eventually, to seek ways to block it.

Transcription Activator Signal Transducer 3 (STAT3) regulates several cellular processes, including cell growth, differentiation, and apoptosis, and is frequently activated during tumor genesis, so STAT3 signaling has been found to be important for the maintenance of cancer stem cell-like subpopulations, including glioblastoma.⁸⁷

Compared to non-tumor neural tissue (n = 8), significantly higher levels of CSF3R transcripts were found in astrocytoma, pilocytic astrocytoma, and glioblastoma.

The present transcription analyses indicate that a significant association between high CSF3R mRNA levels and worse prognosis measured through shorter overall survival was found in patients with gliomas.

Analyzing the 266 glioma samples from the GEO- (GSE 16011) section, higher expression of CSF3R/CD114 was observed, which was associated with a worse prognosis, based on shorter overall survival.

Similarly, there was a significant association between high CSF3R mRNA levels and shorter overall survival in GBM patients (n = 150; p < 0.05).

These initial in silicon findings suggest that further experimental studies should characterize the effects of GCSF/CD114 inhibition in experimental models of GBM.

IDH-wild tumors typically occur in older patients, while IDH-mutated tumors, which correspond to about 10% of cases, affect younger patients and originate from lower-grade gliomas, in addition to having a better prognosis.^{2,4}

No significant impact of CSF3R mRNA expression on overall survival was found when GBM patients

were divided according to HDI status (mutated vs. wild-type), possibly due to the limited number of samples available in each subgroup.

In addition, there was no significant difference in CSF3R levels between GBM with wild-type HDI and those with IDH-mutation. Some IDH1 mutations are considered prognostic markers, with patients with mutated tumors having better overall survival.⁹⁰ Corroborating these data, worse overall survival was observed in patients with GBM IDH wild-type.

One study reported that in mutated wild-type GBM carrying mice, GCSF is secreted by GBM CSCs, and blocking GCSF accelerates tumor progression by acting on the myeloid cells that infiltrate the tumor.⁹¹

STAT3 is involved in mediating the cellular effects of CD114 activation. Several studies have indicated that STAT3 is an oncogene in GBM. Activation of STAT3 is associated with shorter, progression-free overall survival in patients with GBM,⁹² and STAT3 is required for the maintenance of a CSC phenotype in GBM cells.⁹³ STAT3 can have a dual role in the GBM, promoting or suppressing the progression of the GBM.^{94,95}

Future experiments should investigate the role of STAT3 downstream of CD114 in different types of glioma.

CONCLUSION

Exploring the role of CD114 in glioma cell lines, other primary tumors, and the tumor microenvironment in future studies may improve understanding of the role of GCSF and similar growth factors in the progression of CNS malignancies. Genomic analyses are currently the gold standard for categorizing tumor subtypes, still presenting some overlap between groups, but less than classical histology. Biomarkers are essential not only for diagnosis and prognosis but also for personalized therapeutic planning. The search for specific proteins and receptors in CNS cancer cells can determine the identification of molecular targets that, when inoperative, can inhibit the growth, proliferation, and spread of the neoplasm, as well as allow the development of therapies selectively targeted at gliomas. Several strategies for the search for molecularly directed therapies, or targeted therapies, have been developed based on the inhibition of cell signaling component in tumor cells or their microenvironment. Several of these experimental therapies have already been evaluated in clinical trials. Inhibition of growth factor receptors or their ligands is a therapeutic strategy that interrupts the signals that promote cell growth and proliferation, especially in the context of the treatment of gliomas, and although expected, the primary endpoint of increased survival has not yet been achieved.

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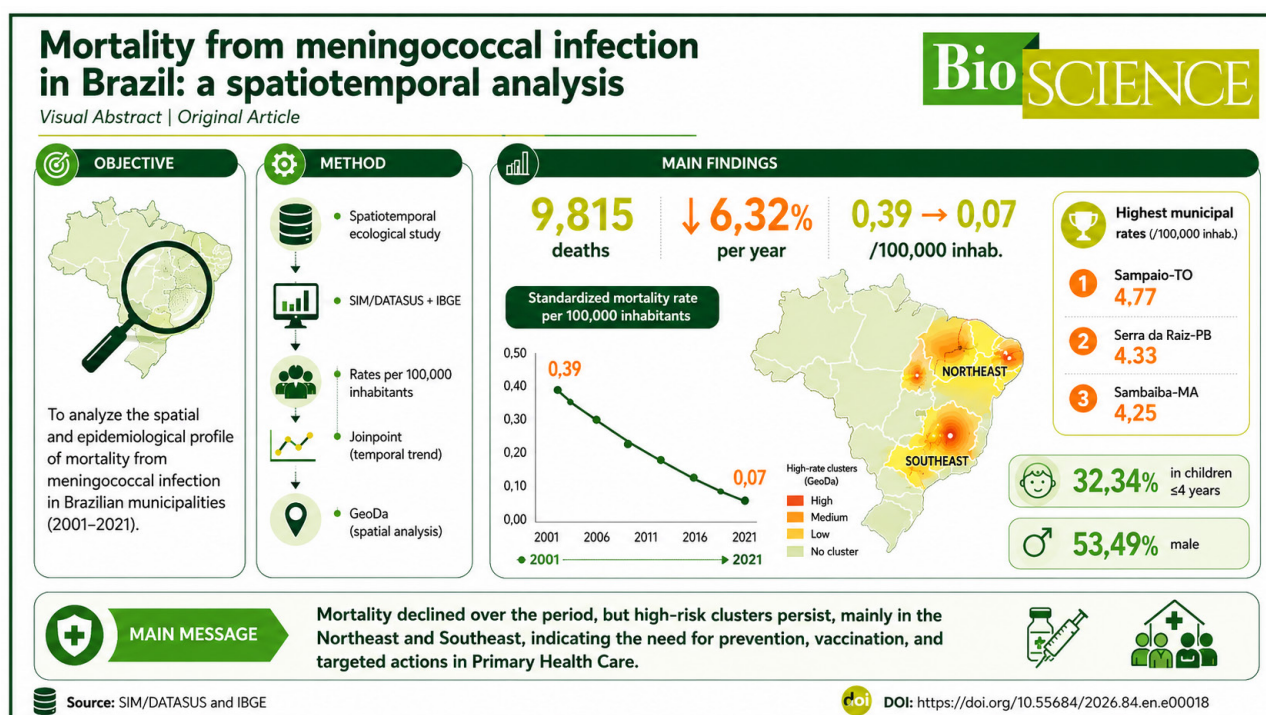
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Mortality due to meningococcal infection in Brazil: a temporospatial analysis

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Central Message

Meningococcal infection (*Neisseria meningitidis*), Gram-negative bacteria, which are normally present as commensals in the normal nasopharyngeal microbiota, can potentially mutate into pathogens. The combination of factors such as the specific characteristics and virulence of the strain involved with the host predisposition can culminate in the disease. Thus, it is pertinent to analyze the spatial and epidemiological profile of mortality from meningococcal infection in Brazilian municipalities.

Perspective

The temporospatial analysis allows the identification of municipalities in the different states with high mortality from meningococcal infection, in addition to presenting differences between mortality rates. In this way, it supports the need for strategies that act according to the reality and particularities of the affected places. Thus, 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 in Primary Health Care.

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ABSTRACT

Introduction: Meningococcal infection characterizes infection by *Neisseria meningitidis*, Gram-negative bacteria, normally present as commensals in the normal nasopharyngeal microbiota, but potentially pathogenic. The combination of factors such as the specific characteristics and virulence of the strain involved with the host predisposition can culminate in the disease.

Objective: To analyze the spatial and epidemiological profile of mortality from meningococcal infection in municipalities in Brazil, from 2001 to 2021.

Method: Epidemiological study focusing on the spatial analysis of mortality between 2001 and 2021. Data from the Mortality Information System (SIM), made available by DATASUS, and population data from the Brazilian Institute of Geography and Statistics (IBGE) were used to calculate crude and standardized mortality rates. The temporal analysis was performed using Joinpoint, while the spatial analysis was performed using GeoDa.

Results: There were 9,815 deaths from meningococcal infection in Brazil. The analysis identified clusters of high rates in the Northeast and Southeast regions. The municipalities with the highest rates were Sampaio, TO (4.77/100 thousand inhabitants), Serra da Raiz, PB (4.33/100 thousand) and Sambaíba, MA (4.25/100 thousand).

Conclusion: The study identified municipalities and clusters with high rates and the need for targeted strategies for disease prevention and control.

KEYWORDS: Spatio-temporal analysis. Meningococcal infections. Epidemiological monitoring.

INTRODUCTION

Meningococcal infection (ICD A39) characterizes infection with *Neisseria meningitidis*, Gram-negative bacteria, normally present as commensals in the normal nasopharyngeal microbiota, but potentially pathogenic. The combination of factors such as the specific characteristics and virulence of the strain involved with the host predisposition can culminate in the disease. Among the invasive conditions, meningitis and sepsis predominate, which, together, represent 90% of the cases; however, infections also present elsewhere.^{1,2}

Symptoms include fever, headache, and stiff neck. In the case of meningococemia, the disease commonly presents as an acute condition, with possible multiple organ failure, shock, and disseminated intravascular coagulation. If it is a syndromic condition, chronic meningococemia, the symptoms are milder and recurrent, affecting mainly the skin and joints.^{3,4}

The overall endemic incidence is 0.5 to 5/100,000, with an increase in the number of cases in winter and spring in temperate climates, a region that comprises 26 countries and is known as the meningitis belt. Vaccination has visible effects on the incidence of meningococcal infections, being the main means of preventing their occurrence.⁵

As it is an infection caused by meningococci (Gram-negative diplococci), the diagnosis has different possible steps and conducts. A relevant detail in the diagnostic approach is that, due to the invasive and severe nature of the disease, antibiotic treatment associated with tests for proper diagnosis should often be taken. Among the possible conducts to be taken to make the diagnosis are blood cultures; however, they are only truly positive in half of patients affected with meningococcal infection; thus, it is necessary to cerebrospinal fluid analysis. Its analysis is valuable and often essential in the search for the pathogen that causes the infection; Gram staining is well observed in about 90% of samples and culture has a sensitivity of approximately 90%. Currently, techniques using polymerase chain reaction are under development, and some are already in use, to improve the processes of the analysis of the liquor and optimize

the diagnostic process. Another tool that can be used in the diagnostic process is the performance of computed tomography of the brain to evaluate evidence of intracranial mass effect.³

The objective of this study was to analyze the spatial and epidemiological profile of mortality from meningococcal infection in municipalities in Brazil, from 2001 to 2021.

METHOD

This is an epidemiological study of secondary data analysis in health with a focus on temporospatial analysis. Data on cases of death due to meningococcal infection and streptococcal septicemia 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 the denominator for the purpose of calculating mortality rates came from DATASUS.

For the analysis of the mortality trend due to meningococcal infection and streptococcal septicemia in Brazil, the period from 2001 to 2021 was selected, in order to better understand the outcome in this historical series. For the study population, individuals were selected according to data available from the Department of Informatics of the Unified Health System (DATASUS) for adults who were registered with deaths from meningococcal infection and streptococcal septicemia. 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 A39 (meningococcal infection) and A40 (streptococcal septicemia) of the International Classification of Diseases (ICD-10) were adopted. Information on the epidemiological profile and frequency of deaths from meningococcal infection and streptococcal septicemia were compiled 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. While 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.

Statistical analysis

Initially, the temporal trend of mortality due to meningococcal infection and streptococcal septicemia 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 from meningococcal infection and streptococcal septicemia in Brazil was studied. Initially (Figure 1) the mean mortality from meningococcal infection and streptococcal septicemia in the Brazilian municipalities were studied. 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. To identify spatial clusters, the Global and Local Moran's 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 $p < 0.05$ to be significant. 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 (Figure 4). The Moran Map graphically demonstrates the degree of similarity between neighbors, being represented by four 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 with low mortality and are close to municipalities that also have low rates; 3) high-low (lower right quadrant): corresponds to municipalities that have high rates and are close to municipalities that have low mortality rates; 4) low-high (upper left quadrant): corresponds to municipalities that have low rates and are close to municipalities with high rates.

The data used to compose the research were available on the internet free of charge for 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 the Ethics Committee.

RESULTS

After analyzing the profile of Brazilian victims of meningococcal infection and streptococcal septicemia, a significant prevalence was identified among individuals aged 1-4 years, totaling 19.22% of the cases. However, it is notable that the incidence of this fatal event is practically comparable in similar age groups, with 13.12% of deaths occurring among children under one year of age. In addition, there was a marked predominance of males, representing 53.49% of the cases. At the same time, most of the victims belonged to the white ethnicity (47.60%)¹ followed by 37.06% among browns, and had 15.67% of singles.

Regarding educational level, it was observed that most deaths occurred among individuals without complete schooling, comprising 20.10% of the cases, followed by 12.45% among those aged one to three years. It is crucial to highlight that most cases of mortality due to meningococcal infection and streptococcal septicemia occurred in the hospital environment, representing 90.14% of the total, followed by the home environment, with 4.20%.

From 2001 to 2021, 9815 deaths from meningococcal infection and streptococcal septicemia were recorded in Brazil. The average mortality in this period was 0.24/100 thousand inhabitants, with the lowest mortality recorded in 2021 (0.07/100 thousand inhabitants) and the highest in 2001 (0.39/100 thousand inhabitants). The analysis of the temporal pattern of mortality in the study period showed a significant mean decrease of 6.32% per year in the mortality rate per 100 thousand inhabitants ($p < 0.05$, Figure 1). Pearson's correlation coefficient was -0.8871 with $p < 0.05$, indicating that there is a significant and inversely proportional linear correlation, over the years, there was a significant reduction in the mortality rate.

Through spatial analysis, Figure 2 shows the spatial dispersion of mortality due to meningococcal infection and streptococcal septicemia in Brazil, with a focus of incidence in the Southeast and Northeast regions, but with the incidence dispersed throughout the country. Sampaio, TO (4.77/100 thousand inhabitants), Serra da Raiz, PB (4.33/100 thousand inhabitants), Sambaíba, MA (4.25/100 thousand inhabitants), Ouroeste, SP (3.80/100 thousand inhabitants) and Arapeí, SP (3.73/100 thousand inhabitants) were the five municipalities that had the highest mortality rate from meningococcal infection and streptococcal septicemia between 2001-2021.

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 Southeast and Northeast regions. Spatial autocorrelation was identified by the Global Moran Index ($I = 0.660$; $p = 0.01$), demonstrating evidence of positive autocorrelation.

TABLE — Epidemiological profile of individuals who died from meningococcal infection in Brazil, between 2001-2021

Education	n	%
None	1973	20.10%
1 to 3 years	1222	12.45%
4 to 7 years	1136	11.57%
8 to 11 years	837	8.53%
12 years and over	286	2.91%
Ignored	4361	44.43%
Marital status	n	%
Single	4223	43.03%
Married	1538	15.67%
Widower	869	8.85%
Legally separated	214	2.18%
Other	105	1.07%
Ignored	2866	29.20%
Place of occurrence	n	%
Hospital	8847	90.14%
Other health facility	388	3.95%
Domicile	412	4.20%
Public road	72	0.73%
Other	81	0.83%
Ignored	15	0.15%
Age Group	n	%
Child 1 year old	1288	13.12%
1 to 4 years	1886	19.22%
5 to 9 years	973	9.91%
10 to 14 years old	563	5.74%
15 to 19 years old	513	5.23%
20 to 29 years old	676	6.89%
30 to 39 years old	528	5.38%
40 to 49 years old	579	5.90%
50 to 59 years old	546	5.56%
60 to 69 years old	494	5.03%
70 to 79 years old	626	6.38%
80 years and over	1138	11.59%
Age ignored	5	0.05%
Gender	n	%
Male	5250	53.49%
Women	4564	46.50%
Ign	1	0.01%
Color/Race	n	%
White	4672	47.60%
Black	651	6.63%
Yellow	21	0.21%
Brown	3637	37.06%
Indigenous	35	0.36%
Ignored	799	8.14%

Source: Department of Informatics of the Unified Health System (2024).

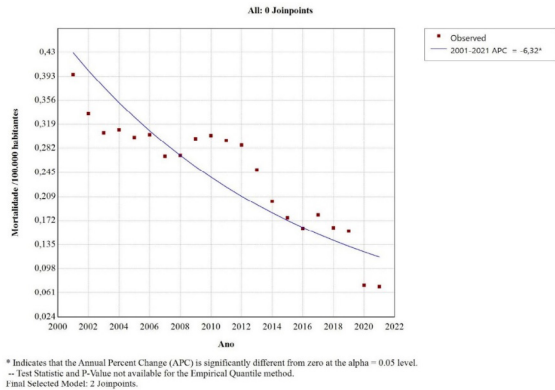


FIGURE 1 — Time pattern of mortality from meningococcal infection in Brazil, between 2001-2021

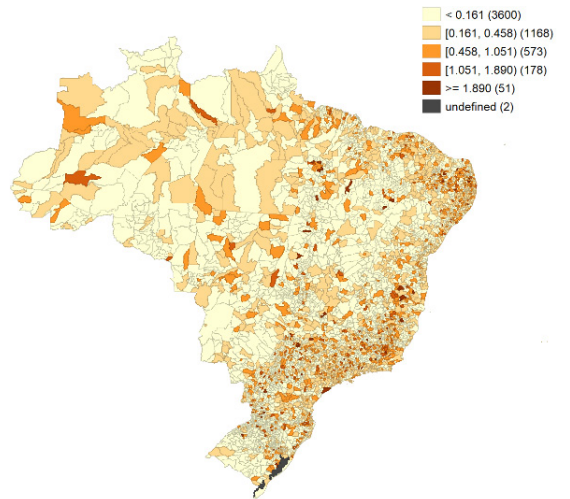


FIGURE 2 — Crude mortality rate from meningococcal infection in Brazil, between 2001-2021

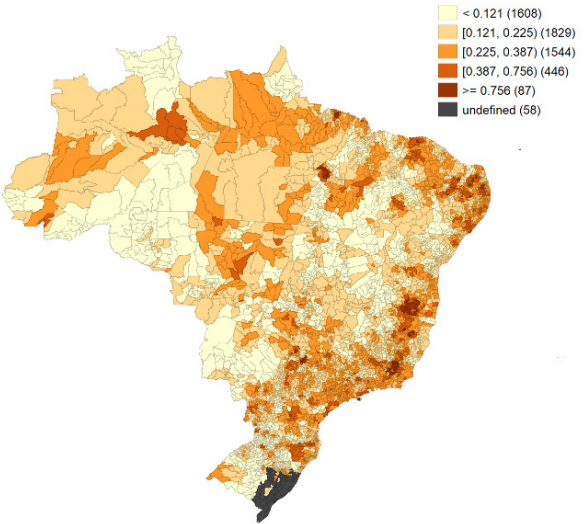


FIGURE 3 — Mortality rate smoothed by the local empirical Bayesian method due to meningococcal infection in Brazil, between 2001-2021

The application of the Local Moran's Index made it possible to identify spatial clusters of both high and low equal values (Figure 4). The high-high pattern was identified mainly in the Northeast and Southeast regions, which indicates similarity between the municipalities in these regions for high mortality values due to the pathology analyzed.

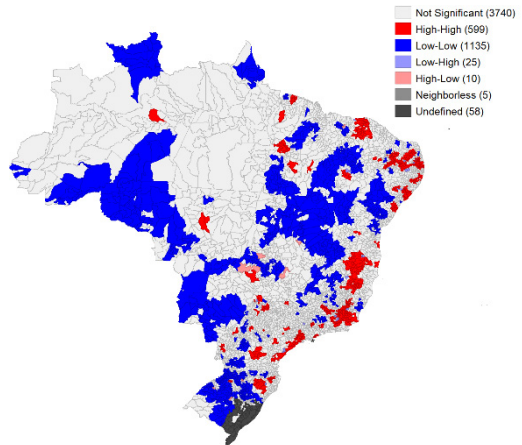


FIGURE 4 — Spatial clusters of mortality due to meningococcal infection in Brazil, between 2001-2021

While the low-low pattern was identified mainly in the Midwest, South, Northeast and North regions, which indicates similarity between the municipalities in these regions for low mortality values from the analyzed disease.

DISCUSSION

Mortality due to meningococcal infection requires careful analysis, given that it is an important cause of infant death. After analyzing the epidemiological data, it is possible to perceive frequency in early childhood, that is, in children up to four years old (32.34%), agreeing with the article by Barroso et al.⁶ that most cases of mortality from meningococcal infection occur in early childhood. It shows that about 2.45 cases of lethality per 100,000 individuals are children under one year of age, but the average incidence would be 0.24 per 100,000 individuals. Reiterating that the main cause of cases is due to facilitated transmission in children's environments such as daycare centers and schools and the immaturity of the immune system, increasing susceptibility to meningococcal infection.⁶⁻⁸

The demographic characteristics of mortality due to meningococcal infection point to a predominance of risk and mortality factors in males (53.49%), especially in those of white ethnicity (47.60%) and with no complete year of schooling (20.10%). Manfred S Green et al.⁹, in their article on the difference between the sexes in the incidence of meningococcal infection, says that there are actually more young men but says that in older people, the majority are women. This higher incidence in men is explained by the authors by genetics and hormonal differences in young men.⁹ The association between low level of education and increased infection highlights how education can function as an important social determinant of health, and that, usually when its rates are low, they are situations in which there are greater social problems and decreased quality of life, which reflect on health-related issues.

In the analysis of spatial data, the Southeast and Northeast regions show higher mortality from meningococcal infection than the others, 4,017 and 1,440 deaths, respectively.⁶⁻⁸ The Northeast region has higher mortality rates due to meningococcal infection, which can be associated with the fact that the region has social ills, even with good development observed in recent years. Such ills can be intensified by the characteristic of accentuated rurality observed in the region, which hinders access to health services that are more concentrated in urban centers, causing less adequate investigation of cases, with consequent worsening of the conditions, in addition to deficient adherence to vaccination. In the Southeast region, the concentration of people, especially in closed places such as subways, buses, and air-conditioned environments, and added to disorderly urbanization - marked by the existence of favelas and peripheries with limited access to adequate housing conditions (Brasil, 2016) - contributes to the dissemination of etiological

agents, especially those of bacterial origin, which have high lethality, with variation in their indexes.⁴

When analyzing the data from the temporal aspect it can be seen that the highest incidence of meningococcal infection was in 2001 with about 0.39/100,000 individuals compared to the lowest incidence which was in 2021 with 0.07/100,000 individuals. According to DATASUS, from 2001 onwards the number of cases was progressively decreasing, that is, from the beginning of the 90s to 2001 it was considerably high and from that point on, it began to decrease, making the year 2001 the year with the highest incidence in the period analyzed in this article.

Limitations

The secondary data used in this study are a limiting factor, which can generate biases, such as underreporting, lack of information and inconsistencies in filling in the causes of death. Associated with this, there is a limitation in the analysis of information on population estimates through the indirect method, as the last census dates from 2010. The results found for the general population may not be repeated at the individual level due to the effects of data aggregation, a characteristic of 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 meningococcal infection.

CONCLUSION

The temporospatial analysis allowed the identification of the municipalities of the different states with high mortality from meningococcal infection, in addition to the differences between the mortality rates between states in Brazil. Thus, the need for strategies that act according to 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 in Primary Health Care (PHC), since it is the level with the greatest and most direct contact with the population and the most efficient with regard to educational and preventive actions that They aim to ensure access and care for the population served, and, consequently, promote health and prevent conditions that culminate in aggravation of meningococcal infection.

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Racial bias in artificial intelligence for mammography: a challenge to diagnostic justice and equity in Brazil

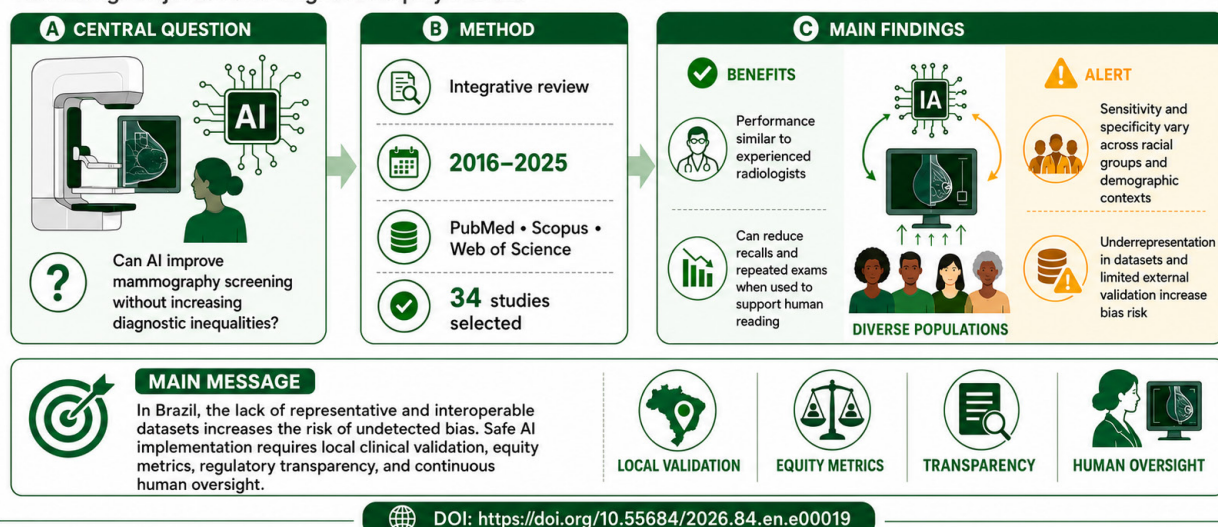
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REVIEW ARTICLE

RACIAL BIAS IN AI FOR MAMMOGRAPHY

A challenge to justice and diagnostic equity in Brazil

BioSCIENCE



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Central Message

The application of artificial intelligence to mammography has shown promise to improve breast cancer screening, reducing interpretive variability and optimizing early detection. However, variations in performance between different population groups and clinical settings raise concerns about the validity and equity of used systems.

Perspective

Responsible adoption of artificial intelligence in mammography requires local clinical validation across different regions and population groups, systematic utilization of equity metrics, regulatory transparency, and ongoing human oversight. The combination of ethical governance, independent auditing, and the participation of professionals and patients is essential for technological gains to translate into sustainable and fair clinical benefits.

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ABSTRACT

Introduction: The application of artificial intelligence to mammography has shown promise to improve breast cancer screening, reducing interpretative variability and optimizing early detection. However, variations in performance between different population groups and clinical settings raise concerns about the validity and equity of the systems used.

Objective: To review the use of artificial intelligence in mammography, focusing on diagnostic performance, representation biases, ethical implications, and regulatory challenges for safe incorporation in Brazil.

Method: Integrative review between January 2016 and January 2025 in the PubMed, Scopus, and Web of Science databases. Multicenter studies, systematic reviews, meta-analyses, and regulatory and ethical analyses were included. Publications without peer review and articles not directly related to mammography were excluded. After screening and critical reading, thirty-four studies were selected for qualitative synthesis.

Results: Deep learning systems perform similarly to experienced radiologists and can reduce the number of repeat scans when used as a support for human reading. However, differences in sensitivity and specificity are observed between racial groups and demographic contexts, associated with the underrepresentation of certain populations in the training sets and the absence of external validation in different scenarios. In Brazil, the lack of representative and interoperable databases increases the risk of undetected biases and limits the generalization of results.

Conclusion: Responsible adoption of artificial intelligence in mammography requires local clinical validation across different regions and population groups, systematic utilization of equity metrics, regulatory transparency, and ongoing human oversight. The combination of ethical governance, independent auditing, and the participation of professionals and patients is essential for technological gains to translate into sustainable and fair clinical benefits.

KEYWORDS: Mammography. Artificial intelligence. Algorithmic bias. Racial disparities. Equity.

INTRODUCTION

Breast cancer remains the most common malignant neoplasm among women, accounting for about a quarter of all new diagnoses annually. In 2020, more than 2.3 million cases and approximately 685 thousand deaths were estimated worldwide.¹ In Brazil, national guidelines recommend biennial mammography for women aged 50-69 years; however, population coverage is heterogeneous, with lower rates in the North and Northeast regions and among black and brown women, reflecting structural inequalities that contribute to diagnoses in more advanced stages.²⁻⁴

In recent years, artificial intelligence (AI) systems applied to mammographic interpretation have demonstrated greater diagnostic accuracy and lower interobserver variability in multicenter studies.⁵⁻⁷ However, external validation results reveal uneven performance between population subgroups, with reduced sensitivity and/or specificity in women from underrepresented groups, especially Hispanic and black, compared to whites.^{8,9} This disparity highlights limitations in the generalization of algorithms, especially in contexts with ethnic and sociocultural diversity, such as Brazil.

In Brazil, the absence of broad, interoperable national repositories stratified by race/color, combined with the dependence on algorithms developed and validated abroad, accentuates the risk of algorithmic bias and diagnostic inequity.^{2,10} These factors can directly impact the time to diagnosis, access to timely treatment, and, consequently, clinical outcomes.

Given this scenario, this review synthesizes the national and international literature on the use of AI in mammography, focusing on diagnostic performance, algorithmic biases, and equity, in addition to discussing ethical, regulatory, and operational implications

for safe and contextualized implementation in the Brazilian health system.

METHOD

An integrative review of the literature on the application of AI in mammography was conducted, covering publications between January 2016 and January 2025. The searches were carried out in the PubMed/MEDLINE, Scopus and Web of Science databases, using combinations of the descriptors "mammography", "artificial intelligence", "algorithmic bias", "racial disparities" and "equity". The selection process followed pre-defined inclusion and exclusion criteria, prioritizing studies of high methodological relevance and thematic relevance.

Meta-analyses, systematic reviews, multicenter observational studies, technical validation trials, imaging databases, as well as regulatory and ethical analyses related to the use of AI in mammography imaging were included. Duplicate studies, non-peer-reviewed preprints, and articles whose main focus was not directly linked to mammography were excluded. At the end of the screening process, thirty-seven studies and sources were considered more relevant for the critical analysis and summarized in the Table.

The full reading and critical evaluation of these studies allowed the systematic extraction of information on the composition of the datasets used, the performance metrics reported, the presence or absence of stratification by race and ethnicity, and the bias mitigation strategies described. The evidence was analyzed in an integrated manner, seeking to identify performance patterns, methodological limitations, and potential ethical and regulatory implications.

In addition, national data from official reports from the National Cancer Institute (INCA) and the Ministry of Health were incorporated, including indicators

of access to screening, staging of diagnosis, and mortality from breast cancer. This integration aimed to contextualize the international findings to the Brazilian epidemiological reality.

RESULTS

The incorporation of AI systems into mammography has evolved consistently, with models based on deep learning, especially convolutional neural networks, achieving performance comparable to that of experienced radiologists in the detection of microcalcifications, architectural distortions, and masses, even in high-volume scenarios.^{5,11} Multicenter trials indicate that the use of AI as a tool to support human double reading increases the cancer detection rate without substantially increasing false positives or unnecessary biopsies, in addition to reducing the number of recalls and optimizing operational flows, especially in environments with a shortage of radiologists.^{6,7,12} However, the generalization of these systems depends critically on the diversity and quality of the training and validation sets. Widely used databases, such as DDSM, INbreast, CMMD, and OPTIMAM, have limited racial and geographic composition, often without complete sociodemographic metadata, which restricts external validity and increases the possibility of sampling bias.¹³⁻¹⁶ In line with these limitations, external validation studies document decreases in sensitivity and/or specificity in underrepresented subgroups.^{8,9} In Brazil, the literature points to potential operational benefits of AI, such as screening of presumably normal tests and prioritization of suspected cases, but relevant structural barriers persist: absence of interoperable and representative national repositories, dependence on imported solutions, and limited integration between information systems, which compromise broad clinical validation.²

Accumulated evidence demonstrates that the performance of AI algorithms applied to mammography can vary across population groups. This variation relates to the underrepresentation of Black, Brown, Indigenous, and other minority women in training sets and the scarcity of validation in demographically diverse contexts.^{10,17} In external validation of an ensemble model of deep learning in a diverse cohort (37,317 exams; Athena/UCLA network), Hsu et al. observed that the high performance reported in more homogeneous cohorts was not generalized, with significantly lower sensitivity and specificity in specific subgroups, including Hispanic women and women with a previous history of breast cancer.⁸ In a convergent manner, algorithms applied to historically underserved populations may have a higher rate of underdiagnosis.⁹ In addition to sample composition, the domain shift phenomenon reduces the generalization of models trained in homogeneous populations when applied to different epidemiological contexts.^{18,19} In Brazil, the lack of repositories stratified by race/color and the adoption of algorithms developed abroad

without local validation increase the risk of diagnostic error in underrepresented subgroups.² Mitigating these disparities requires stratified performance assessment and the use of equity-specific metrics, such as equalized odds, nonsense impact ratio, and demographic parity, reported prior to implementation and monitored in post-market surveillance.^{19,20} Even so, most published studies on AI for mammography do not report results stratified by race or ethnicity, which substantially limits the assessment of equity.^{20,21}

Inequalities in mammographic screening in Brazil constitute a determining context for the safe incorporation of AI. Despite being provided for in the National Oncological Care Policy and guaranteed by the SUS, mammographic coverage remains below the 70% target recommended by the World Health Organization. A population-based ecological study estimated a median of only 21.6% coverage among the health micro-regions (interquartile range from 8.1% to 37.9%)² and, according to the 2019 National Health Survey (PNS), 58.3% of women aged 50 to 69 years had a mammogram in the previous two years, with lower percentages in the North (43.2%) and Northeast (49.5%) regions.²² Analyses of the PNS of 2013 and 2019 identified brown/black color, lower income and schooling, and residence in the North and Northeast regions among the determinants of not taking the test, evidencing racial and socioeconomic inequities of access.^{3,23} These disparities are accentuated where there is a lower density of equipment and professionals, in addition to relevant logistical barriers, such as long commutes in rural and riverside areas.² During the COVID-19 pandemic, the number of screening mammograms in the SUS fell by about 44% in 2020, with reductions ranging from 25% in the North to 48% in the Northeast, accompanied by an increase in the proportion of diagnoses in advanced stages.^{24,25} In this scenario, the adoption of AI models trained on homogeneous populations, without stratified local validation and subgroup monitoring, may inadvertently widen inequalities in accuracy and access, if mitigation measures such as representative national repositories, interoperability of systems, stratified indicators, and independent audits are not implemented.^{2,7}

The regulation of AI applied to mammographic screening requires a framework that ensures clinical performance, safety, and equity. International guidelines converge on the need for representative pre-market validation and post-implementation surveillance with transparency of results by subgroup.^{20,21,26} In the United States, the Food and Drug Administration (FDA) classifies such systems as Software as a Medical Device (SaMD) and recommends validation with stratified samples, as well as post-market monitoring and version control.^{21,26} In the UK, the MHRA adopts principles aligned with the European AI Act, emphasizing traceability, disclosure of metrics and mitigation of inequalities.^{27,28} The AI Act classifies healthcare applications as high-risk, requiring algorithmic governance, robustness

testing, independent audits, and reporting of equity indicators.²⁸ In Brazil, the regulation of medical devices still lacks specific requirements for AI models, with no clear distinction between static and adaptive models and without requiring representative local clinical validation.²⁹ This regulatory gap favors the use of algorithms trained in different demographic contexts, with potential bias described in previous studies.^{8,9} The equity assessment should incorporate specific metrics, such as equalized odds, disparate impact ratio, and adjusted demographic parity, with confidence intervals, calibration by subgroup, and pre-specified non-inferiority margins.^{18,19} For the national context, it is recommended that regulatory approval be conditioned to multicenter validation in the country, stratified by race/color, age, breast density, region, and socioeconomic level, including relevant clinical outcomes. Post-market surveillance should provide for independent audits, public stratified performance reports and recalibration mechanisms. A national registry of algorithms, containing information on data provenance, versioning, and equity metrics, would contribute to transparency and governance.³⁰

The ethical and epistemological dimension of AI in mammography transcends technical evaluation. Algorithmic bias reflects inequalities in the processes of data production and curation, which determine who is represented and who remains invisible.^{10,31} Models trained in homogeneous populations tend to show performance degradation in minority subgroups, infringing the bioethical principle of justice.^{32,33} Automation bias, in turn, can lead to uncritical acceptance of algorithmic outputs, especially under care pressure, requiring significant human-in-the-loop oversight, transparency about uncertainties, traceability of decisions, and override protocols.^{34,35} In addition, there is the dimension of epistemic injustice: when certain bodies and clinical signs are underrepresented in the data, they become less recognized as legitimate sources of knowledge.^{17,36} In the Brazilian context, the dependence on imported solutions and the scarcity of stratified databases increase this mismatch between the model and the reality of care. Technical strategies, such as targeted data augmentation, sample reweighting, subgroup calibration, and threshold adjustments, can reduce disparities, as long as they are accompanied by equity metrics and relevant clinical outcomes.¹⁸ The adoption of ethics-by-design, transparent governance, and user and patient participation is essential for performance gains to translate into distributed benefit rather than the amplification of inequalities.^{30,32,33}

Finally, future perspectives point out that the integration of AI into mammographic screening in Brazil has the potential to expand early detection and standardize readings, as long as it is supported by validation in diverse populations and continuous monitoring with stratified performance.^{18,20} The creation of multicenter and interoperable national repositories, with standardized sociodemographic annotation and detailed clinical and technical

variables, is a priority.^{10,30} Evidence generation should occur in pragmatic trials conducted in the country, with relevant clinical outcomes and pre-specified equity metrics.^{19,20} In clinical operation, AI should act as a support for medical judgment, with continuous training, override protocols, and performance drift surveillance.^{34,35} Representative data, stratified multicenter validation, and inclusive governance are essential conditions for AI innovation to contribute to reducing, not widening, inequalities in the early diagnosis of breast cancer.^{10,20}

As mentioned, the search included thirty-seven studies and sources, compiled and synthesized in the Table.

DISCUSSION

The findings of this review indicate that AI applied to mammography represents a substantial advance in breast cancer screening, with the potential to expand early detection and optimize diagnostic flows.^{5-7,12} However, the consolidation of this promise depends on structural, regulatory, and ethical conditions that ensure consistent and equitable performance.^{18,20,21} The literature demonstrates that, although deep learning systems can achieve accuracy similar to that of experienced radiologists, the added clinical benefit is highly sensitive to the diversity of training and validation sets.¹³⁻¹⁶ The lack of demographic representativeness, especially in relation to race, ethnicity, and socioeconomic context, reduces the external validity of algorithms and can produce systematic biases that perpetuate diagnostic inequalities.^{2,8-10}

These disparities do not stem only from technical limitations, but from historical processes of data production and circulation that reflect preexisting social and racial inequalities.^{10,31} Algorithmic bias, by reproducing patterns of exclusion observed in clinical practice and health systems, acquires ethical and political relevance.³⁷ Differences in sensitivity and specificity documented between different populations illustrate that the generalization of models without local validation can directly compromise the principle of diagnostic justice.^{8,9} In the Brazilian context, this issue is particularly critical: the country combines wide population heterogeneity with weak data infrastructure, resulting in a high risk of adopting models developed in different epidemiological and technical environments.^{2,3}

The integrated analysis of the studies shows that the simple incorporation of AI into tracking does not guarantee a reduction in inequalities. On the contrary, when applied uncritically, the technology can accentuate asymmetries in access and diagnostic accuracy.^{2,12,19} This finding reinforces the need for a systemic approach, in which technological innovation, public policy, and ethical governance are articulated. Multicenter validation models, with stratification by subgroups and continuous monitoring, should be a regulatory requirement.^{20,21,26} International

TABLE — Summary of the studies incorporated in this review¹⁻³⁰

Author(s) and year	Type of study	Objectives	Method	Conclusion
Deng et al. (2025)	Systematic review/global burden (GBD)	Estimate the global, regional, and national burden of breast cancer (1990-2021) and projections to 2050	Systematic analysis of data from the Global Burden of Disease Study 2021	Breast cancer remains the most incident neoplasm in women, with an increasing and uneven burden between regions
Nogueira et al. (2019)	Ecological study / inequities	To analyze inequities in access to mammographic screening in Brazil	Analysis of population data on access to mammography by region and sociodemographic characteristics	Access to mammography is unequal in Brazil, with lower coverage in socially disadvantaged regions and groups
Silva et al. (2024)	Population-based study	To examine ethnic disparities in breast cancer patterns in Brazil	Analysis of population-based cancer registries	There are relevant ethnic disparities in breast cancer patterns and outcomes in Brazil
Santos et al. (2023)	Estimates Report (INCA)	Estimate the incidence of cancer in Brazil for 2023-2025	Estimates based on data from Brazilian cancer registries (INCA)	Provides official incidence estimates, supporting the planning of screening in the country
McKinney et al. (2020)	Multicenter validation study	Evaluate an AI system for mammographic screening in UK and US databases	Comparison of Deep Learning Model Performance with Radiologists in Retrospective Cohorts	The AI system achieved performance comparable to that of radiologists, reducing false-positives and false-negatives
Elhakim et al. (2023)	Retrospective multicenter study	To assess the accuracy of AI in detecting breast cancer across the screened population	Retrospective analysis of AI performance in a tracking population	AI showed good diagnostic accuracy in a real population screening scenario
Sharma et al. (2023)	Multicenter study (multi-vendor)	Evaluate AI as an independent reader in the double reading of the trace	Evaluation of multiple AI systems on 275,900 mammograms	AI can act as an independent reader in dual reading, maintaining performance and reducing workload
Hsu et al. (2022)	External validation study	Externally validate an AI model in a diverse cohort	Ensemble model validation in 37,317 exams (Athena/UCLA network)	High performance did not generalize to a diverse cohort, with lower sensitivity/specificity in subgroups (e.g., Hispanic women)
Seyyed-Kalantari et al. (2021)	Analytical equity study	Assess AI underdiagnosis bias in underserved populations	Analysis of AI models in chest X-rays by subgroup	AI models can disproportionately underdiagnose historically underserved groups
Larrazabal et al. (2020)	Experimental study	Evaluate the effect of representation imbalance on training sets	Classification experiments varying the composition of the dataset	Representation imbalances in data produce biased classifiers
Lundervold & Lundervold (2019)	Narrative review	Review Deep Learning Applications in Medical Imaging	Literature review on neural networks in medical imaging (with a focus on MRI)	Deep learning has become central in medical image analysis, with increasing performance
Zeng et al. (2024)	Systematic review	Characterize the frequency and type of AI errors in the trace reading	Systematic review of studies on AI errors in mammography	AI makes mistakes with identifiable patterns, reinforcing the need for human oversight
Lee et al. (2017)	Database description	To make available curated base of mammography (CBIS-DDSM) for research	Curator and standardization of the DDSM suite for assisted detection/diagnosis	It provides a standardized public base, but with limited demographic representation
Moreira et al. (2012)	Database description	Present the INbreast full-field digital mammography base	Construction and characterization of the INbreast bank	It provides a database of high-quality images, with a restricted population coverage
Cai et al. (2023)	Database description	Provide mammography base with biopsy-confirmed types (CMMD)	Online base building with biopsy confirmation	Provides annotated data for machine diagnostics, with specific population composition (China)
Halling-Brown et al. (2021)	Database description	Present the OPTIMAM database of mammography images and clinical data	Large-scale resource building of clinical images and metadata	Offers a large volume of images, but with limited racial/geographic representation
Gichoya et al. (2022)	Modeling study	Assess whether AI recognizes patient race in medical images	Multicenter modeling in different imaging modalities	AI infers race from images, creating hidden, unauditable bias risk
Garrucho et al. (2022)	Multicenter technical study	Evaluate domain generalization in deep learning mass detection	Multicenter study of domain generalization in mammography	Domain displacement reduces the generalization of models between centers/populations
Gianfrancesco et al. (2018)	Perspective/Analysis Article	Discuss potential biases of machine learning algorithms with medical record data	Conceptual analysis of sources of bias in health data	Health data can introduce systematic biases, requiring equity metrics and vigilance
Kalbiner et al. (2024)	Systematic review and meta-analysis	Evaluate guidelines and reporting quality in medical AI	Systematic review/meta-analysis of reporting guidelines	There are relevant gaps in standardization and transparency in the reporting of medical AI studies
Muralidharan et al. (2024)	Scoping Review	Map reporting gaps in FDA-approved AI devices	Authorized AI Devices Scope Review	Many authorized devices have incomplete reporting on validation and subgroups
IBGE – PNS 2019 (2021)	National Health Survey	To estimate mammography coverage and health indicators of the Brazilian population	National Health Survey 2019 (population-based household survey)	Mammography coverage (50-69 years) of 58.3% in 2019, lower in the North (43.2%) and Northeast (49.5%)
Silva et al. (2025)	Cross-sectional study (PNS 2013/2019)	Identify social determinants associated with mammography	Analysis of the 2013 and 2019 National Health Survey	Brown/black skin, lower income/schooling and residence in the North/Northeast were associated with not taking the test
Furlan et al. (2023)	Ecological study (Brazil)	To assess the impact of COVID-19 on mammographic screening in Brazil	Comparative analysis of mammograms in the SUS (pre-pandemic vs. pandemic)	There was a drop of ~44% in mammograms in 2020, with regional variation (North 25% to Northeast 48%)
Rocha et al. (2023)	Ecological study (Brazil)	To assess the effects of COVID-19 on screening and staging in the SUS	Poisson regression on SUS data (2013-2021)	Drop in screening and increase in diagnoses in advanced stages during the pandemic
Gerke et al. (2020a)	Regulatory perspective article	Defend a systemic view to regulate AI/ML as a medical device	Regulatory analysis of software as a medical device (SaMD)	AI/ML regulation requires a systemic approach, with post-market validation and monitoring
MHRA (2022)	Regulatory document	Establish guidelines for software and AI as a medical device in the UK	UK Agency Regulatory Programme/ Roadmap (MHRA)	Emphasizes traceability, performance transparency, and mitigation of inequalities
Laux, Wachter & Mittelstadt (2024)	Regulatory analysis	Analyze the European Union's AI Act and risk classification	Critical analysis of the European regulatory framework for AI	The AI Act treats healthcare applications as high-risk, requiring governance and auditing
Jambor (2025)	Regulatory analysis (Brazil)	Evaluate SaMD regulation with a focus on inclusion and equity in AI in health	Analysis of the Brazilian regulatory framework for SaMD/LA	Brazil lacks specific local validation and equity requirements for AI in health
Gebru et al. (2021)	Methodological article	Propose standardized documentation of datasets (datasheets)	Proposal for a data documentation framework	Standardized data documentation increases model transparency and governance
Mittelstadt et al. (2016)	Conceptual review	Mapping the ethical debate on algorithms	Literature review on algorithm ethics	Identifies ethical dimensions (evidence, traceability, fairness) of the use of algorithms
Chen et al. (2020)	Perspective Article	Discuss the use of AI to address health disparities	Conceptual analysis of equity in AI in health	AI can reduce or widen disparities, depending on data and governance
Gerke et al. (2020b)	Ethical-legal chapter/analysis	Discuss ethical and legal challenges of AI-driven healthcare	Review of ethical, legal and regulatory challenges	AI in healthcare raises justice, transparency, and accountability challenges that require governance
Lyell & Coiera (2017)	Systematic review	Analyze automation bias and verification complexity	Systematic review of studies on automation bias	Automation bias increases with the verification burden, requiring supervisory safeguards
Goddard et al. (2012)	Systematic review	Evaluate frequency, mediators and mitigators of automation bias	Systematic review of the literature	Automation bias is frequent and can be mitigated by system design and supervision
By Proost & Pozzi (2023)	Bioethical Testing	Discuss the potential for epistemic unfairness in conversational AI	Ethical-philosophical analysis	AI systems can generate epistemic injustice by making certain groups invisible
Obermeyer et al. (2019)	Observational/analytical study	Investigate racial bias in population health management algorithm	Analysis of a commercial algorithm applied to a large population	Algorithms can reproduce structural racial bias even without explicitly using race

experience shows that robust frameworks, such as those of the FDA, the Medicines and Healthcare products Regulatory Agency, and the European AI Act, favor greater transparency, traceability, and risk mitigation.^{21,27,28} The absence of equivalent requirements in Brazil represents a significant gap that potentially generates inequities.²⁹

In addition to the technical and regulatory dimensions, this review highlights epistemological aspects that are often neglected. The production of knowledge in medical AI has been marked by geographic and institutional concentration, with a predominance of data from a few centers and homogeneous populations.^{10,31} This concentration generates what can be described as algorithmic epistemic injustice: certain bodies and contexts remain less visible to machine learning, which restricts the legitimacy of their clinical experiences as a source of knowledge.^{17,36}

In the case of mammography, this translates into models that are potentially less sensitive to radiological patterns associated with certain groups, age groups, or breast densities, which may reinforce historical exclusions.¹⁷ The response to this problem is not limited to technical adjustments, but requires participatory governance, ethics of co-authorship, and active involvement of affected communities in the development and validation cycle.³³

From an operational point of view, evidence suggests that AI can be particularly useful in health systems with a shortage of radiologists, such as Brazil, working in the screening of presumably normal exams and in the prioritization of suspected cases.^{2,6,7} However, efficiency should not be pursued at the expense of equity. Reduced recalls and increased productivity, while desirable, translate into population benefit only when accompanied by equivalent performance across subgroups.^{18,20,21} The implementation of equity metrics, with longitudinal monitoring and public transparency, is a necessary condition to legitimize the clinical and regulatory use of AI.^{19,20}

The ethical debate about the role of human oversight also emerges as central. Automation bias, characterized by the uncritical acceptance of algorithmic outputs, can weaken clinical judgment and obscure limitations of the model.³⁵ Human-in-the-loop strategies, override protocols, and interfaces that make uncertainty and decision justification visible are indispensable components of responsible use.³⁴ In addition, post-implementation surveillance should include automatic detection of data drift and performance, with objective triggers for recalibration and revalidation.^{18,20}

The analysis of structural inequalities in Brazilian mammography screening provides essential context for the incorporation of AI. Low coverage, regional and racial barriers, and dependence on imported models indicate that technology, if poorly implemented, can reproduce and even amplify the inequalities already documented.^{2-4,24} On the other hand, if accompanied by public policies aimed at data representativeness,

interoperable digital infrastructure, and independent auditing mechanisms, AI can work as an instrument for correcting inequities.^{2,28}

Finally, the convergence between data science, regulatory policy, and bioethics points to the need for an ethics-by-design paradigm, in which equity is not just a result to be measured, but a constitutive principle of technological development.^{30,33,36} The creation of multicenter national repositories, the requirement for stratified local validation, the public transparency of metrics, and the inclusion of patients and professionals in decision-making processes are the pillars of a responsible innovation ecosystem.^{20,28,30} From this perspective, AI is no longer a mere instrument of diagnostic efficiency and becomes a component of a broader agenda of diagnostic justice and the strengthening of the SUS as a State policy.

In summary, the ethical and equitable integration of AI into mammography requires overcoming the logic of technological adoption centered on average performance and recognizing that the clinical value of innovation depends on its ability to benefit populations that have historically remained on the margins of diagnostic progress in a fair and sustainable way.^{30,32,33}

CONCLUSIONS

The application of AI to mammography demonstrates potential to expand breast cancer detection and reduce recall when employed as a complement to human reading. However, the heterogeneity of performance between subgroups shows that aggregate metrics do not ensure diagnostic equity and may hide clinically relevant losses in underrepresented populations. Equity, therefore, should be treated not as a by-product of efficiency, but as a central criterion of validation and surveillance. In the Brazilian context, responsible incorporation requires local multicenter validation with stratified samples, systematic use of equity metrics, and transparent post-market surveillance by subgroup, in line with international regulatory benchmarks. The availability of representative databases, associated with robust governance and public technical documentation, is an essential condition to avoid the uncritical transfer of trained models in different demographic contexts. In clinical practice, AI should act as an instrument to support medical judgment, and not as a substitute for human decision. Continuous supervision, explicit exposure of uncertainty, and override protocols are indispensable elements of safety and legitimacy. Participatory implementation models and independent auditing strengthen trust and allow you to identify failures not captured by aggregated metrics.

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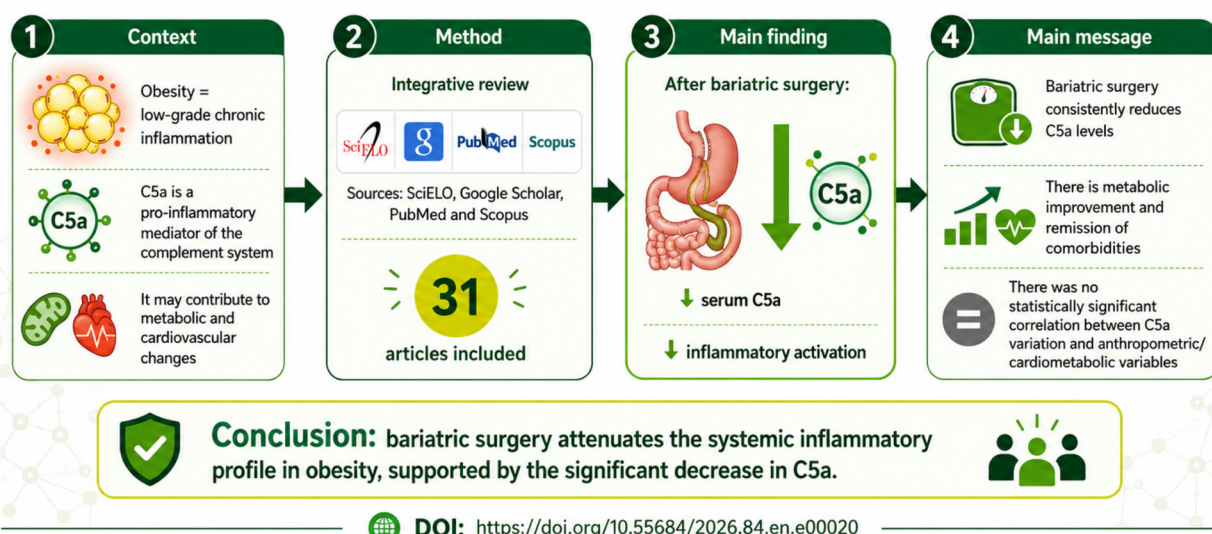
Does bariatric surgery reduce inflammatory activation in obesity? Evidence by complement fraction C5a

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Does bariatric surgery reduce inflammatory activation in obesity?

Evidence from the complement C5a fraction

BioSCIENCE



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Central Message

Obesity is a state of chronic low-grade inflammation, which plays a central role in the genesis of several metabolic and cardiovascular comorbidities. Among the mediators of this process, the complement system stands out, whose activation contributes decisively to the perpetuation of the inflammatory response

Perspective

Serum pro-inflammatory C5a levels showed a significant and consistent reduction after the surgical intervention. Although there was a robust reduction in C5a associated with metabolic improvement, no statistically significant correlations were observed between C5a variation and anthropometric and cardiometabolic variables. However, bariatric surgery is effective in resolving comorbidities and reducing the systemic inflammatory profile, supported by the significant drop in C5a levels.

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ABSTRACT

Introduction: Obesity is a state of chronic low-grade inflammation, which plays a central role in the genesis of several metabolic and cardiovascular comorbidities. Among the mediators of this process, the complement system stands out, whose activation contributes decisively to the perpetuation of the inflammatory response.

Objective: To review the changes in the serum concentration of the C5a fraction of the complement system in obese patients undergoing Roux-en-Y gastric bypass, and to investigate their possible correlation with changes in metabolic parameters.

Method: Integrative review based on online search obtained through virtual platforms with a search for DEC descriptors "complement, C5a, obesity and inflammation" related to the theme, with AND or OR search, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms.

Result Considering only those that had a greater relationship with the theme, 31 articles were read in full. **Conclusion:** Bariatric surgery promotes a significant reduction in serum C5a levels, suggesting attenuation of inflammatory activation mediated by the complement system.

KEYWORDS: Complement. C5a. Obesity. Inflammation.

INTRODUCTION

Obesity has become an epidemic that affects the entire society, imposing a significant burden on health systems and greatly increasing population morbidity and mortality. Currently, it is considered by the WHO (World Health Organization) as one of the main global risk factors in public health. This chronic condition is closely linked to the development of associated comorbidities, such as metabolic syndromes (type 2 diabetes mellitus and dyslipidemias), cardiovascular diseases, high risk of malignant neoplasms and arthropathies.^{1,2} In addition to mechanical factors, it is characterized by a state of chronic low-grade inflammation driven by dysfunctional white adipose tissue (BAD) that acts as an active endocrine organ, increasing cardiovascular risk through the dysregulated secretion of adipokines and other signaling molecules.^{3,4} In addition, macrophages infiltrate the BAD, which secrete pro-inflammatory cytokines (TNF- α , IL-6) and contribute to metabolic stress.⁵

The complement system is an essential component of innate immunity, consisting of a serial enzymatic cascade that aims at the removal of pathogens by lysis, opsonization and the elimination of cellular debris.⁶ This mechanism has three activation pathways: the classical one, triggered mainly by antibodies; the lectin pathway, activated by microbial carbohydrates; and the alternative.^{7,8} These pathways converge to the formation of C5 convertase, which culminates in the production of the membrane attack complex (C5-C9, or MAC) and the release of potent anaphylatoxins, such as C3a and C5a.⁹ C5a is a key anaphylatoxin at the interlink between inflammation and metabolism. It acts through G-protein-coupled receptors (C5aR) and is a crucial element in the recruitment and activation of inflammatory cells and in the upregulation of adhesion molecules, favoring neutrophil-endothelial interactions.^{5,8,10}

The link between obesity and complement is strengthened by complement factor D (adipsin). This factor, secreted by adipocytes among other cell types, is directly involved in the activation of the alternative pathway, playing a critical role in the production of C3a

and C5a. Adipsin regulates adipose tissue homeostasis and has been associated with metabolic disorders, demonstrating a direct role of BAD in amplifying the complement inflammatory cascade.¹¹

Bariatric surgery is a treatment option for severe obesity, promoting significant and sustained weight loss, with a consequent decrease in the incidence of associated diseases.^{12,13} This intervention induces remarkable remission of the inflammatory process and substantial improvement in metabolic status.⁵ However, the scientific literature is scarce in the detailed evaluation of the behavior of the C5a component in obese individuals and on the impact of weight loss induced by bariatric surgery in this context.¹¹

It is in this gap that the present study is inserted, which aims to review the behavior of serum C5a levels in obese individuals undergoing bariatric procedures in Roux-en-Y bariatric procedures, its possible association with changes in the anthropometric and metabolic profile, adding information on the role of complement modulation in the postoperative response and in the improvement of comorbidities.^{14,15}

METHOD

Integrative review made by collecting information for reading and analysis from online research on virtual platforms. Initially, a search was performed for DEC descriptors related to the theme, using the following terms: "complement, C5a, obesity and inflammation" with a search AND or OR, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms, and considering only those that were more related to the theme, the texts were read in full, including 31 articles in this review.

DISCUSSION

The official parameter for the determination and classification of obesity, already well known, is the Body Mass Index (BMI), calculated by the ratio between weight (kg) and the square of height (m²) and defines obesity as grade I BMI between 30-34.⁹ kg/m²; grade II

(severe) between 35-39.⁹ kg/m², and grade III (morbid) BMI ≥ 40 kg/m². Although several predisposing factors contribute to obesity - including metabolic, hormonal, genetic and psychosocial factors - global rates continue to rise.^{16,17} Many researchers consider obesity to be a multifactorial disease, in which, despite genetic inheritance, environmental factors such as the consumption of high-fat diets and a sedentary lifestyle play a critical role in increasing body fat levels and the risk of chronic diseases.¹⁴ Type 2 diabetes mellitus (DM 2) is characterized by chronic hyperglycemia, resulting from insufficient insulin production or deficiency of cellular sensitivity to this hormone¹⁸, with obesity being the most significant risk factor in its development.¹⁹ This risk is exacerbated by insulin resistance caused by increased adipocyte volume, especially in abdominal fat. In a scenario of insulin resistance, the anti-inflammatory mechanisms of insulin are compromised, favoring pro-inflammatory signaling.²⁰

Adipokine and cytokine synthesis by adipose tissue

Adipose tissue is composed of adipocytes, cells primarily responsible for storing triglycerides, the body's main energy reserve. However, adipose tissue is metabolically active, exerting a vital endocrine function in the synthesis and secretion of various hormones and cytokines, collectively known as adipokines.²¹

Resistin is a cytokine that modulates the action of insulin and glucose and lipid homeostasis. This adipokine contributes significantly to metabolic stress induced by positive caloric balance,⁵ also having pro-inflammatory properties and being secreted by adipocytes, monocytes, and macrophages.²² Leptin and adiponectin are also adipokines that participate in energy regulation and inflammatory responses. Leptin regulates energy balance by promoting satiety via the hypothalamus. In obese individuals, the serum leptin concentration is elevated due to leptin resistance, caused by the increase in body fat percentage.⁷ On the other hand, adiponectin acts as a cardiovascular protection factor and is an important anti-inflammatory protein. However, its synthesis is typically decreased in obese patients, increasing the risk of comorbidities.⁵

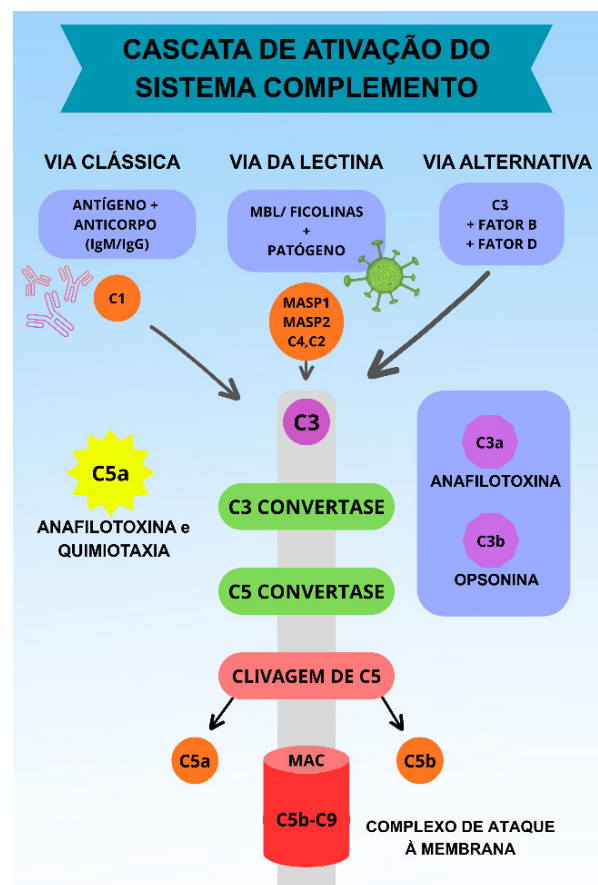
The complement system

The complement system, discovered by Jules Bordet in 1890, is a crucial mediator of the immune response, belonging to the innate immune system. Its main function is to complement the defense mechanisms against pathogens and promote the elimination of apoptotic cells and cellular debris, also influencing the adaptive response through opsonization and potentiation of the action of antibodies.^{6,7}

Complementing the aforementioned 3-way activation system (Figure), it is worth understanding how each one acts. The classical pathway is triggered by antigen-antibody complexes and involves recognition by C1q and subsequent activation of C1r and C1s, culminating in the formation of C3 convertase (C4b2a).^{6,23} The lectin pathway is initiated by the binding of mannose-binding lectin (MBL) or phycolins to microbial surface

carbohydrates. This complex activates serine proteases (MASP1 and MASP2) and cleaves C4 and C2, also resulting in C3 convertase.^{7,23} The alternative pathway has a low-level spontaneous activation mechanism known as "tick over", where C3 is cleaved, binding to factor B. Cleavage by factor D originates C3 convertase (C3bBb).⁷

The three pathways converge to the cleavage of the C3 protein, followed by the action of C5 convertase over C5. This cleavage produces C5a, a highly inflammatory peptide, and C5b. The final step results in the formation of the membrane attack complex (MAC), which promotes osmotic lysis by inserting pores into the cell membrane.^{5,23}



Source: Mariana D S Testa, 2025

FIGURE — Add-on system activation cascade

The pathophysiological role of C5a

C5a is the soluble fragment from the cleavage of C5. It is a potent pro-inflammatory peptide, acting through its G-protein-coupled receptors, which are chemoattractant and anaphylatoxin, cell activation, and cell adhesion and adaptive response.

In chemoattractant and anaphylatoxin, C5a recruits immune cells to the site of infection. It is classified as an anaphylatoxin due to its ability to act on mast cells and endothelial cells to promote a local inflammatory response that, in high concentrations, can lead to generalized circulatory collapse.

Cell activation promotes the activation of resident mast cells, leading to the release of inflammatory mediators, such as histamine and TNF- α .⁷

In cell adhesion and adaptive response, the action of

C5a contributes to the initiation of the adaptive immune response by recruiting phagocytic cells and accelerating the movement of antigen-presenting cells (APCs) to local lymph nodes.⁷

Complement system and obesity

The inflammatory process in obesity focuses on adipose tissue, where fat accumulation and adipocyte hypertrophy promote pathogenic changes. These alterations contribute to the increase of pro-inflammatory cytokines and, consequently, to the production and high serum levels of the C3 and C4 components of the complement system, which is associated with the induction of metabolic and cardiovascular diseases.^{5,24} Activation of the complement system in obesity culminates in the cleavage of C5 into C5a. However, the precise involvement of the C5a–C5aR axis in the pathological mechanisms of obesity and insulin resistance, while crucial, still requires further investigation.²⁴

Bariatric surgery and obesity control

Clinical treatment for obesity, based on lifestyle changes and pharmacological interventions, often encounters barriers in achieving lasting weight reduction goals.^{5,25} Due to the low efficacy in weight maintenance with clinical treatment alone, bariatric surgery has been consolidated as the most effective intervention for severe obesity. It promotes significant and lasting weight loss, favoring the remission of associated diseases, increasing longevity and improving quality of life. Currently, surgical risks are considered low.²⁶ The new guidelines of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)²⁷ expanded the indications for patients with a BMI between 30-35 with uncontrolled T2DM. Among the techniques, gastric bypass with Roux-en-Y intestinal bypass is the most used in Brazil, providing a loss of 70-80% of excess weight and being highly effective in the remission of comorbidities.²⁸⁻³¹

CONCLUSION

Serum levels of the pro-inflammatory anaphylotoxin C5a showed a significant and consistent reduction after the surgical intervention. Although there was a robust reduction in C5a associated with metabolic improvement, no statistically significant correlations were observed between C5a variation and anthropometric and cardiometabolic variables. In summary, bariatric surgery is effective in remission of comorbidities and in reducing the systemic inflammatory profile, supported by the significant drop in C5a levels.

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