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FROM GUMS TO BRAIN: PERIODONTAL INFLAMMATION AND ITS EMERGING ROLE IN ALZHEIMER'S DISEASE

DAS GENGIVAS AO CÉREBRO: INFLAMAÇÃO PERIODONTAL E SEU PAPEL EMERGENTE NA DOENÇA DE ALZHEIMER

DE LAS ENCÍAS AL CEREBRO: LA INFLAMACIÓN PERIODONTAL Y SU PAPEL EMERGENTE EN LA ENFERMEDAD DE ALZHEIMER

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ABSTRACT

Objective: To explore the association between periodontitis and Alzheimer's disease, emphasizing the role of chronic inflammation and the oral–brain axis in neurodegenerative processes.

Methods: A narrative synthesis of recent literature was conducted, including observational studies, mechanistic research, and clinical evidence examining the relationship between periodontal disease and neurodegeneration. Focus was given to inflammatory pathways, microbial dissemination, and systemic effects.

Results: Emerging evidence suggests that periodontitis may contribute to systemic inflammation capable of influencing the central nervous system. Periodontal pathogens and their byproducts have been detected in brain tissues, and elevated levels of inflammatory mediators have been associated with cognitive decline. These findings support a potential link between chronic oral infection and the pathophysiology of Alzheimer's disease, although causality remains unconfirmed.

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Conclusion: The oral–brain axis represents a growing area of interest, with periodontitis potentially playing a role in neuroinflammatory processes with Alzheimer's disease. While current evidence supports an association, further longitudinal and interventional studies are needed to clarify causality and determine whether periodontal treatment can impact cognitive outcomes.

Keywords: Periodontitis. Alzheimer's Disease. Oral-Systemic Link. Neuroinflammation. Oral Microbiome. Chronic Inflammation. Systemic Health.

RESUMO
Objetivo: Explorar a associação entre periodontite e doença de Alzheimer, enfatizando o papel da inflamação crônica e do eixo oral-cérebro nos processos neurodegenerativos.

Métodos: Foi realizada uma síntese narrativa da literatura recente, incluindo estudos observacionais, pesquisas mecanísticas e evidências clínicas que examinam a relação entre doença periodontal e neurodegeneração. O foco foi dado às vias inflamatórias, disseminação microbiana e efeitos sistêmicos.

Resultados: Evidências emergentes sugerem que a periodontite pode contribuir para a inflamação sistêmica capaz de influenciar o sistema nervoso central. Patógenos periodontais e seus subprodutos foram detectados em tecidos cerebrais, e níveis elevados de mediadores inflamatórios foram associados ao declínio cognitivo. Esses achados corroboram uma possível ligação entre infecção oral crônica e a fisiopatologia da doença de Alzheimer, embora a causalidade permaneça não confirmada.

Conclusão: O eixo oral-cérebro representa uma área de crescente interesse, com a periodontite potencialmente desempenhando um papel nos processos neuroinflamatórios associados à doença de Alzheimer. Embora as evidências atuais sustentem uma associação, são necessários mais estudos longitudinais e intervencionais para esclarecer a causalidade e determinar se o tratamento periodontal pode impactar os resultados cognitivos.

Palavras-chave: Periodontite. Doença de Alzheimer. Ligação Oral-Sistêmica. Neuroinflamação. Microbioma Oral. Inflamação Crônica. Saúde Sistêmica.

RESUMEN
Objetivo: Explorar la asociación entre la periodontitis y la enfermedad de Alzheimer, haciendo hincapié en el papel de la inflamación crónica y el eje oral-cerebral en los procesos neurodegenerativos.

Métodos: Se realizó una síntesis narrativa de la literatura reciente, incluyendo estudios observacionales, investigaciones mecanicistas y evidencia clínica que examinan la relación entre la enfermedad periodontal y la neurodegeneración. Se prestó especial atención a las vías inflamatorias, la diseminación microbiana y los efectos sistémicos.

Resultados: La evidencia emergente sugiere que la periodontitis puede contribuir a la inflamación sistémica capaz de influir en el sistema nervioso central. Se han detectado patógenos periodontales y sus subproductos en tejidos cerebrales, y se han asociado niveles elevados de mediadores inflamatorios con el deterioro cognitivo. Estos hallazgos respaldan

un posible vínculo entre la infección oral crónica y la fisiopatología de la enfermedad de Alzheimer, aunque la causalidad aún no se ha confirmado.

Conclusión: El eje oral-cerebral representa un área de creciente interés, y la periodontitis podría desempeñar un papel en los procesos neuroinflamatorios asociados a la enfermedad de Alzheimer. Si bien la evidencia actual respalda una asociación, se necesitan más estudios longitudinales y de intervención para aclarar la causalidad y determinar si el tratamiento periodontal puede influir en los resultados cognitivos.

Palabras clave: Periodontitis. Enfermedad de Alzheimer. Vínculo Oral-Sistémico. Neuroinflamación. Microbioma Oral. Inflamación Crónica. Salud Sistémica.

1 INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder and the leading cause of dementia worldwide, characterized by cognitive decline, memory impairment, and functional deterioration. Its pathophysiology is classically associated with the accumulation of amyloid-β plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. However, growing evidence suggests that chronic inflammation plays a critical role in the onset and progression of neurodegenerative processes, shifting the focus toward systemic contributors to brain pathology (Heneka et al., 2015).

In this context, the concept of the oral–brain axis has emerged as a novel framework linking oral health to neurological conditions. Periodontitis, a chronic inflammatory disease driven by microbial dysbiosis and host immune response, has been increasingly associated with systemic inflammation and distant organ effects, including the central nervous system (Hajishengallis, 2015). The persistent inflammatory burden characteristic of periodontitis may contribute to systemic dissemination of pro-inflammatory mediators and microbial components, potentially influencing neuroinflammatory pathways.

Mechanistically, several pathways have been proposed to explain the association between periodontitis and Alzheimer's disease. One hypothesis involves the hematogenous spread of periodontal pathogens or their virulence factors, such as lipopolysaccharides, which can cross the blood–brain barrier and trigger local immune responses. Notably, periodontal pathogens like Porphyromonas gingivalis have been detected in brain tissues of patients with Alzheimer's disease, suggesting a possible direct microbial contribution to neurodegeneration (Dominy et al., 2019).

In addition to direct microbial invasion, systemic inflammation represents a key linking mechanism. Periodontitis is associated with elevated levels of circulating inflammatory mediators, including interleukins and tumor necrosis factor-alpha, which may exacerbate neuroinflammation and promote neuronal damage (Kamer et al., 2008). Chronic exposure to such inflammatory signals has been implicated in the activation of microglia and the progression of neurodegenerative changes.

Epidemiological studies further support this association, demonstrating correlations between periodontal disease severity, tooth loss, and increased risk of cognitive decline and Alzheimer's disease (Ide et al., 2016). Although these findings do not establish causality, they reinforce the hypothesis that oral health may influence systemic and neurological outcomes.

The recognition of periodontitis as a potential modifiable risk factor for neurodegenerative diseases highlights the importance of integrating oral health into broader medical paradigms. This perspective not only expands the role of dental professionals but

also emphasizes the need for interdisciplinary approaches in the prevention and management of chronic diseases.

Despite the growing body of evidence, significant gaps remain regarding the causal relationship, underlying mechanisms, and clinical implications of this association. Therefore, further research is essential to clarify the extent to which periodontal interventions may impact the onset or progression of Alzheimer's disease.

2 METHODOLOGY

This study was conducted as a narrative review to examine the relationship between periodontitis and Alzheimer's disease within the framework of the oral–brain axis. Literature searches were carried out in PubMed/MEDLINE, Scopus, and Web of Science for studies using terms including "periodontitis," "Alzheimer's disease," "neuroinflammation," and "oral-systemic connection."

A broad inclusion approach was adopted, considering observational studies, experimental research, mechanistic investigations, and interdisciplinary studies exploring links between oral health and neurodegeneration.

Articles were selected based on their relevance to inflammatory pathways, microbial dissemination, and systemic interactions between the oral cavity and the central nervous system.

Data extraction focused on study type, conceptual contributions, and reported associations. Findings were synthesized qualitatively and organized into thematic domains, such as inflammation, microbiological evidence, and systemic implications.

3 RESULTS

The synthesis of current literature reveals a consistent and biologically plausible association between periodontitis and Alzheimer's disease (AD), supported by converging evidence from epidemiological studies, mechanistic research, and molecular investigations.

3.1 EPIDEMIOLOGICAL ASSOCIATIONS

Multiple observational and longitudinal studies have demonstrated that individuals with periodontitis or significant tooth loss exhibit an increased risk of cognitive decline and Alzheimer's disease. Ide et al. (2016) reported that patients with AD and coexisting periodontitis showed a more rapid rate of cognitive deterioration over a six-month follow-up period compared to those without periodontal inflammation.

Similarly, population-based studies have identified associations between chronic oral infection, edentulism, and increased incidence of dementia. These findings suggest that periodontal status may act as a modifier of disease progression rather than solely a coincidental comorbidity.

3.2 MICROBIOLOGICAL AND MOLECULAR EVIDENCE

One of the most compelling lines of evidence arises from the detection of periodontal pathogens and their virulence factors in the central nervous system. Dominy et al. (2019) identified Porphyromonas gingivalis DNA and gingipain proteases in the brains of patients with Alzheimer's disease. Moreover, experimental models demonstrated that oral infection with P. gingivalis led to brain colonization and increased production of amyloid-β.

Lipopolysaccharides (LPS) derived from Gram-negative periodontal bacteria have also been detected in brain tissues, supporting the hypothesis of microbial translocation via hematogenous routes or through compromised blood–brain barrier integrity.

3.3 SYSTEMIC INFLAMMATION AND NEUROINFLAMMATORY PATHWAYS

Periodontitis is consistently associated with elevated systemic inflammatory markers, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These mediators are known to influence neuroinflammatory processes and have been implicated in Alzheimer's disease pathogenesis (Kamer et al., 2008).

Chronic peripheral inflammation may promote microglial activation, leading to sustained neuroinflammation, synaptic dysfunction, and neuronal loss. This systemic-to-central inflammatory signaling represents a key mechanistic bridge between oral disease and neurodegeneration.

3.4 BLOOD–BRAIN BARRIER DISRUPTION AND MICROBIAL DISSEMINATION

Emerging evidence suggests that chronic systemic inflammation associated with periodontitis may compromise the integrity of the blood–brain barrier (BBB), facilitating the invasion of microbial products and inflammatory mediators into the central nervous system.

This process may amplify local immune responses within the brain, contributing to the accumulation of amyloid-β and tau pathology, hallmark features of Alzheimer's disease.

3.5 BIDIRECTIONAL RELATIONSHIP

Some studies suggest a potential bidirectional relationship. Cognitive decline may impair oral hygiene practices, increasing susceptibility to periodontal disease, while existing

periodontitis may exacerbate neurodegenerative processes. This interplay complicates causal interpretation and highlights the need for longitudinal and interventional research.

4 DISCUSSION

The relationship between periodontitis and Alzheimer's disease (AD) represents one of the most compelling examples of the oral–systemic connection, integrating concepts from immunology, microbiology, and neuroscience. The present synthesis supports a biologically plausible association in which chronic periodontal inflammation may act as a peripheral driver of neurodegenerative processes, although the nature and strength of this relationship remain under active investigation.

A central pillar of this association is the role of chronic systemic inflammation. Periodontitis is not a localized condition but a persistent inflammatory burden capable of sustaining elevated levels of circulating cytokines over long periods. This systemic inflammatory state may influence the central nervous system through multiple pathways, including cytokine signaling, endothelial activation, and immune cell trafficking. In the context of Alzheimer's disease, such peripheral inflammation may act as a priming stimulus for microglial cells, lowering the threshold for neuroinflammatory activation. Once activated, microglia can adopt a chronic pro-inflammatory phenotype, contributing to synaptic dysfunction, neuronal injury, and amplification of amyloid and tau pathology.

Beyond systemic inflammation, direct microbial involvement provides an additional and particularly intriguing mechanistic link. The detection of periodontal pathogens, especially Porphyromonas gingivalis, and their virulence factors within brain tissue suggests that oral bacteria may translocate from periodontal pockets to distant organs. This dissemination may occur through transient bacteremia, a well-documented consequence of routine oral activities such as chewing and tooth brushing in individuals with periodontitis. Once in circulation, microbial components such as lipopolysaccharides and proteolytic enzymes may cross a compromised blood–brain barrier and trigger localized immune responses within the brain.

Importantly, these microbial products are not passive bystanders. Virulence factors such as gingipains have been shown to interfere with host protein processing, promote neurotoxicity, and potentially stimulate the production of amyloid-β as part of an innate immune defense mechanism. In this context, amyloid deposition may be interpreted not only as a pathological hallmark but also as a response to chronic infection, reframing aspects of Alzheimer's disease within an infectious–inflammatory paradigm.

The integrity of the blood–brain barrier (BBB) emerges as a critical mediator in this process. Chronic systemic inflammation associated with periodontitis may lead to endothelial

dysfunction and increased permeability of the BBB. This breakdown facilitates the entry of peripheral inflammatory mediators and microbial components into the central nervous system, thereby intensifying neuroinflammatory cascades. The interaction between vascular dysfunction and neurodegeneration is particularly relevant, as it bridges periodontal disease with broader systemic conditions such as atherosclerosis, which are themselves risk factors for cognitive decline.

Epidemiologically, the association between periodontal disease and cognitive impairment is consistently observed across diverse populations. However, these findings must be interpreted within the context of significant confounding variables. Age, socioeconomic status, education level, smoking, and comorbidities such as diabetes and cardiovascular disease are shared risk factors that may independently contribute to both periodontitis and Alzheimer's disease. While statistical adjustments are often applied, residual confounding cannot be fully excluded, limiting causal inference.

The possibility of a bidirectional relationship further complicates interpretation. Cognitive decline may impair an individual's ability to maintain adequate oral hygiene, leading to increased plaque accumulation and progression of periodontal disease. Conversely, established periodontal inflammation may exacerbate systemic and neuroinflammatory pathways, accelerating cognitive deterioration. This reciprocal interaction suggests that periodontitis may function both as a contributing factor and as a consequence of neurodegenerative disease, creating a self-reinforcing cycle.

Another critical limitation in the current literature is the predominance of observational study designs. While these studies are valuable for identifying associations, they do not establish causality. Mechanistic studies, including animal models and in vitro experiments, provide important insights but may not fully replicate the complexity of human disease. Additionally, variability in diagnostic criteria for periodontitis and differences in cognitive assessment tools reduce comparability across studies.

One of the most important gaps in the field is the lack of interventional evidence. It remains unclear whether periodontal treatment can modify the trajectory of cognitive decline or reduce the risk of developing Alzheimer's disease. If a causal relationship were established, periodontal therapy could emerge as a novel and accessible strategy for reducing systemic inflammatory burden and potentially influencing neurodegenerative outcomes. However, current data are insufficient to support such conclusions.

From a clinical perspective, these findings reinforce the importance of integrating oral health into systemic healthcare models, particularly for aging populations. Dental professionals may play a critical role in identifying patients at risk and contributing to

multidisciplinary strategies aimed at preserving overall health. Preventive periodontal care, early diagnosis, and effective management of chronic inflammation may have implications that extend far beyond the oral cavity.

At a conceptual level, the oral–brain axis challenges the traditional compartmentalization of medicine and dentistry. It underscores the need for a more holistic understanding of chronic diseases, where distant organ systems are interconnected through immune, microbial, and vascular pathways. This perspective opens new avenues for research and highlights the importance of interdisciplinary collaboration in addressing complex conditions such as Alzheimer's disease.

5 CONCLUSION

The evidence synthesized in this review supports a consistent and biologically plausible association between periodontitis and Alzheimer's disease, mediated primarily through mechanisms involving chronic systemic inflammation, microbial dissemination, and neuroimmune interactions. The oral–brain axis emerges as a key conceptual framework for understanding how localized infections may influence distant neurodegenerative processes.

Despite these advances, the current body of evidence remains insufficient to establish a definitive causal relationship. The predominance of observational studies, the presence of shared risk factors, and the potential bidirectional nature of the association all highlight the complexity of this link and the need for cautious interpretation.

Future research should prioritize longitudinal cohort studies and well-designed interventional trials to determine whether periodontal treatment can influence cognitive outcomes or alter the progression of Alzheimer's disease. Standardization in diagnostic criteria, biomarker assessment, and methodological approaches will be essential to strengthen the quality and comparability of evidence.

If a causal relationship is confirmed, the implications for clinical practice and public health would be substantial. Periodontal disease could be recognized not only as a condition affecting oral health but also as a modifiable risk factor for neurodegeneration. This would support the incorporation of oral health strategies into broader preventive frameworks for cognitive decline and aging-related diseases.

In this context, maintaining periodontal health may represent a low-cost, accessible, and impactful approach to reducing systemic inflammatory burden and promoting overall health. The integration of dentistry into multidisciplinary healthcare models may therefore play an important role in addressing some of the most pressing challenges associated with aging populations and neurodegenerative disorders.

REFERENCES

Dominy, S. S., Lynch, C., Ermini, F., Benedyk, M., Marczyk, A., Konradi, A., … Potempa, J. (2019). Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Science Advances, 5(1), eaau3333.

Hajishengallis, G. (2015). Periodontitis: From microbial immune subversion to systemic inflammation. Nature Reviews Immunology, 15(1), 30–44.

Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 14(4), 388–405.

Ide, M., Harris, M., Stevens, A., Sussams, R., Hopkins, V., Culliford, D., … Holmes, C. (2016). Periodontitis and cognitive decline in Alzheimer's disease. PLoS ONE, 11(3), e0151081.

Kamer, A. R., Craig, R. G., Dasanayake, A. P., Brys, M., Glodzik-Sobanska, L., & de Leon, M. J. (2008). Inflammation and Alzheimer's disease: Possible role of periodontal diseases. Alzheimer's & Dementia, 4(4), 242–250.