Interrelation between periodontal and Alzheimer's disease: Integrative review

https://doi.org/10.56238/sevened2024.010-045

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ABSTRACT

Introduction: Studies point to a two-way relationship between Periodontal Disease (PD) and Alzheimer's Disease (AD), based on the inflammatory reaction, since these pathologies have a similar systemic inflammatory profile. The link between PD and AD can be explained by the spread of infectious or inflammatory agents that migrate from the oral cavity to the brain. Objective: To understand the relationship between Periodontal Disease and the development of Alzheimer's Disease. Methodology: A bibliographic search was carried out in the MEDLINE databases (PubMed), without restriction of dates, with text in English and Portuguese, applying the descriptors "Alzheimer's disease"; "Periodontal Disease"; "Microbiota"; "Alzheimer disease"; "Periodontal disease"; "Microbiota" isolated or combined using the Boolean operators "and" and "or". Results: 35 publications were obtained, using the keywords presented in the work. Following inclusion and exclusion criteria, 21 studies were used for careful reading and categorization. Conclusion: The literature supports the existence of a bidirectional relationship between periodontal disease and Alzheimer's disease, which occurs through the presence of a similar inflammatory mechanism. However, it is pertinent to develop new, more rigorous clinical studies to better understand the association of these diseases, which is essential for the development of more effective prevention and treatment strategies for patients suffering from both conditions. Early identification of these interrelationships can lead to a better quality of life for patients and a reduction in associated health conditions.

Keywords: Alzheimer's disease, Periodontal Disease, Microbiota, Neuroinflammation, Brain-mouth connection.

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INTRODUCTION

The terminology "Periodontal Disease" (PD) encompasses the pathologies Gingivitis and Periodontitis, which affect, respectively, the gums and the periodontal ligament. These diseases are multifactorial in nature and among their causes are bacteria, which are part of the natural microbiota of the subgingival biofilm. The products of the metabolism of these bacteria induce the gingival epithelium to release cytokines and chemokines, which act as signals, attract the defense cells of the human immune system and trigger an inflammatory process. The study of these pathogenic bacteria present in injured periodontium has been the focus of recent research, since they may be associated with other systemic diseases, such as Alzheimer's (Silva *et al*., 2015).

According to Castellani, Rolston and Smith (2010), Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, whose most characteristic symptom is the loss of recent memory, which can drastically affect daily activities and, depending on the stage in which it is, can lead to more serious systemic complications. This is a disease that mainly afflicts the senile population, with its highest prevalence of involvement after the age of 65. Alzheimer's, according to its progression, can affect the individual's body in several ways, and one of them is in relation to the immune system and inflammation mechanisms.

Studies point to a bidirectional relationship between Periodontitis and Alzheimer's, based on the inflammatory reaction, since these pathologies have a similar systemic inflammatory profile (Noble *et al.,* 2024). The link between PD and AD can be explained by the spread of infectious or inflammatory agents that migrate from the oral cavity to the brain (Ranjan; Abhinay; Mishra, 2018; Ashraf *et al*., 2019). According to Miklossy and McGeer (2016), a seven-fold higher density of oral bacteria is found in the brain tissue of deceased AD patients compared to controls. In particular, *Porphyromonas gingivalis*, the main pathogen of periodontitis, is significantly identified in the brains of patients who have died from AD (Dominy *et al*., 2019).

However, a broader understanding of the relationship between PD and AD still needs further study. Thus, this study is an integrative review of the literature on the interrelationship between PD and AD, with the objective of better understanding the bidirectional relationship that involves them, through their common inflammatory and immunological reactions, in addition to seeking ways to contribute to the health of the population affected by these pathologies.

METHODOLOGY

This work was an integrative literature review, with a quantitative descriptive character, conducted according to the Preferred Reporting Items For Systematic Reviews and Meta-Analyses (PRISMA, 2020). According to Souza, 2010, the integrative review provides a synthesis and practical implementation of the studies, promoted by the Evidence-Based Practice (EBP),

constituting a broader perspective by allowing the use of the integration of experimental and non-experimental studies, associating theoretical and empirical data. Thus promoting data analysis of research necessary for the development of critical thinking.

Searches for scientific literature were carried out in the MEDLINE database (PubMed), applying the key terms, alone or combined through the Boolean operators "*and*" and "*or*". The descriptors used for the research were: "Alzheimer's disease"; "Periodontal Disease"; "Microbiota"; "Neuroinflammation"; "Brain-mouth connection"; *Alzheimer's disease; "Periodontal disease"; "Microbiota"; "Neuroinflammation" and "Brain-mouth connection".*

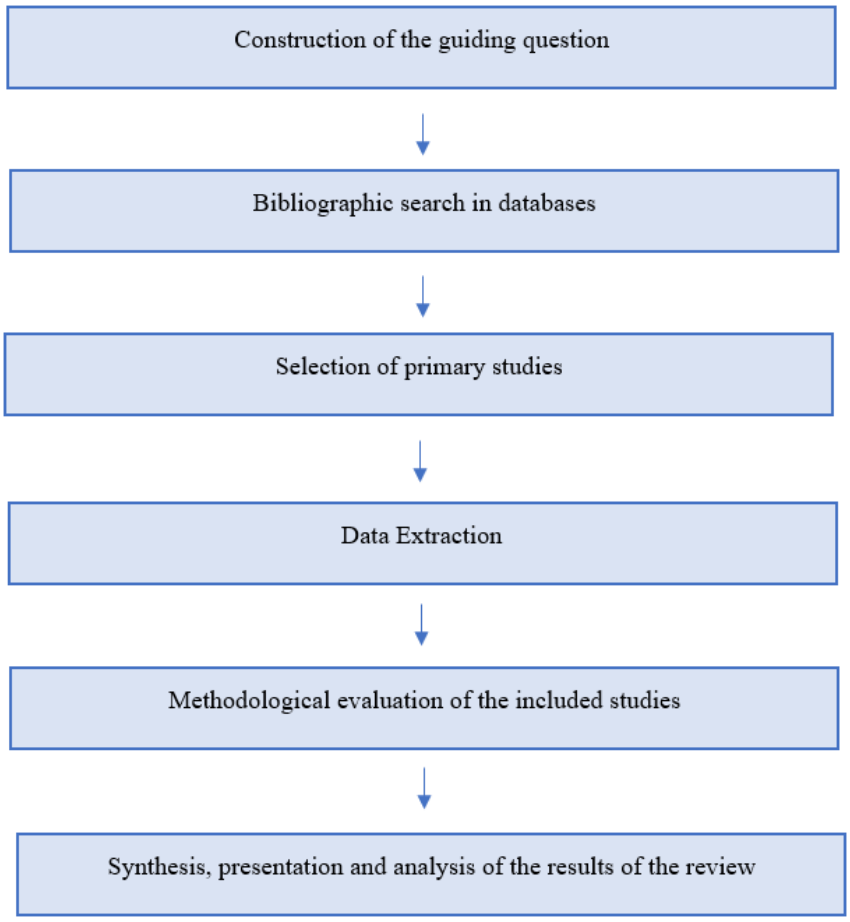
As an inclusion strategy , articles and books published without date restriction were selected, resulting from the recent discussion of the theme, in English and Portuguese. Subsequently, duplicates, papers with titles and abstracts that diverged from the theme of this study, as well as articles that did not have free and full access, were excluded.

For the organization and analysis of the data, a table was presented that summarizes the articles used, including the author's name, year of publication, title and conclusion.

Thus, the following steps were followed: construction of the guiding question; bibliographic search in the databases; selection of primary studies; data extraction; methodological evaluation of the included studies; synthesis, presentation, and analysis of the results of the review (PAGE *et al*., 2021). The guiding questions were: How is the relationship between Periodontal Disease and Alzheimer's established? How can the inflammatory system be related to the development of dementia?

The cataloging, management, reading, identification of duplicate articles, creation of a virtual library, standardization of references and filing of articles were done using the Mendeley Desktop software (Windows 10 - version 1803).

Figure 1. Flowchart of the steps followed for the elaboration of the article



Source: Authors

THEORETICAL FRAMEWORK

PERIODONTITIS

PD is a chronic inflammatory disease induced by bacterial biofilm attached to tooth structures that has the potential to induce a systemic response by the host, presenting bacterial antibodies in plasma serum and elevated inflammatory cytokines (Noble *et al*., 2014). According to Bui *et al.* (2019), PD is one of the most common oral diseases in adults, affecting billions of people worldwide, and is considered a pandemic by the US Centers for Disease Control and Prevention, with the potential to generate a reduction in quality of life, speech impairment and low self-esteem in patients.

Based on the assumption defended by Dioguardi *et al*. (2020), *Aggregatibacter actinomycetemcomitans* (Aa) is a pathogen that has its direct action by activating the secretion of pro-inflammatory cytokines by microglia, with cytokines being responsible for periodontal destruction. The authors Kwno, Lamter and Levin (2021), argue that subgingival microbial infection occurs by Gram-negative anaerobic pathogens, among which are *Porphyromonas Gingivalis, Tannerella Forysthia and Treponema Denticola,* the lipopolysaccharides of these pathogens act by inciting macrophages and other inflammatory cells of the host to produce a series of pro-inflammatory cytokines.

Pro-inflammatory cytokines (TNF-α, IL-1, INF-γ and PGE2) can be found in the periodontal pocket, which is a source for inflammatory intermediates to be released, thus representing a risk for the development of systemic diseases (Dioguard *et al*., 2020).

ALZHEIMER'S DISEASE

AD is an irreversible progressive neurodegenerative disorder that culminates in loss of memory, thinking, and reduced learning capacity, with the potential to progress to death (Bui *et al*., 2019).

The brain has distinct inflammatory processes, which contributes to the development of AD, with complement activation and expression of cytokines and chemokines (Bui *et al*., 2019). In the new AD research framework, developed in 2018, it was established that AD is defined based on evidence from biomarkers of β-amyloid (Aβ) and tau pathology (Jack et al., 2018).

Jeong, Sangyun (2017) draws attention to the two types of AD development, the familial early-onset (EO-FAD), which constitute less than 5% of cases, and the sporadic late-onset (LO-SAD), which in most cases is due to multiple genetic susceptibilities and environmental factors.

According to Mila-Alomà *et al*. (2020), pathophysiological events begin to be identified in early stages, with neural and axonal damage, synaptic dysfunction, neuroinflammation and glial response, and co-pathology of α-synuclea or TDP-43. They are neuropathologically characterized by neuritic plaques, neurofibrillating tangles (NFTs), β-amyloid peptides, and hyperphosphorylated tau (pTau) (Sangyun Jeon, 2017).

According to Dioguardi *et al.* (2020), the deposition of β-amyloid is neurotoxic, causing disturbances in calcium hemostasis and free radical production. The β-amyloid hypothesis suggests that the deposition of insoluble Aβ in the brain is the main cause of AD, however, the severity and advancement is correlated with pTau at abnormally high levels (Sangyun Jeon, 2017).

PERIODONTITIS - ALZHEIMER'S INTERRELATIONSHIP

Periodontal pathogens not only have the ability to invade the periodontium, but also to overcome the epithelium of the periodontal pocket, being able to percolate into the bloodstream and promote the release of pro-inflammatory toxins with significant potential to reach the brain (Licardo *et al*., 2020).

According to Dominy *et al.* (2019), among the pathogens found in PD, *Porphyromonas gingivalis and Gingipains* stand out. *Porphyromonas gingivalis* is essential for the development of CP and a risk factor for the development of β-amyloid (Aβ) plaques, while the toxic byproduct of the bacterium "*Gingipains*" has been found in the brains of AD patients, which is related to detrimental effects on pTau. Hading; Singhrao (2011) reported on the performance of autopsy in AD patients, in

which the presence of two histological markers was observed, Aβ plaques and intraneuronal neurofibrillary tangles; the presence of these markers was a characteristic of AD.

Noble *et al.* (2014), argue that periodontitis is related to cognitive impairment and dementia. The authors describe the systemic inflammation profile of AD and CP as similar, and a relationship was identified between high serum IgG to the pathogen *Porphyromonas gingivalis*, and the decay of cognitive tests in a patient >60 years of age in the Third National Health and Nutrition Examination Survey (NHANES-III). In addition, it was observed that the level of TNF-α (Tumor Necrosis Factor Alpha) combined with periodontal IgG titers are different between AD patients and patients with normal cognitive functions.

However, the understanding of the bidirectional relationship between AD and PD is problematized based on the principle that patients with Alzheimer's disease have a higher incidence of periodontal disease with longitudinal manifestations than patients who do not have it (Harding; Singhrao, 2021).

The relationship between the two comorbidities can be explained by changes in the behavior of people affected by AD, such as frequent memory lapses (Harding; Singhrao, 2021). In this context, periodontitis becomes even more common, since the advancement of AD reduces the ability to care for oral hygiene, facilitating the accumulation of plaque and the onset of periodontal disease (Ide *et al*., 2016).

RESULTS AND DISCUSSION

In the search, 21 articles were obtained, using the keywords described in the present study. According to the inclusion and exclusion criteria, 27 publications were included in the final for careful reading and categorization.

Chart 1 shows a summary of the articles selected to be used in the discussion, respectively in terms of authors/year, article title, and conclusion.

Chart 1 – Categorization of articles selected for discussion.

AUTHOR/YEAR	TITLE	CONCLUSION
Abbayya *et al.,* 2015	Association between Periodontitis and Alzheimer's Disease	Abbayya *et al.,* 2015, presented inflammation as a link in the relationship between PD and AD, caused by the infiltration of inflammatory mediators into the systemic circulation, which leads to the worsening of systemic disease.
Borsa *et al.,* 2021	Analysis of the link between periodontal diseases and Alzheimer's disease: a systematic review	The study by Brosa *et al.,* 2021, presents the link between Alzheimer's and periodontal diseases. It establishes that patients with AD have a lack of oral hygiene and a greater predisposition to periodontitis, as well as periodontal bacteria have been found in AD patients, contributing to higher risks of incidence/mortality.
Bui *et al.,* 2019	Association between periodontal pathogens and systemic disease.	In the study, it was observed that individuals with poor oral health and chronic periodontitis (CP) had a higher prevalence of brain injury than those who had periodontal health.
Domyni *et al.,* 2019	*Porphyromas gingivalis* in brains with Alzheimer's disease: evidence for the cause of the disease and treatment with small molecule inhibitors	The analysis carried out by Domyni *et al.,* 2019, determines the relationship between periodontitis and Alzheimer's disease, in addition to pointing to the use of the potent Kgp inhibitor to reduce P. gingivalis infection in the brain, in order to prevent and delay neurodegeneration in AD patients.
Hajichengallis A. Savakis (2021)	Local and Systemic Mechanisms Linking Periodontal Disease and Inflammatory Comorbidities	In the investigation carried out by Hajishenfallis and Chavakis, microbial clinical markers of periodontitis associated with Alzheimer's mortality were presented. An increase in endothelial permeability was suggested, which would allow hematocephalic installation and, as a consequence, an increase in β-amyloid (Aβ) plaques.
Jiang *et al.,* 2021	Association Between Chronic Periodontitis and Alzheimer's Disease Risk: Combination of Text Mining and GEO Dataset	In their analysis, Jiang *et al* established the core function of the research candidates' enriched genes and signaling cascade. They concluded that there is a strong probability of a correlation between CP and AD, which favors the establishment of the diagnosis and treatment of Alzheimer's in patients with chronic periodontitis.

Licardo *et al.,* 2020	Potential bidirectional relationship between periodontitis and Alzheimer's disease	In their research, Licardo *et al.,* concluded the coexistence of periodontitis and AD. However, it draws attention to the need to know which of the pathologies is the predecessor, since people with periodontitis have a high risk of developing AD and patients with Alzheimer's have poor oral health, making them more prone to the development of periodontitis. At the same time, it emphasizes the need for oral hygiene care to avoid an extra-neural source of inflammation and to prevent the onset of neurodegeneration.
Noble *et al*., 2014	Serum levels of IgG antibodies to the periodontal microbiota are associated with incident Alzheimer's disease	In the study, Noble *et al.,* 2014, affirm the association of serum IgG levels of the periodontal microbiota with the risk of developing AD.

Source: Authors

The bidirectional relationship between PD and AD is a topic that, although relatively recent, has attracted the attention of many researchers. Due to its importance, increasingly controlled research is being carried out in order to reach a consensus on the supposed relationship between the two pathologies.

Bui *et al.* (2019) in their study, observed that individuals with poor oral health and chronic periodontitis (CP) had a higher prevalence of brain injury than those who had periodontal health.

Licardo *et al*. (2020) argue that periodontal pathogens are not restricted only to the periodontium, being able to reach the brain through the bloodstream. Domyni *et al* (2019) reinforce this claim when they say that a toxic byproduct of the bacterium *Gingipains* has been found in the brains of AD patients. Noble *et al.* (2014) contribute by stating that periodontitis and Alzheimer's have a similar systemic inflammatory profile. This information leads the scientific community to believe in evidence that points to a consistent relationship between CP and AD.

It is also worth remembering that AD can be considered a predisposing factor for PD for another reason besides the inflammatory mechanism: senile individuals affected by Alzheimer's have greater difficulty in oral hygiene. Which, in turn, through the mechanisms that have already been discussed, can lead to Periodontal Disease. Therefore, oral hygiene strategies should be discussed with the responsible medical team, in addition to family caregivers. All this while avoiding any extra-neuronal source of inflammation, which could aggravate the patient's systemic condition (Liccardo *et. al.,* 2020).

Also according to Liccardo *et al.,* 2020, oral treatment in general greatly helps the levels of inflammatory mediators in the body, which consequently helps to combat or at least relieve the symptoms arising from other systemic diseases that are also mediated by inflammatory mechanisms.

Jiang *et al.,* 2021 report that in addition to the involvement of inflammatory mediators in periodontitis in their study, CP may be a product of gradual neural degeneration in the aging process. Suggesting as a method of AD progression, to prevent or delay chronic inflammatory diseases.

According to the research of Hajishengallis and Chavakis (2021), *P. gingivalis* (one of the main ones involved in Periodontitis) was found in significant quantities in the brains of cadavers diagnosed with Alzheimer's. This pathogen is believed to have the ability to increase vascular endothelial permeability, which may grant it passage through the blood-brain barrier.

Abbayya *et al.*, 2015, point to the involvement of the bacteria *Chamydia pneumoniae* and *Treponema* and the spirochete *Borrelia burgdorferi*, which were found in the blood and cerebrospinal fluid of Alzheimer's patients, in addition to the presence of *Treponema* in the trigeminal glands, supporting the invasion of microorganisms by neural pathways. It was also found that glial and neural cells in contact with *Borrelia burgdorferi* synthesized βAPP and P-Taus. Therefore, the involvement of periodontal bacteria in the development of neuroinflammation, caused by the invasion of these bacteria in the brain both by the systemic circulation and by the peripheral nerve pathways, is suggested.

In addition, there is evidence that presents the association of patients with AD and PD with exacerbated cognitive decline, in addition to presenting an increase in the pro-inflammatory state and a reduction in the anti-inflammatory state. It was found that the load of the bacterium *Fusobacterium nucleatum* (Fn) is substantially higher in patients with AD, in addition to the fact that AD is higher in people with high levels of IgG antibody to *Actinomyces neasludii* (An), which is even more evident when there are high levels of *Eubacterium nodatum* (En) (Bossa *et al.*, 2021).

So far, evidence indicates that there is indeed a bidirectional relationship between the two diseases, with periodontitis bacteria being responsible for triggering/aggravating the dementia process and, therefore, the dementia process interfering with oral hygiene habits, aggravating periodontitis. However, it is necessary to carry out more studies on the subject, with long-term follow-up of clinical cases, so that this relationship can be better established.

CONCLUSION

The literature currently seems to converge on the affirmation of the link between periodontal diseases and Alzheimer's disease, through the sharing of a similar inflammatory mechanism. However, new clinical trial studies, better constructed and more rigorous in the diagnostic criteria of the pathologies studied, are essential to try to better understand the association between AD and PD.

A better understanding of it will allow the implementation of effective prevention and even treatment measures. Thus, PD therapy may represent a lever in a global strategy for the management of the prevalent and disabling disease that is AD.

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