Review Article

Periodontitis and Neuropathic Diseases: A Literature Review

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ABSTRACT

Aim: This narrative review aimed at identifying the existing scientific literature investigating periodontitis and neuropathic diseases. **Materials and Methods:** A search of the literature published between 2000 and 2022 was carried out in the electronic databases of Scopus and PubMed. Studies in which the eligible articles were mainly published in English were included. Descriptive correlational studies, case–control studies, comparative studies, and cohort studies were also included. The following main keywords were used: "Neuropathic diseases," "Periodontitis," "Alzheimer's disease," and "Porphyromonas gingivalis." **Results:** This narrative review found that cognitively impaired persons with severe periodontitis had a higher prevalence and incidence of periodontal diseases than the rest of the population. A significant positive correlation of salivary interleukin (IL)-1beta and immediate recall scores involved in cognition was also evident. It indicates that the most investigated parameter was whether there is any common link between periodontal disease and neurodegeneration. No randomized controlled clinical studies were found in the current literature review. **Conclusions:** Based on the literature reviewed, there is currently no strong scientific evidence to support or discourage the cause–effect relationship of periodontal diseases and neurodegenerative diseases.

Keywords: *Neuropathic diseases, periodontitis, review*

Introduction

Periodontal disease affects about 50% of the world's population, which is why it is considered one of the most prevalent diseases in adults. It is classified as gingivitis and periodontitis, which can affect the alveolar bone causing its destruction and resulting in the loss of the affected teeth.[1] Periodontitis, being an inflammation, causes the release of proinflammatory cytokines at the systemic level, which leads to the acceleration of various chronic systemic inflammatory diseases such as vascular diseases. There is information linking chronic inflammation to brain immune cells activation, leading to neuroinflammation.[2]

Neurodegenerative disorders are neuropathic diseases that affect millions of people due to aging, and this is increasing due to advancing life expectancy.[3] In the 1980s, the term neuroinflammation was discussed in Alzheimer's disease through a consortium of immunohistochemistry of activated microglia, which was found in later years in another neurodegenerative disease such as Parkinson's disease, which leads us to believe that this is related to different diseases classified as neuropathic.[4]

Inflammation plays an essential role in the degenerative disease process.[5] The immune response against periodontal pathogens increases proinflammatory cytokines levels, which are released into the systemic circulation. These anti-inflammatory molecules could destroy brain microvascular endothelial cells. This can cause microcell activation and

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Table 1: Study characteristics

Author	Study design	Sample	Conclusions
Hategan *et al*.[32]	Cross-sectional study	Forty people: 10 with aggressive periodontitis, 20 with mild periodontitis, and 10 with no signs of periodontitis	People with chronic periodontitis had an impaired episodic delayed memory compared with people with mild periodontitis or no periodontitis. Significant positive correlation between salivary interleukin-1 beta and immediate recall scores related to cognition.
Franciotti *et al*.[33]	Pilot comparative study	Seventy-eight persons: 21 with neurodegenerative diseases, 28 with non-neurodegenerative diseases, and 29 healthy persons	People with neurodegenerative disease had higher levels of *P. gingivalis*. Oral pathogens induced a response of the brain-oral system.
Malone *et al*.[34]	Analytical, correlational study	Hepatitis C virus patients with Medicare claims 2014–2017	Periodontal patients with hepatitis C virus had an almost 1.35-fold increased risk of Alzheimer's disease and related dementias.
Tran *et al*.[35]	Descriptive study	Clinical isolate of *P. gingivalis*, microglia cells, and human neural progenitor cells	Evidence of *P. gingivalis*-induced neurodegeneration and a critical role of microglia in response to bacterial infection. Three factors were found in Alzheimer's disease, including bacterial infection, neuroinflammation, and neurodegeneration.
Leblhuber *et al*.[36]	Descriptive study	Twenty patients with primary degenerative dementia	Periodontal patients with *P. gingivalis* presented a lower Mini-Mental State Examination and a clock drawing test with poor results.
John *et al*.[37]	Cross-sectional descriptive study	Thirty-two patients with Parkinson's disease	Parkinson's disease affected the ability to manage oral hygiene. However, no significant relationship between periodontal health duration and the Parkinson's disease severity.
Rozas *et al*.[38]	Case–control study	Oral microbiota, hard and soft tissues of patients with Parkinson's disease	The mouth in Parkinson's disease maintains a microbial community that is common in general diversity. Parkinson's disease symptoms linked to the mouth would contribute to the oral microbiota.
Ide *et al*.[10]	Observational cohort study	Fifty-two people with mild dementia	The presence of periodontitis was associated with the upregulation of systemic proinflammatory state identified by increased serum CRP, tumor necrosis factor alpha, and TNFα/IL-10 ratios in participants with Alzheimer's disease.

adverse effects, leading to neuronal damage.[6] Elevated cytokine concentration occurs in Alzheimer's patients which is due to acute and chronic inflammatory responses in the body.[7] Besides, periodontal infection leads to the survival of harmful microbes.[8] In fact, inflammation is believed to play an important role, and etiology and pathogenesis of neurodegenerative diseases are not well characterized.[9] Therefore, periodontal diseases may contribute with the appearance and development of neurodegenerative diseases.[10]

The objective of this literature review was to describe the relationship between neuropathic degenerative diseases and periodontal disease.

Materials and Methods

Data extraction and search strategy

An unrestricted electronic search was performed in the PubMed and Scopus databases. The principal keywords used were: Neuropathic diseases, Periodontitis, Alzheimer's disease, Porphyromonas gingivalis. The following search strategy was established and adapted to each database evaluated:

Periodontitis: "periodontal"[All Fields] OR "periodontally" [All Fields] OR "periodontically"[All Fields] OR "periodontics" [MeSH Terms] OR "periodontics" [All Fields] OR "periodontic" [All Fields] OR "periodontitis" [MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides" [All Fields]

Neuropathic: "neuropathic"[All Fields] OR "neuropathics"[All Fields]

diseases: "disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease's"[All Fields] OR "diseased"[All Fields]

Inclusion criteria

Eligible articles included those published in English. Descriptive correlational studies, case–control studies,

comparative studies, and cohort studies were also included.

Exclusion criteria

Conference abstracts and editorials, book reviews, empirical reports, and letters from the editor were excluded.

Results

This narrative review found that cognitive impairment people with severe periodontitis had a greater prevalence and incidence of periodontal diseases than the rest of the population. There was also evidence of a significant positive correlation of salivary IL-1beta and immediate recall scores that were involved in cognition.[11-16] Increasing evidence supports the bidirectional brain-oral axis between periodontal diseases and the risk of neurodegenerative diseases [Table 1]. Also, oral bacteria diminish the elaboration of bacteria antibodies causing an adverse result on disease progression.[11-13]

One epidemiological study reported by Noble *et al.*[14] had investigated periodontal disease relative to poor cognition. They found a serological marker of periodontitis associated with cognitive impairment. In addition, the data collected in this review demonstrated the causal associations between the sub-gingival pathobiome under the influence of *Porphyromonas gingivalis* and Alzheimer's disease development.[15]

Periodontitis and alzheimer's disease

Periodontitis is a chronic multifactorial inflammatory disease owing to oral pathogens and is evidenced by serum antibodies to common periodontal microorganisms, such as *P. gingivalis*, and elevations of serum inflammatory markers of IL-6 and C-reactive protein.[11]

Alzheimer's disease is considered a neurodegenerative disease and is defined by a slow and gradual loss of the nervous system function. Furthermore, a serious condition affecting the brain is encephalitis, which is believed to be involved in the origin of Alzheimer's disease. In the brains of autopsied Alzheimer's patients, there was an accumulation of activated microglia around senescent plaques. In other research, there were indications that *P. gingivalis* was associated with alterations in episodic and spatial memory in Alzheimer's disease patients. In contrast, microorganisms containing Aβ are believed to deposit in brain tissue, leading to the formation of neural plaques that damage cranial nerves and exacerbate Alzheimer's disease.[12] Periodontal diseases can directly and indirectly exacerbate dementia, which is defined as a significant or complete loss of intellectual abilities in a gradual process.[13]

P. gingivalis in neuropathies

Several periodontal pathogens such as *P. gingivalis, Prevotella intermedia, Actinomycetes, mycobacteria, Tannerella forsythiensis, and Echinella currue* are involved in the development of various inflammatory diseases in distant organs, such as Alzheimer's disease. In particular, the association between *P. gingivalis* and Alzheimer's disease has attracted the attention of several researchers.[1] Alzheimer's disease followed by Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's chorea are the main known neurological diseases.[14]

P. gingivalis can modify the activity of ATP/P2 × 7 signaling molecules. Lipopolysaccharides are the building blocks for the surface membrane of Gram-negative microorganisms. Lipopolysaccharide from *P. gingivalis* is a crucial contributor to Alzheimer's disease neurodegeneration. This is due to pattern recognition receptors such as Toll-like radioreceptors, which can distinguish bacteria pathogen molecular patterns to promote antibacterial activity.[15] It can also stimulate CD14, which begins the augmentation of proinflammatory cytokines expression.[16]

Other studies focussed on the inflammatory mediator's detection in plasma from confirmed cases of periodontal bacteria associated with Alzheimer's disease and confirmed the contribution of systemic inflammatory markers from oral bacteria.[10]

Inflammatory pathways in periodontitis

Inflammation is part of the complex biological response of body tissues that helps the organism to fight against things that harm it. Ferrari and Tarelli[17] reported the effect of peripheral infections in Parkinson's disease progression. They concluded that these peripheral immune challenges increased the disease symptoms. In this regard, brain inflammation of animal models was regulated by chronic microglial activation. Nevertheless, inflammatory cells were released and contributed to the activation of microglia, initiating neurodegeneration.[18] It has been suggested that periodontitis may lead to the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease through two vehicles: inflammatory periodontitis and systemic and bacterial/viral effects.[1]

Both mechanisms follow these three pathways: Bacteria incursion and discharge of inflammatory mediators starting from the mouth into the general circulation.[19] Systemic periodontal inflammation can influence the central nervous system (CNS) such as declining dopaminergic neurons and activating microglia in the substantia nigra.[20]

The CNS can be penetrated by proinflammatory molecules through multiple pathways. Areas of the brain that do not have a blood–brain barrier are prone to be trespassed. Likewise, they sometimes pass-through blood–brain barrier-fenestrated capillaries, through transporters that are specific for cytokines.[19] In contrast, endothelial cells located in the brain activate and generate signaling molecules that are associated with cytokines and nitric oxide or prostanoids.[20] In the humoral pathway, the blood–brain barrier allowed any element that passes from the blood to the brain. When an infection occurs, there is a high probability that the blood–brain barrier is damaged, which can lead to the discharge of inflammatory cytokines.[21]

Pathophysiological role between Alzheimer's disease and periodontal disease

The transit of infectious agents and inflammatory mediators into the general circulation are mechanisms to explain this association. Bacteremia is developed when the immunological, physical, and chemical barriers of the oral cavity are impaired. There is evidence that this happens when performing certain daily activities such as oral hygiene or during mastication.[22]

Periodontal bacteria and their products can cause inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF). The receptors of these cytokines can emerge as saturated when there is constant bacterial exposure, with cytokines flowing into the systemic circulation.[23] Systemic inflammation in periodontal disease advanced stages is caused when periodontal patients have higher levels of C-reactive protein compared with healthy controls.[24]

Discussion

Periodontal disease is an influential factor in neurodegenerative diseases as it contributes to their onset through peripheral inflammation caused by periodontal bacteria. This literature review discussed different ways in which periodontal disease directly and indirectly exacerbates the condition of a neurodegenerative disease such as dementia. Three possibilities may explain the biological vehicles by which periodontitis originates neuroinflammation.[4]

Peripheral proinflammatory cytokines generated by the systemic inflammation of periodontitis go to the brain tissue via neural, humoral, and cellular pathways. Systemic cytokines mobilize primary afferent nerves through the neural pathway reaching various hypothalamic nuclei in the brain. The stimulation of endothelial cells and an increment in monocytes activate microglia, producing proinflammatory cytokines, proteases, and chemokines.[4,22-24]

Periodontal bacteria can occupy the brain throughout the bloodstream as circulating bacterial molecules can penetrate the brain. Ilievski *et al.*[25] demonstrated that *P. gingivalis* DNA was detected by quantitative polymerase chain reaction in the brains of orally infected *P. gingivalis* mice. Furthermore, leptomeninges could be a communication link between periodontal pathogens and microglia. The brain parenchyma surface is covered by leptomeninges with a physical limit at the blood–cerebrospinal fluid barrier. When leptomeningeal cells were activated by circulating *P. gingivalis*, they subsequently produced proinflammatory cytokines. These cytokines may activate microglia to promote neuroinflammation, so transducing peripheral inflammation into neuroinflammation by leptomeninges could be detrimental.[26] In this regard, Mandrekar-Colucci and Landreth[27] reported that patients with Alzheimer's disease have sustained brain inflammation. This response occurs naturally to infection and injury in the acute phase of inflammation, but an imbalance of anti-inflammatory mediators and pro-inflammatory mediators causes acute inflammation into chronic inflammation. This is called neuroinflammation as it occurs in the brain.

Amyloid beta peptide accumulation activates the residents of the CNS which are phagocytes known as microglia; when this process occurs a change occurs in their morphology and function, releasing inflammatory mediators and initiating the phagocytosis of plaques. This explains that there is a protective phase and a neurodegenerative phase, i.e., an acute phase and a chronic phase, respectively.[28] The inflammatory process in Alzheimer's disease is attributed to large numbers of microglia. Zhan *et al.*[29] demonstrated that pathogens such as *P. gingivalis*, *Actinobacillus actinomycetemcomitans*, and *T. forsythia* can promote local inflammatory damage which under chronic conditions is considered a trigger of neuroinflammation. This is explained by the presence of lipopolysaccharides which are considered the fundamental lipid building blocks of the bacterial cell wall. They can activate microglia which would cause proinflammatory cytokines to be released, as well as interleukins and TNF-alpha, components associated with increased neuroinflammation.

Periodontitis can be found in patients with neurodegenerative diseases, as these patients may be less skilled to brush their teeth, floss, and visit a dentist. Tzeng *et al.*[30] reported that periodontal patients had increased risk of developing dementia. Periodontitis was related to an incremented risk of developing dementia and revealed that patients with at least 8 years of periodontal problems had a significantly higher risk of developing dementia and neurodegenerative

diseases. However, Uppoor *et al.*[31] concluded that due to the lack of longitudinal studies measuring inflammatory mediators and cognitive status, there was no direct evidence suggesting periodontal disease in the pathogenesis of Alzheimer's disease. Thus, to sum up, periodontal systemic inflammation and the passage of bacteria products into the brain may promote Alzheimer's disease development.[10,30-38] It is also important to identify the role of biomarkers in the process and development of oral diseases.[39-41]

The main limitation of this study was the scarcity of updated evidence on the relationship between periodontal disease and certain degenerative diseases of neurological origin. Another limitation was that this study only approached the subject from a narrative approach, so it is suggested that a more robust methodological design such as a systematic review and/or meta-analysis be carried out when there are more quality clinical studies published.

Conclusion

Within the limitations of this literature review, it can be concluded that there is currently little evidence linking periodontitis and neuropathic diseases.

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Conflicts of interest

Nil.

Authors' contribution

JC, RR, FM-T: conception. AM-D, MEG, FM, FM-T: design of the manuscript, review for relevant intellectual content, writing-review and editing, and final approval of the version to be published. JC, RR, FM-T, AM-D, FM, MEG: writing original draft.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

Data of literature search are available on appropriate request to the corresponding author.

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