REVIEW ARTICLE

CONTENTS

Periodontitis as a systemic inflammatory disorder – implications for cardiovascular and neurodegenerative diseases

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ABSTRACT

Aim: Periodontitis is a chronic inflammatory condition associated with oral microbiome dysbiosis and the dominance of Gram-negative bacteria such as Porphyromonas gingivalis. It is characterized by progressive destruction of the supporting tissues of the tooth, leading to loss of connective tissue attachment, resorption of the alveolar bone, and, consequently to tooth loosening and loss. If left untreated, it leads to recurrent bacteremia and persistent systemic inflammation. The aim of this study is to discuss the mechanisms linking periodontitis to cardiovascular and neurodegenerative diseases.

Materials and Methods: A comprehensive literature review was conducted examining clinical studies, systematic reviews, and meta-analyses assessing the impact of periodontal disease on the development of cardiovascular and neurodegenerative diseases.

Conclusions: Chronic activation of the immune response, oxidative stress, and lipid metabolism disorders promote endothelial dysfunction and the progression of atherosclerosis, increasing the risk of cardiovascular events. At the same time, systemic inflammation can affect the permeability of the blood-brain barrier and exacerbate neuroinflammatory processes, promoting β-amyloid accumulation and the progression of Alzheimer's disease. Analysis of the literature indicates the significant, albeit complex, nature of these relationships, emphasizing the importance of prevention and treatment of periodontal disease as part of comprehensive patient care. The key in the approach to periodontal patients is an interdisciplinary perspective, integrating dentistry, cardiology, neurology, and geriatrics.

KEY WORDS: prophyromonas gingivalis, cardiovascular disease, Alzheimer's disease

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INTRODUCTION

The human oral microbiome consists of hundreds of microorganisms, the composition of which changes dynamically depending on the host environment. When healthy, it remains in balance, and Gram-positive bacteria dominate the composition of dental plaque. However, certain factors such as the presence of carbohydrates, a decrease in pH, or poor oral hygiene can disrupt homeostasis and increase the proportion of Gram-negative anaerobic bacteria. This leads to oral dysbiosis, which in turn leads to pathologies such as periodontitis [1]. This is a progressive disease in which bacteria trigger a cascade of inflammatory reactions, leading to the destruction of the tissues supporting the teeth, i.e., the periodontium. Periodontitis is the sixth most common disease in the world, with an overall prevalence of 45-50% [2, 3].

Periodontal disease is mainly associated with infection with *Porphyromonas gingivalis* as well as *Prevotella intermedia*, *Treponema denticola, Tannerella forsythia, Campylobacter rectus, Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum*. These microorganisms penetrate the subgingival tissues, cause bacteremia, and release inflammatory mediators and toxins which, once in the bloodstream, disrupt the body's homeostasis and contribute to the development of systemic inflammation [1, 4]. Chronic, persistent inflammation predisposes the body to many systemic diseases, including cardiovascular and neurodegenerative diseases.

Cardiovascular diseases are one of the leading causes of death worldwide [5, 6]. In Europe, they account for 3.9 million deaths, which is about 45% of all deaths. More specifically, the main causes of death are ischemic heart disease, stroke, and heart failure caused by hyper-

tension [2]. At the core of most cardiovascular diseases lies atherosclerotic disease. It is characterized by progressive narrowing of the vascular lumen caused by the accumulation of atherosclerotic plaques, accompanied by endothelial dysfunction and a persistent low-grade chronic inflammatory state [6, 7].

Despite the multifactorial pathogenesis of periodontitis and cardiovascular diseases, current scientific reports indicate a significant relationship between these conditions [8]. One of the proposed mechanisms linking these diseases is the systemic inflammatory response of the body to periodontopathogenic bacteria and their products, which, once they enter the bloodstream, may promote the formation, maturation, and destabilization of atherosclerotic plaques [7].

Alzheimer's disease (AD) is the most common neurodegenerative disease, accounting for approximately 50–60% of all cases of dementia. It is characterized by memory loss, impaired language function, impaired visual-spatial abilities, impaired judgment, and personality changes. A growing number of studies indicate that periodontal pathogens are associated with this form of dementia. Many publications have shown that periodontal disease, led by the pathogenic bacterium - Porphyromonas gingivalis, may indirectly contribute to the development of Alzheimer's disease [4, 9]. Chronic inflammation and recurrent bacteremia associated with periodontal disease can induce neuroinflammatory and neurodegenerative processes, promoting the deposition of β-amyloid plaques, the formation of neurofibrillary tangles, and neuronal damage characteristic of Alzheimer's disease [10].

AIM

The aim of this study is to understand the potential mechanisms linking periodontal inflammation to the development of cardiovascular disease and Alzheimer's disease.

MATERIALS AND METHODS

A comprehensive literature search was conducted across PubMed from 2020 to 2025 to identify studies investigating the association between periodontitis and systemic diseases, specifically cardiovascular disease and Alzheimer's disease. Search terms included "periodontitis", "cardiovascular disease", "Alzheimer's disease", "inflammation", "Porphyromonas gingivalis", and "neurodegenerative disorders" as well as related variations. We included systematic reviews and meta-analyses, randomized controlled trials, prospective and retrospective original research, narrative reviews, protocol papers, and case series.

REVIEW AND DISCUSSION

PATHOGENESIS OF PERIODONTAL DISEASE

Periodontal disease is the result of chronic dysbiosis of the oral microbiome, characterized by an increased presence of pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum,* and *Treponema denticola* [11,12]. Disruption of the microbiological homeostasis of the oral cavity promotes the formation of dental plaque, deepening of periodontal pockets, and the development of chronic inflammation. Inflamed periodontal tissues are more susceptible to mechanical microtrauma caused by daily hygiene activities such as brushing and flossing. The accompanying bleeding allows periodontopathogenic bacteria and their products to enter the bloodstream, leading to transient bacteremia [11]. Gram-negative bacteria associated with dysbiotic biofilm, such as

P. gingivalis and *Tannerella forsythia*, initiate the influx of neutrophils and the production of lipid mediators (including prostaglandin E2), which promotes local inflammation and bone resorption [3]. These pathogens further disrupt the host's immune and lipid homeostasis [12]. Microorganisms use specialized mechanisms to deliver virulence factors, including outer membrane vesicles (OMVs), which enable interaction with pattern recognition receptors (PRRs) in distant tissues, initiating a systemic inflammatory response [12]. Periodontal disease generates chronic inflammation that can affect distant organs. Patients with periodontitis show elevated levels of inflammatory markers such as CRP (C-reactive protein), proinflammatory cytokines (IL-1, IL-6, IL-8, TNF), and leptin, while simultaneously showing decreased concentrations of anti-inflammatory markers such as interleukin 10 (IL-10) and adiponectin [11, 13].

PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

Chronic periodontal dysbiosis leads to persistent systemic inflammation, which disrupts endothelial function and promotes the development of cardiovascular disease. Gram-negative pathogens, such as *Porphyromonas gingivalis*, activate molecular pattern recognition receptors (TLR2/MyD88), increasing the expression of NADPH oxidase (NOX4) and the production of superoxide anion ($O_2^{\bullet-}$). As a result, oxidative stress increases, limiting the availability of nitric oxide (NO), intensifying lipid peroxidation, and causing endothelial dysfunction - a key stage in the development of atherosclerosis. In addition, P. gingivalis lipopolysaccharide causes post-translational modifications of LDL

molecules, increasing their atherogenic properties and facilitating their uptake by macrophages, which promotes the formation of foam cells and the progression of atherosclerotic changes. At the same time, HDL dysfunction is observed, manifested by a reduction in their anti-inflammatory properties and a limitation of their ability to remove cholesterol from macrophages, which further enhances the process of atherogenesis [12]. Chronic inflammation caused by periodontal dysbiosis, oxidative stress, endothelial dysfunction, and lipid metabolism disorders constitute the molecular basis for the observed links between periodontal disease and cardiovascular pathologies [14]. These mechanisms translate into real changes in vascular function: patients with periodontitis show increased carotid intima-media thickness (CIMT), reduced flow-mediated dilation (FMD) and greater arterial stiffness measured by pulse wave velocity (PWV) [11].

At the same time, periodontal disease is associated with an increased risk of coronary artery disease, heart attack, stroke, and peripheral artery disease (PAD) [11]. In addition, a higher risk of heart failure and atrial fibrillation in people with periodontitis [11].

Chronic inflammation, activation of pattern recognition receptors (TLR2/MyD88), increased oxidative stress via NOX4, LDL modifications, and HDL dysfunction observed in people with periodontal disease are clinical parameters that directly affect vascular function and the development of cardiovascular diseases [14].

PERIODONTAL DISEASE AND NEURODEGENERATION

Inflammation is a common risk factor for both periodontal disease and the most common neurodegenerative disease, Alzheimer's disease (AD), affecting the development and progression of both conditions. Periodontal disease leads to local degradation of tooth supporting tissues, neutrophil and macrophage infiltration, and increased activity of metalloproteinases and serine proteases. Chronic periodontitis causes systemic inflammation, manifested by elevated concentrations of IL-1β, IL-6, IL-8, TNF-α, and CRP, which may modulate the course of neurodegenerative diseases [15]. Preclinical studies have shown that periodontal pathogens can increase the permeability of the blood-brain barrier, including by reducing claudin-5 expression and degrading collagen and fibronectin in the brain endothelium, which facilitates the penetration of inflammatory mediators and bacteria into the brain [15].

In AD, the accumulation of β-amyloid peptide activates microglia and astrocytes via Toll-like receptors (TLR2/TLR4) and the NF-κB pathway, enhancing the secretion of proinflammatory cytokines, reactive oxygen species, and other neuroinflammatory mediators, which promotes amyloidogenesis, hyperphosphorylation of tau protein, Aβ accumulation, and the formation of neurofibrillary tangles, ultimately leading to neuronal degeneration [15]. Recent clinical studies conducted by Gil-Montoya et al. indicate that severe or moderate periodontitis in older adults with mild cognitive impairment (MCI) is associated with a higher risk of abnormal β-amyloid accumulation in the brain, as demonstrated in amyloid-PET studies, while individuals with mild periodontitis or healthy periodontium did not show such an association.

These findings support the hypothesis that chronic inflammation associated with periodontal disease may contribute to the initiation or acceleration of amyloid protein accumulation in the brain, regardless of the patient's cognitive status [16]. A study by Ide et al. showed that active periodontitis in patients with AD is associated with faster cognitive decline, regardless of the number of teeth lost. An increase in pro-inflammatory status and a decrease in anti-inflammatory status were observed, supporting the hypothesis that systemic inflammation links periodontal disease to neurodegeneration. These data suggest that the treatment and prevention of periodontal disease may help preserve cognitive function in patients with AD [13].

THE ROLE OF THE DENTIST

The dentist is responsible for the prevention and treatment of periodontal disease. Prevention includes patient education, daily oral hygiene, and regular checkups, which slow the progression of periodontal disease and thus reduce the risk of cardiovascular complications. The treatment of periodontal disease includes standard non-surgical methods such as scaling and root planing, often supplemented with antibiotic therapy, and in more severe cases, surgical procedures aimed at reducing inflammation and regenerate periodontal tissues [11, 14].

In patients with Alzheimer's disease, the presence of active periodontitis is associated with a faster decline in cognitive function, regardless of the initial condition, which emphasizes the importance of periodontal prevention and treatment in potentially slowing down the progression of the disease [13].

INTERDISCIPLINARY PATIENT CARE – DENTISTRY AND GENERAL MEDICINE:

Considering the latest research, periodontal disease is not only a local condition, but a chronic inflammatory

disease that is a risk factor for the development of systemic diseases, including cardiovascular and neurodegenerative diseases such as Alzheimer's disease [11, 15]. Numerous studies have shown that patients with AD have poorer oral health than older people without dementia and increasing difficulties in daily hygiene with more severe dementia can exacerbate this problem [13]. Chronic inflammation in periodontal disease can lead to neuroinflammatory processes and blood-brain barrier dysfunction, potentially accelerating neuronal degeneration [16]. In addition, chronic periodontitis, associated bacteremia, and increased concentrations of circulating inflammatory factors may contribute to the progression of atherosclerosis and coronary artery disease [11].

Effective care for patients with periodontal disease, therefore requires an interdisciplinary approach, integrating dentistry, cardiology, neurology, and geriatrics. A joint diagnostic and therapeutic strategy enables early detection of risk factors, treatment of periodontitis, and monitoring of cardiovascular health and cognitive function, which can greatly contribute to slowing the progression of both systemic and neurodegenerative diseases.

CONCLUSIONS

A review of the literature on the links between periodontal disease and cardiovascular and neurodegenerative diseases points to a complex but significant relationship. Periodontal disease is not only a local oral health problem but also a potential factor influencing the development of systemic diseases. Complex mechanisms involving chronic inflammation, bacteremia, and systemic immune response indicate the multidirectional nature of this relationship. However, it should be emphasized that periodontal disease, cardiovascular disease, and Alzheimer's disease all have multifactorial etiologies, and the observed associations require further clinical research to clearly define cause-and-effect relationships. Taking into account current data, the role of the dentist goes beyond the treatment of local lesions - effective care of periodontal patients requires an interdisciplinary approach.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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