REVIEW ARTICLE

CONTENTS

Actual scientific data in comorbid periodontal diseases and heart-vessel pathology

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ABSTRACT

Aim: The aim of this study is to review and analyze contemporary scientific and professional literature to investigate the role of periodontal diseases in the development and progression of cardiovascular diseases. Specifically, this study aims to deepen our understanding of the pathogenetic mechanisms underlying periodontitis in this category of patients and the reciprocal aggravating influence of these pathologies on each other

Materials and Methods: bibliometric and analytical methods applied to data from international scientific sources investigating the role of periodontal diseases in the pathogenesis of cardiovascular diseases.

Conclusions: The growing body of evidence indicates a significant comorbidity between periodontal diseases and cardiovascular diseases. Given the systemic impact of periodontitis on cardiovascular health, there is a pressing need for enhanced periodontal care and further research to better understand this complex relationship

KEY WORDS: periodontitis, cardiovascular diseases, atherosclerosis, microorganisms, risk factors

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INTRODUCTION

The close relationship between oral health and overall health is supported by current epidemiological studies and is increasingly substantiated by modern scientific advancements.

In the context of the global COVID-19 pandemic, the study of the impact of periodontal infection on the development and progression of cardiovascular diseases has become particularly relevant. The pandemic has presented healthcare systems with unprecedented challenges, emphasizing the necessity of comprehensive patient care. Periodontitis, as a chronic inflammatory disease, can significantly impact overall health, particularly in patients with COVID-19 who already have cardiovascular conditions. Such patients require more vigilant monitoring and a comprehensive treatment plan.

Epidemiological studies have demonstrated a strong association between periodontal disease and an increased risk of cardiovascular events, including atherosclerosis, coronary heart disease, and myocardial infarction. Systemic inflammation, endothelial dysfunction, and the translocation of oral pathogens into the circulation are believed to be the primary mechanisms linking periodontal disease to cardiovascular disease. The situation is exacerbated by the frequent underdiagnosis and undertreatment of periodontal infections, which elevates the risk of cardiovascular complications. Considering periodontal health in cardiology patients can significantly improve prognosis and reduce the likelihood of complications.

The urgency of this issue lies in the need to develop effective preventive and therapeutic strategies aimed at improving periodontal health and reducing the risk of cardiovascular disease. This involves integrating dental and medical approaches in patient care and raising awareness among both healthcare providers and patients about the crucial connection between oral health and coronary heart disease.

AIM

The aim of this study is to review and analyze current scientific literature to examine the role of periodontal diseases in the development and progression of cardiovascular pathology. Specifically, this study aims to deepen our understanding of the pathogenetic mechanisms underlying periodontitis and the mutual influence of these pathologies on each other.

MATERIALS AND METHODS

This study utilized bibliometric and analytical methods to systematically review global research examining the association between periodontal diseases and coronary heart disease.

REVIEW AND DISCUSSION

Cardiovascular diseases pose a significant global health burden. In Europe alone, nearly 4 million people die from these conditions annually, accounting for 44% of all deaths [1, 2].

Beyond traditional cardiovascular risk factors, the growing burden on global and regional healthcare systems is exacerbated by new challenges such as air pollution and the uncertain long-term consequences of COVID-19 on cardiovascular disease patterns [3].

Consequently, cardiovascular diseases continue to be a major public health concern. The full-scale war in Ukraine, which began in 2022, has led to a further, dramatic increase in the prevalence of cardiovascular diseases, following the initial surge post-COVID-19. In addition to the existing challenges, the population is now facing extremely high levels of psychological stress, while the destruction of parts of the healthcare infrastructure, disruptions in the supply of medications and medical equipment, and a growing unmet need for medical care have exacerbated the situation [5, 6].

Cardiovascular disease (CVD) is a general term for a group of disorders of the heart and blood vessels. Atherosclerosis (AS) is one of the primary causes of cardiovascular diseases. It is a progressive disease characterized by the accumulation of plaques, consisting of lipids, cellular waste products, and fibrous tissue, in the arterial intima. Traditionally, AS was understood as a disease initiated by the accumulation of low-density lipoproteins within the arterial wall, leading to the formation of atherosclerotic plaques [7].

Subendothelial accumulation of modified low-density lipoproteins (LDL) triggers a chronic inflammatory response. The interplay of oxidative stress, growth factors, cytokines, and the recruitment of monocytic macrophages and smooth muscle cells within this microenvironment ultimately contributes to plaque formation.

AS is a chronic disease that progresses asymptomatically for many years. Clinical manifestations typically arise when advanced atherosclerotic lesions cause significant stenosis or thrombosis, leading to ischemia of the heart (coronary heart disease), brain (ischaemic stroke), or lower extremities (peripheral vascular disease) [8].

Multiple studies have consistently demonstrated a correlation between microorganisms and their toxins and the pathogenesis of atherosclerosis [9].

Chronic vascular inflammation, initiated by endothelial injury, is a complex process modulated by a combination of traditional and emerging risk factors. CVD can be prevented by modifying risk factors for atherosclerosis. Including factors that influence systemic inflammatory burden. Oral diseases, particularly periodontitis, are factors that directly or indirectly contribute to systemic inflammation.

Scientific advancements have revealed increasingly strong associations between periodontal diseases and cardiovascular risk factors [10].

Chronic oral infections, including periodontitis, increase the risk of systemic diseases. A growing body of research points to a bidirectional relationship between systemic diseases and periodontal disease, suggesting that systemic diseases can both contribute to the development of periodontal disease and vice versa [11-13].

Recent studies have introduced a paradigm shift, recognizing dental diseases, especially periodontitis, as a new modifiable risk factor for CVD [14, 15].

A potential mechanism underlying this link is that localized periodontal infection induces a chronic inflammatory state. Periodontal infection can exert both direct and indirect effects on systemic health. Direct mechanisms involve the direct migration of pro-inflammatory bacteria from the oral cavity into the cardiovascular system. Indirect mechanisms operate through the activation of systemic immune responses, leading to a sustained chronic inflammatory state [14].

They describe at least four main pathogenetic mechanisms by which oral inflammation, particularly periodontal infection, influences the development and progression of CVD: (1) bacteremia, where oral bacteria enter the bloodstream and penetrate the arterial wall; (2) systemic inflammation induced by pro-inflammatory mediators released from oral inflammatory foci into the bloodstream; (3) autoimmune reactions against host proteins triggered by the host's immune response to specific components of oral pathogens; and (4) proatherogenic effects caused by specific bacterial toxins released by oral pathogens [16].

A normal oral microbiome forms a structured "biofilm" in which bacterial communities are embedded in an extracellular matrix, providing protection and resistance to the penetration of external agents. Nevertheless, alterations in the quantitative and qualitative makeup of the biofilm, disrupting homeostasis, elicit a complex host immune-inflammatory response. An acute inflammatory response, manifesting as gingivitis, is first observed on both supragingival and subgingival dental plaque. This response is perpetuated by a coordinated effort involving innate immune cells such as resident epithelial cells and fibroblasts, phagocytic cells like

macrophages and neutrophils, as well as complement proteins and neuropeptides. During this phase, cytokines like tumor necrosis factor (TNF-α), interleukin (IL)-1β, and interleukin (IL)-6, secreted by resident cells, play a central role in stimulating the migration of cells to the site of infection. They also enhance the expression of adhesion molecules on the vascular endothelium, facilitating neutrophil recruitment, and promote the production of additional pro-inflammatory cytokines. The removal of plaque results in the resolution of inflammation and the restoration of individual homeostasis. Prolonged dental plaque persistence results in the activation of the adaptive immune system. This involves antigen presentation by lymphocytes, macrophages, and dendritic cells, and is regulated by adaptive immune cytokines like interferon (IFN)-γ, interleukin (IL)-2, and interleukin (IL)-4 [17].

Periodontitis, a remitting chronic inflammation associated with microbes, develops due to the proliferation of pathogenic microorganisms, their toxin production, and their ability to penetrate tissues. Key periodontal pathogens, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Treponema denticola, and Prevotella intermedia, are anaerobic Gram-negative bacteria. These organisms, upon reaching a critical mass within subgingival biofilm and in the presence of various local and systemic predisposing factors, initiate inflammatory responses [18, 19].

In a dysbiotic subgingival microbiome, the host immune system is chronically activated, primarily by IL-1, IL-8, TNF-α, prostaglandins, and matrix metalloproteinases (MMPs). These inflammatory mediators influence the functions and activity of leukocytes, osteoblasts, and osteoclasts, leading to characteristic destruction of the periodontal ligament, connective tissue, and alveolar bone [20].

The progressive destruction of periodontal tissues, including bone resorption and extracellular matrix degradation, results from a shift in the balance between osteogenesis and osteoclastogenesis in favor of the latter. This is regulated by a complex inflammatory-induced osteoclastogenesis pathway involving the receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL), as well as IL-1β, IL-6, and TNF-α. Extracellular matrix (ECM) degradation occurs due to increased regulation of the expression of a family of 23 Zn2+ and Ca2+-dependent enzymes known as matrix metalloproteinases (MMPs). These enzymes are involved in the degradation of gingival and periodontal ligament collagen, which occurs in periodontitis during the catabolism of connective tissue [17].

Specific bacteria from the periodontal pocket can penetrate the epithelial barrier and enter the systemic circulation. Thus, inflammatory mediators from the periodontium enter the bloodstream and activate acute-phase proteins in the liver, such as C-reactive protein (CRP), which further exacerbates systemic inflammation.

Patients with periodontal disease have an average of twice the risk of developing coronary heart disease, including myocardial infarction. The increased risk of systemic diseases in patients with periodontitis may be associated with a higher prevalence and severity of bacteremia caused by oral microorganisms. Such bacteremias are often caused by species such as Streptococcus sanguis and Porphyromonas gingivalis, which can contribute to thrombus formation by promoting platelet aggregation and binding to endothelial cells. We suggest that chronic oral infections, particularly periodontitis, may be a contributing factor in the development and progression of atherosclerosis [21, 22].

Increased vascular permeability results in the leakage of periodontopathogens into the bloodstream. These are transported through the blood vessels to other target tissues. The finding of subgingival plaque microorganisms in the blood of individuals with coronary artery disease provides evidence to support the notion that oral pathogens can translocate from the oral cavity to the arterial system, thereby intensifying the inflammatory response and promoting the development or exacerbation of cardiovascular complications [23].

An increasing number of studies have described the detection of periodontopathogens far beyond their primary localization.

Verica Pavlic and colleagues (2021) utilized polymerase chain reaction to detect the presence of five periodontal pathogens (Porphyromonas gingivalis (P.g.), Aggregatibacter actinomycetemcomitans (A.a.), Tannerella forsythia (T.f.), Treponema denticola (T.d.), and Prevotella intermedia (P.i.)) in subgingival plaque and atherosclerotic plaques obtained from carotid and coronary arteries in patients who underwent aortocoronary bypass grafting and carotid endarterectomy. In atherosclerotic plaques of carotid arteries, P.g., A.a., T.f., T.d., and P.i. were detected in 26.7%, 6.7%, 66.7%, 10.0%, and 20.0% of cases, respectively. In coronary arteries, P.g. was found in 39.3%, A.a. in 25%, T.f. in 46.4%, T.d. in 7.1%, and P.i. in 35.7% of cases. This study not only allowed us to hypothesize a link between periodontopathogenic bacteria and atherosclerosis but also demonstrated a correlation between the detection of five periodontal pathogens in atherosclerotic carotid and coronary arteries and the degree of periodontal inflammation [24].

A nationwide retrospective cohort study in Taiwan investigating the association between carotid atherosclerosis and periodontitis revealed that male patients

with periodontitis had a significantly higher risk of developing atherosclerosis compared to those without a history of periodontitis [25].

Periodontal pathogens have been identified as major risk factors contributing to the pathogenesis of atherosclerosis. This is supported by the results of epidemiological studies, as described in the work of Huang, X., and colleagues (2023). Epidemiological evidence suggests a strong association between periodontitis and an increased risk of atherosclerosis and cardiovascular events. Atherosclerotic plaques contain a variety of periodontal pathogens, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum. The study delves into the mechanisms by which these pathogens contribute to AS, including endothelial damage, immune response activation, and foam cell formation, highlighting the need for further investigation [26].

Clinical and microbiological research conducted by Mazur I.P. et al. provides evidence of periodontal pathogen DNA in cardiac valve tissue. The study found that 100% of patients with valvular heart disease undergoing cardiac surgery had generalized periodontitis of varying severity. The high level of gingival bleeding on probing (mean ± SD: 2.93 ± 0.07) was likely due to systemic antiplatelet therapy. The study found that 100% of patients had both staphylococci and streptococci in their periodontal pockets and heart valves. The high prevalence of periodontal pathogens identified in both periodontal pockets and excised heart valves using real-time PCR suggests a significant risk of hematogenous spread, transient bacteremia, and infective endocarditis. A significantly higher prevalence of P. gingivalis was observed in both periodontal pockets (86.7±12.4%) and heart valves (60.0±17.8%) ($p < 0.01$). A diverse range of bacteria, including T. denticola (40.0%), T. forsythia (36.7%), P. intermedia (10.0%), and A. actinomycetemcomitans (10%), were identified in heart valves. The presence of periodontal pathogens in aortic and mitral heart valves may contribute to a worsening of heart disease and heart failure [27].

Patients with advanced periodontitis who experience recurrent abscesses are more likely to develop heart failure with reduced ejection fraction. The amount of plaque buildup has also been linked to an increased risk of atrial fibrillation [14, 28, 29].

Hypertension, defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, is the most common cardiovascular disease. Prospective studies have shown a significant association between periodontal disease and an increased risk of developing hypertension, with a hazard ratio of 1.68 (95% CI: 0.85-3.35). Patients with periodontal disease had significantly higher mean systolic blood pressure (SBP) [weighted mean difference (WMD) 4.49 mmHg; 95% CI: 2.88-6.11] and diastolic blood pressure (DBP) (2.03 mmHg; 95% CI: 1.25-2.81) compared to those without periodontal disease [30]. Cross-sectional studies have consistently demonstrated a positive association between the extent of tooth loss and the prevalence of hypertension, with individuals experiencing greater tooth loss exhibiting higher systolic blood pressure. A statistically significant association between tooth loss and the development of hypertension has been consistently demonstrated in meta-analyses [31].

CONCLUSIONS

The findings of our review of the current scientific literature support the following conclusions:

- the rising rates of periodontal diseases and cardiovascular diseases, and their associated comorbidities, highlight the urgent need for further research and interventions in public health;
- new data emerging from updated research on the pathogenesis of periodontal disease highlights its systemic implications as an infectious process;
- periodontal care for patients with cardiovascular diseases needs further scientific investigation and practical refinement.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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