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The Association Between Periodontitis and Cardiovascular Disease: Clinical Implications for Treatment and Prevention

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Abstract

Introduction and purpose: Chronic inflammation in the oral cavity poses significant risks to both the heart and the circulatory system. A growing number of studies indicate a correlation between periodontal health and the likelihood of developing cardiovascular conditions, including myocardial infarction, coronary artery disease, hypertension, and stroke. This review aims to summarize recent reports, define current state of knowledge, and propose optimal treatment and prevention strategies.

State of knowledge: Risk factors such as obesity, smoking, and genetic predisposition contribute to the development of both PD and cardiovascular diseases (CVDs). Inflammation serves as a common factor linking the two conditions, with periodontal pathogens directly affecting cardiovascular health. Epigenetic mechanisms, particularly in response to environmental stimuli, further exacerbate the relationship between PD and CVDs. Additionally, the oral microbiome plays a crucial role, with periodontal pathogens infiltrating systemic circulation and triggering immune-inflammatory responses that promote cardiovascular damage.

Conclusions: People with periodontitis have a higher risk of CVDs, especially when other risk factors such as smoking and obesity are present. Periodontal treatment has been demonstrated to enhance cardiovascular health parameters. Implementing preventive strategy, addressing both periodontitis and cardiovascular risk factors, could potentially decrease morbidity and mortality associated with cardiovascular disease.

Keywords: Periodontitis, periodontal diseases, cardiovascular diseases, inflammation

1. Introduction

Periodontitis (PD) is a chronic inflammatory disease caused by dysbiosis of the oral microbiota, resulting in progressive destruction of the tissues surrounding the teeth and ultimately their loss [1]. This process is initiated by the accumulation of a microbial biofilm at and below the gingival margin, which activates the host immune-inflammatory response [2]. It has been documented that half of the world's population is affected by PD, significantly impacting their dietary habits, lifestyle management, and self-confidence [3]. PD not only impacts the periodontium, but it also exerts effects on organs beyond the oral cavity. Recent findings indicate a correlation between PD and the risk or development of systemic diseases and conditions. Especially, onset and progression of cardiovascular diseases (CVDs), such as hypertension (HT), coronary artery disease (CAD), stroke, myocardial infarction (MI) or heart failure (HF), might be directly or indirectly related to the local inflammatory response in PD [4,5]. The aim of this review is to determine the association between PD and CVDs, explaining their biological mechanisms and clinical implications.

2. Risk factors

CVDs represent the most common non-communicable diseases linked to mortality worldwide, accounting for about one third of global deaths [6]. They are relatively common in patients with PD, and an increased risk of CVDs is associated with PD independent of sex [7] Risk factors involved in PD and CVD are determined both genetically and behaviorally [8-10]. Certain shared factors exist among individuals with PD and CVDs, like obesity or overweight, minimal physical activities, smoking habits, male gender, low socioeconomic position, advanced age, and limited educational attainment [11]. Smokers have four to five times greater odds of having PD than non-smokers and there’s a relationship between intensity of smoking and the severity of PD [12]. Additionally, systemic conditions like diabetes mellitus and immunodeficiency disorders compromise the host's ability to combat periodontal pathogens, exacerbating disease severity. Hormonal changes associated with puberty, pregnancy, and menopause can also influence periodontal health, leading to increased susceptibility to gingival inflammation.

3. Pathophysiology and biological mechanisms

3.1 Inflammation

Both the pathogenesis, progression, and clinical manifestations of CVDs and PD are influenced by inflammation [13-15]. PD triggers a local and systemic inflammatory and immune response, leading to increases in white blood cell count, C-reactive protein (CRP), fibrinogen, cell adhesion molecules, and proinflammatory cytokines [16, 17]. Furthermore, the activation of immune receptors, such as toll-like receptors (TLRs), by periodontal pathogens triggers the production of inflammatory mediators and the upregulation of adhesion molecules on endothelial cells, facilitating the migration of leukocytes into the periodontal tissues. This leads to the formation of inflammatory infiltrates within the gingiva and the release of destructive enzymes, such as matrix metalloproteinases (MMPs), which degrade the extracellular matrix components of the periodontium, including collagen and elastin. Importantly, the inflammatory response in periodontitis is not limited to the oral cavity but can also have systemic effects. Periodontal pathogens and inflammatory mediators can enter the bloodstream through ulcerated gingival tissues or the periodontal pocket, leading to bacteremia and systemic inflammation, potentially infiltrating the cardiovascular system and increasing cardiovascular risk. It was suggested that targeted inflammation suppression further reduces the risk of cardiovascular events associated with CVD [21-25].

3.2 Epigenetic

Recent studies indicate the main role of epigenetics in linking PD with cardiovascular risk. Oral epithelial cells, acting as the body's primary defense against pathogens, undergo epigenetic modifications upon exposure to bacteria and their metabolites. These modifications alter signaling pathways and gene expression, impacting the dynamics and function of inflammatory cells [26, 27]. Environmental factors trigger epigenetic processes and alterations in gene expression, leading to changes not encoded in DNA sequences. Epigenetics arranges extensive chromatin remodeling through chemical modifications, ultimately modulating gene expression. Factors like smoking, toxin exposure, radiation, and infections significantly affect epigenetic dynamics [28].

Epigenetic mechanisms, including non-coding RNA-mediated gene regulation, DNA methylation, and post-transcriptional modifications to histones, play crucial roles. Single nucleotide polymorphisms add complexity by interacting with epigenetic mechanisms controlling gene expression. The pathophysiology of CVDs is heavily influenced by epigenetic changes and micro-RNA, contributing to the formation and susceptibility of atherosclerotic plaques. Epigenetic alterations, particularly in response to environmental stimuli, may affect an individual's predisposition to acquiring CVD risk factors [30-33]. Persistent inflammation and the presence of Gram-negative bacteria in the oral cavity due to inadequate dental hygiene can impact DNA methylation patterns and histone modifications in individuals with periodontitis [33]. Key inflammatory cytokines like IL-1 and IL-6 are integral to PD development, with their effects regulated by epigenetic pathways [34]. Environmental factors play a crucial role in causing epigenetic changes relevant to disease progression, potentially influencing an individual's susceptibility to CVDs risk factors. Alterations in miRNA expression are observed in almost all CVDs, such as ventricular hypertrophy, heart failure, and arterial hypertension. For instance, miR-155 regulates the expression of the angiotensin II type 1 receptor, positively correlated with blood pressure. Similarly, in periodontal disease, miRNAs control aspects of innate and adaptive immunity [35-37].

3.3 Oral Microbiome

The initiation of PD involves the infiltration of bacteria, particularly Gram-negative anaerobic species, or their byproducts into the periodontal tissues, resulting in tissue damage [38]. The ulcerated pocket epithelium provides a direct portal of vascular entry for periodontal pathogens, e.g. *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Eikenella corrodens*, and *Fusobacterium nucleatum* to the systemic circulation, which may affect other organ systems [39]. It has been described that gut microflora has a significant impact on initiation of CVDs [40]. Similarly, oral microorganisms may be harmful for the cardiovascular system. These bacteria produce virulence factors such as lipopolysaccharide (LPS) and lipoteichoic acid, which interact with epithelial cells in the periodontal sulcus [41]. Immune responses involving defensins, proinflammatory cytokines, and polymorphonuclear cells (PMNs) are triggered, leading to vasodilation, cell adhesion

molecule upregulation, and release of reactive oxygen species and enzymes. The infiltration of oral bacteria from the oral cavity into the systemic circulation triggers a cascade of immune-inflammatory responses, resulting in the release of various pro-inflammatory mediators (such as IL-1, IL-6, TNF-α, and MCP-1), acute phase proteins, C-reactive protein (CRP), fibrinogen, and free radicals into the bloodstream [42]. These inflammatory agents significantly affect the cardiovascular system, altering lipid metabolism, causing endothelial damage, and increasing blood hypercoagulability and platelet activity. Consequently, this elevates the risk of developing conditions such as atherosclerosis, arterial calcification, fibrogenesis, and cardiovascular tissue damage. Numerous studies have supported the association between heightened oral bacteria, bacteremia, and CVDs [43]. Furthermore, molecular mimicry between oral bacteria and host proteins has been proposed as a potential mechanism linking PD to CVDs. For instance, heat shock proteins (HSPs) produced by periodontal pathogens share structural similarities with human HSPs, leading to cross-reactive immune responses that may exacerbate vascular inflammation and plaque formation. The chronic inflammatory state associated with PD can promote systemic inflammation and endothelial dysfunction, contributing to the development of CVDs [44].

4. Association of PD with selected CVDs

4.1 Myocardial infarction

MI and PD share numerous common risk factors, including diabetes, smoking, and infection. Multiple studies have indicated a correlation between PD and a heightened risk of MI [45]. There were findings that revealed poorer oral health among MI patients compared to healthy controls. Additionally, research has shown that periodontal pathogens can induce MI in animal models. Epidemiological investigations consistently affirm an association between PD and an elevated risk of MI, regardless of traditional cardiovascular risk factors [46, 47]. However, further research is necessary to fully understand the precise mechanisms underpinning the relationship between periodontal disease and MI.

4.2 Stroke

The risk of stroke is significantly increased by the presence of PD [48]. Periodontal disease or poor oral hygiene may lead to local infection, inflammation, and systemic inflammatory reactions, which are important mediators of development of stroke. [49]. The possibility of stroke in patients with severe periodontitis and moderate periodontitis is 2.55 times and 1.71times as high as those without periodontitis. Dental health management may be of benefit to stroke prevention [50].

4.3 Coronary artery disease

Several biological mechanisms potentially link PD to CHD etiologically. Firstly, PD has been theorized as a chronic infection leading to sustained inflammation. Numerous studies have confirmed this hypothesis, demonstrating elevated levels of fibrinogen, CRP, serum amyloid A, and Von Willebrand factor in individuals with PD [51-53]. Specific interventions targeting PD have shown reductions in systemic inflammation markers [54, 55]. Furthermore, intensive periodontal treatment has been associated with improved endothelial function, as evidenced by a randomized controlled trial among individuals with PD [56]. Secondly, the intermittent bacteremia associated with PD may exacerbate the chronic inflammatory state or directly affect endothelial surfaces. For instance, there was a study that found a high prevalence of oral pathogens in carotid endarterectomy specimens [57, 58]. Additionally, prospective studies have linked severe periodontal disease to increased carotid artery intima-media wall thickness, suggesting a potential role in atherosclerosis [59, 60]. Thirdly, evidence suggests heightened platelet activation in vivo among individuals with periodontal disease, possibly contributing to plaque instability and thrombosis [61]. Lastly, animal studies have demonstrated a correlation between exposure to periodontal pathogens and the formation of atheromas [62].

4.4 Hypertension (HT)

The association between PD and HT is still being explored. Various mechanisms potentially explaining this association include endothelial dysfunction triggered by the systemic inflammation characteristic of PD, oxidative stress, inflammatory agents, and bacteremia [63]. Conversely, elevated blood pressure levels have been noted to exacerbate PD

by inducing microcirculatory alterations and subsequent ischemia in the periodontium, thereby promoting PD [64]. Moreover, periodontitis-induced inflammation can lead to oxidative stress and dysregulation of the renin-angiotensin-aldosterone system (RAAS), exacerbating hypertension. For instance, periodontal pathogens may activate the RAAS, promoting vasoconstriction and sodium retention, thereby elevating blood pressure [65]. Moreover, successful periodontal treatment has been shown to improve blood pressure control in hypertensive patients, further supporting the relationship between these conditions [66].

4.5 Heart failure

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. HF is caused by several underlying heart diseases such as coronary heart disease, arrhythmia, valvular disease, and cardiomyopathy [67]. Periodontal disease is highly prevalent in heart failure patients regardless of the cause of HF. Periodontitis might produce a biological burden of endotoxin and inflammatory cytokines that initiates and exacerbates inflammation [68]. Studies have shown that inflammatory factors can lead to ventricular remodeling, which in turn affects the development of HF. In recent studies, it demonstrated that the enhanced antibody level against *P. gingivalis* was associated with a high prevalence of heart failure [69] Repeated systemic bacterial dissemination triggers immune and acute phase reactions leading to systemic inflammation and subsequent atherogenesis and thromboembolic events [70].

5. Treatment and preventive strategies

PD should be treated as early as possible. Mild to moderate cases can usually be managed by nonsurgical treatments, including auxiliary antibiotics, scaling, and root planning. For severe cases that cannot be fully controlled by nonsurgical treatments, surgical methods can reduce pocket depth and generate anatomical contours at the periodontal interface [71]. Some recent interventional trials have shown that periodontal treatment can decrease markers of systemic inflammation [72]. While vitamin D is primarily recognized for its role in regulating calcium and phosphorus metabolism, it extends its influence beyond skeletal homeostasis to encompass various physiological effects. Recent studies indicate that vitamin

D acts as an immunomodulator, targeting diverse immune cells and modulating both innate and adaptive immune responses [73, 74]. Consequently, it plays a pivotal role in maintaining immune homeostasis. Several epidemiological studies have established a connection between insufficient vitamin D levels and heightened susceptibility to immune-mediated disorders, including cardiovascular diseases [75]. Adequate vitamin D levels are believed to partly mitigate the risk of these prevalent diseases. Studies have shown that low serum vitamin D levels are independently linked to periodontal and cardiovascular diseases [76]. Notably, vitamin D insufficiency correlates with elevated circulating CRP levels, which can be mitigated by vitamin D supplementation. Hence, the heightened CRP levels observed in periodontal and cardiovascular diseases may serve as an indicator of vitamin D insufficiency [77].

Moreover, promoting good oral hygiene practices, including regular brushing, flossing, and routine dental check-ups, is crucial for preventing the development and progression of PD [78]. Additionally, adopting a healthy lifestyle that includes a balanced diet rich in fruits, vegetables, and whole grains, along with regular physical activity, can help reduce systemic inflammation and improve overall cardiovascular health [79]. Smoking cessation is also important, as tobacco use not only exacerbates PD but also increases the risk of cardiovascular complications [80]. Furthermore, early detection and management of risk factors, such as diabetes and hypertension, through regular medical screenings and appropriate treatment are essential for preventing both PD and CVDs.

5. Conclusion

PD and CVD are both major health issues. Both diseases are complex in nature and share an important number of risk factors. Collaboration between oral health care professionals and cardiologists is essential to effectively manage these conditions, including implementing early detection strategies for PD in primary medical care settings.

The current body of literature strongly supports the association between cardiovascular risk and PD. The underlying mechanisms include inflammation, epigenetics, epithelial dysfunction, oral microbiome dysbiosis, and the efficacy of periodontal treatment.

Further research is necessary to determine exact mechanisms and novel interventions aimed at improving oral health and reducing cardiovascular risk.

Disclosures

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Authors contribution

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