



Periodontal Inflammation and the Risk of Cardiovascular Disease

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Abstract

Purpose of Review The role of oral bacteremia and periodontal inflammation driving atherosclerosis is still under investigation. This review article highlights the role of periodontal inflammation and oral microorganisms in the development and progression of atherosclerosis and cardiovascular diseases.

Recent Findings Association between periodontal and cardiovascular diseases has been well characterized, but causal correlation is yet to be established. For instance, untreated gingivitis can progress to periodontitis. Periodontal disease has been associated with several systemic diseases one of which is atherosclerosis. One possible association that was documented in literature is that poor oral hygiene leads to bacteremia, which in turn can cause bacterial growth over atherosclerotic coronary artery plaques and possibly worsen coronary artery disease.

Summary It is crucial that clinicians understand the association between periodontal and cardiovascular disease. A comprehensive treatment for periodontitis and re-establishment of a healthy periodontium can help in reduction of overall inflammation in the body. This may play an important role in prevention of cardiovascular disease, though future research is needed to establish this.

Keywords Periodontitis · Inflammation · Atherosclerosis

Introduction

Periodontal disease (PD) and cardiovascular disease (CVD) are both highly prevalent globally with a high healthcare burden worldwide [1]. Multiple epidemiologic and observational studies have consistently demonstrated that PD is independently associated subclinical and clinical CVD across diverse populations [1]. Both conditions are multifactorial and share

many risk factors—with inflammation playing an important role in their pathogenesis (Fig. 1). Recent evidence from large cohort studies have shown that periodontitis is associated with increased coronary artery disease (CAD) and all-cause mortality risk; moreover, this association also extended to subclinical CVD as well as stable CAD [2•]. In addition, genetic studies have also suggested a shared susceptibility gene that is involved in the pathogenesis of both PD and CVD [3].

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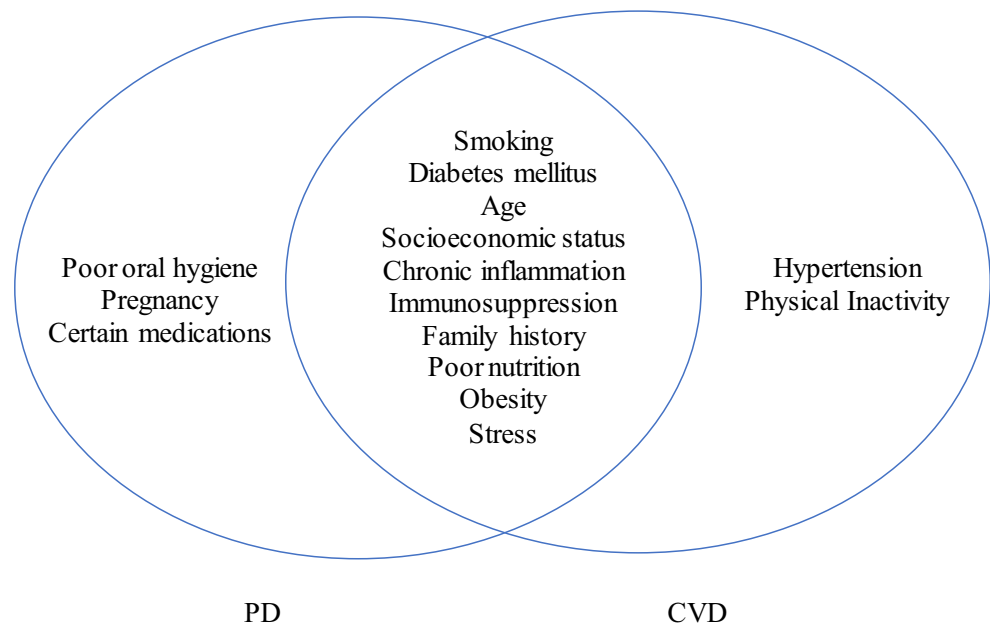
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Fig. 1 Risk factors for periodontal disease (PD) vs. cardiovascular disease (CVD)



However, multifaceted and chronic nature of both diseases makes it difficult to establish a definitive causative relationship. We aimed to review the evidence supporting the link between these two disease states.

Role of Microorganisms Linking Periodontitis and CVD

PD encapsulates a broad range of chronic inflammatory conditions that affect the gingiva, bone, and periodontal ligaments supporting the architecture of the teeth; in fact, chronic inflammatory PD affects about 20–50% of the population around the world, thus presenting a high global burden [4]. Importantly, patients with periodontitis were found to have an elevated and accelerated risk of CVD, including CAD, stroke, myocardial infarction (MI), and atherosclerosis, independent of traditional cardiovascular risk factors such as obesity and hypertension [5]. Microorganisms involved in PD include gram-negative anaerobic bacteria such as *Porphyromonas gingivalis*, *Campylobacter rectus*, *Tannerella forsythia*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum*. These organisms can be found in a complex biofilm in the oral cavity known as the dental plaque [6, 7]. Interestingly, the bacterial burden of these species in subgingival plaque samples has been shown to be associated with subclinical carotid intima media thickening even beyond traditional cardiovascular risk factors [8]. One of the several factors that facilitate the translocation of the bacteria is that the oral cavity is highly vascularized and the sulcular epithelium is relatively thin and friable [5]. Therefore, procedures such as brushing and mastication might disturb

this epithelium and possibly contribute to an occult or overt bacteremic state [9, 10]. Moreover, as periodontitis is considered an inflammatory condition, the dilated periodontal vasculature can facilitate bacteremia. It is postulated that this transient bacteremia leads to bacterial invasion of endothelial cells. Moreover, bacteria commonly found in the oral cavity have been frequently detected at sites where atherosclerotic lesions commonly occur and also by polymerase chain reaction locally in atherosclerotic plaques [5]. While these and many other studies have alluded to a link between oral infection/PD and CVD, causality is yet to be established. More mechanistic studies are needed to link PD and CVD; however, there are a few proposed mechanisms to support this relationship. Anaerobic bacteria biofilm formation leads to an inflammatory process, which later spreads to the deeper connective tissues. This inflammatory process is mediated by osteoclasts that are primarily triggered by the pro-inflammatory molecule PGE₂ and which are clinically detected in a periodontal pocket. This leads to the destruction of the periodontal supporting tissues and alveolar bone loss [7, 10]. Heightened immune cell response in form of polymorphonuclear leucocytes, macrophages, and lymphocytes infiltrate the connective tissue adjacent to the periodontal pocket. As a result, this inflamed and infected periodontium acts as a reservoir of gram-negative bacteria and their products such as lipopolysaccharide (LPS; activators of B-lymphocytes) and pro-inflammatory cytokines [9, 10]. The organism most commonly found in patients with periodontitis is *Porphyromonas gingivalis*. This microorganism is known to produce proteolytic enzymes such as gingipain which is known to cause proteolysis of CD14 molecule. CD14 molecule normally acts as a leukocyte receptor of LPS, thus suppressing the immune

response to bacterial antigens. Gingipain also helps bacteria survive in the plaque by degrading proteins into peptides and amino acids. LPS binds to Toll-like receptors, mainly receptors 2 and 4, triggering the host epithelial cells to release pro-inflammatory cytokines including $\text{TNF}\alpha$, $\text{IL-1}\beta$, $\text{IFN-}\gamma$, and PGE_2 [7, 9, 10]. Elevated inflammatory biomarkers, including CRP and IL-6, have been repeatedly observed in periodontitis which in turn have been linked to an increased CVD risk independently [11].

Relationship Between PD, Inflammation, and CVD

It is well known now that inflammation is critical to the development of atherosclerosis [12–14] and it has been recently shown that treating inflammation is associated with reduction in cardiovascular risk [15]. This risk is in part due to increased monocyte activation which in turn leads to elevated systemic inflammation [16]. Prior studies have proposed that chronic inflammation due to high burden of periodontal microorganisms [17] as well as subsequent inflammatory responses (molecular mimicry, direct vascular injury) potentially account for the relationship seen between periodontitis and elevated CVD risk [9, 18]. Inflammatory responses to many of these pathogens have been known to induce cross-reactive antibodies which potentially accelerate inflammation-driven atherosclerosis [19].

Furthermore, several studies indicate that periodontitis patients have a more atherogenic lipid profile in the form of elevated LDL, triglycerides, small dense LDL, as well as VLDLs, along with decreased levels of HDL concentration. Moreover, oxidized LDL is also found to be at higher levels in periodontitis which in turn has been shown to promote atheroma development [20]. Although mechanistic insight for such observations have not been fully characterized, it is believed that bacterial endotoxins and the release of systemic inflammatory modulators such as $\text{IL-1}\beta$ and $\text{TNF}\alpha$ affect hepatic and adipose cells metabolism and cause lipoproteins mobilization into the blood, which theoretically offers protection by binding endotoxins enhancing their excretion [20].

PD and Acute Coronary Syndrome

Periodontopathic bacteria triggers an immunologic and inflammatory response generating oxidative stress [21]. Oxidative stress is important in the pathogenesis of both acute coronary syndrome (ACS) and chronic PD. Both DNA and RNA are damaged by oxidative stress. 8-Hydroxyguanosine is one of the most stable biomarkers of DNA damage shown to be elevated in PD and ACS [22]. Salivary assays for 8-hydroxyguanosine, malondialdehyde, protein carbonyl assay,

and total antioxidant capacity on early morning samples collected after an overnight fast and blood sample assays for fibrinogen and CRP all exhibit elevated levels indicating their association, thus serving as potential non-invasive diagnostic tool [23] (Table 1).

PD and CAD

There is evidence to suggest that increasing PD severity carry proportionally higher risk of CAD by about 24 to 35% [24]. Moreover, studies have also looked into the relationship between PD and aortic vascular inflammation which in turn is a surrogate of coronary disease [25•]. Furthermore, a recent study explored the relationship between PD and coronary artery calcification and found that PD correlates positively and linearly with the presence of coronary artery calcification [26].

PD and Stroke

PD was first shown to be related to an increase in carotid artery intima media thickness in a cohort at high risk of atherosclerosis. Subsequent studies have shown that up to 31.3% of PD patients have unilateral carotid calcifications demonstrating increased subclinical carotid disease. Other studies have shown that PD is associated with higher levels of circulating CRP compared with controls and that carotid artery intima media thickness is greater in patients with PD, with elevated CRP correlating with an increase in carotid artery intima media thickness [8]. A case-control study furthermore showed a significant relationship between stroke and periodontal index [27]. Chronic periodontitis was found to be associated with lacunar infarcts and linked to increased levels of CRP and TNF [28].

PD and Atrial Fibrillation

Inflammation is suspected of having a potential role in atrial fibrillation (AF) development, associated with coagulation cascade derangements and propagation of thrombosis [29]. Patients with PD have been associated with high systemic inflammation as well as with incidence rate of AF of 200 cases per 10^5 person-year compared with 181 cases per 10^5 person-year in patients without PD [30]. A study carried out in an animal model showed that periodontitis was associated with enhanced immune activation in the atrial myocardium, which in turn deranged the electrophysiologic properties of the atrium. Atrial effective refractory period shortened along with increase in progression of AF inducibility [31].

Table 1 Key points connecting periodontal disease (PD) and cardiovascular disease (CVD)

Bacterial translocation in PD	Inflammation in PD and CVD
-In periodontal disease, periodontal vasculature is dilated and facilitates bacteremia	-Periodontitis produces elevated levels of inflammatory mediators (CRP, haptoglobin, fibrinogen, TNF- α , IL-6, fibrinogen)
-When the sulcular epithelium is disturbed, bacteria translocate into the bloodstream	-Inflammatory mediators may modify serum lipid, inflammatory cell, and endothelial cell receptors, contributing to plaque development
-Beginning with PGE2, an inflammatory cascade creates a reservoir of gram-negative bacteria and pro-inflammatory products (LPS) in the periodontium	-Elevated CRP correlates with an increase in CIMT in PD patients, ultimately conferring increased stroke risk
-Common dental plaque anaerobic bacteria have been found particularly in locations where atherosclerotic plaques are found (coronary arteries)	-Patient with periodontitis has higher levels of LPS-LDL and oxLDL, which are modified lipid forms that promote atheroma development
-Pathogens induce cross-reactive antibodies, which then produce inflammation systemically and within atheromas	-Salivary assays for 8-hydroxyguanosine, malondialdehyde, protein carbonyl assay, and total antioxidant capacity are elevated in both chronic PD and ACS patients

Limitations and Effects of PD Treatment on CVD

Although there have been many pathophysiological hypotheses and findings to support the association between PD and CVD, it is possible that the link is not causal. It has been previously reported that at least part of the association between PD and CVD is explained by adjustment for traditional risk factors such as smoking, diabetes mellitus, age, and socioeconomic conditions [32, 2]. Additionally, periodontal therapy (scaling, root planing, antibiotic treatment) has been shown to reduce levels of pro-inflammatory markers (CRP, TNF- α , and IL-6), further corroborating the periodontium as a source for these inflammatory mediators [33]. However, this has not been shown in a large randomized clinical trial. To date, one pilot randomized control study, the periodontitis, and vascular event investigation, was done which compared single full-mouth scaling and root planing with only community care in 301 patients with stable CAD over 6 to 25 months. The results were inconclusive, and the study had low statistical power. The association between PD and CVD events was present but not strong, with hazard ratios of ≈ 1.2 in adjusted analyses [34].

Conclusion

There appears to be a positive association between PD and CVD, with inflammation playing a critical role as the mediator. While most of the previous studies have assessed major outcomes such as MI, heart failure, stroke, or CV-related mortality, only a few studies have focused on subclinical surrogate markers of CVD. Future studies should utilize new imaging

techniques, such as positron emission tomography, nuclear magnetic resonance, echocardiography, and coronary computed tomography to detect subclinical atherosclerosis and evaluate how it may relate to PD.

Given periodontitis is a chronic condition, a long-term approach, rather than a single treatment, would likely be needed to achieve sustained improvement in periodontal health. Whether treatment of periodontal disease reduces cardiovascular disease and events has yet not been established. Randomized clinical trials involving standardized periodontal disease definitions and standardized periodontal interventions are required to demonstrate that PD treatment is beneficial to CVD risk reduction. In particular, future studies could benefit from expanding on how decreases in markers of systemic inflammation and endothelial function from periodontal therapy affect CV event and risk. With increasing investigation of the role of periodontal disease in CVD, periodontal disease may potentially become a CVD risk factor. However, more studies are required to explore the causative aspects of PD and the cardiovascular benefits of periodontal therapy.

Compliance with Ethical Standards

Conflict of Interest Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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