

# Impact of Periodontitis on Cardiovascular Diseases

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## ABSTRACT

**Cardiovascular diseases (CVDs) are the leading cause of global morbidity and mortality. Recently, an increasing amount of preventive and therapeutic scrutiny has been directed towards lifestyles and their effect on CVDs. Maintaining good dental health is a lifestyle behavior that can help prevent periodontitis (PD), tooth caries, and tooth loss. Published scientific data is persuasive that dental infections, such as PD, have significant deleterious effects on the cardiovascular system. This paper briefly reviews the association of PD with CVDs.**

**Keywords:** Periodontitis, caries, tooth loss, cardiovascular disease.

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## I. INTRODUCTION

It is estimated that periodontitis (PD) may affect 20% to 50% of the world population [1]. The oral cavity has more than 700 species of bacteria [2]. Some bacteria, such as *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* and spirochetes like *Treponema denticola* are pathogenic and cause infective PD [3]. *P. gingivalis* is the major invading pathogen in PD [4]. PD not only results in periodic bacteremia [5] but also causes systemic inflammatory changes [6], both of which may adversely affect distant organs and systems in the body [7]. Chronic ailments linked with PD include pulmonary diseases, diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus [8]. PD can also affect pregnancy, with adverse outcomes [9]. According to the Global Burden of Diseases, from 1990 to 2017, oral diseases such as PD and caries, contributed the most years lost to disability for 354 diseases and injuries across 195 countries [10]. PD also has profound negative effects on the cardiovascular system, imparting significant morbidity and mortality [11]-[13].

## II. DISCUSSION

Cardiovascular diseases (CVDs) include coronary artery disease (CAD), coronary heart disease (CHD) hypertension (HTN), stroke, CBVD, heart failure (HF), infective endocarditis (IF), cardiac arrhythmias including atrial fibrillation (AF), pericarditis, peripheral arterial disease (PAD), deep vein thrombosis (DVT) and vasculogenic erectile dysfunction (ED) [14], [15]. CVDs are the leading cause of morbidity and mortality in the world [16], [17].

Scientific meta-analytic studies have found a strong and consistent evidence that PD is associated with atherosclerosis [18] and an increased risk of future CVD events [19]. PD may also worsen pre-existing CVD [20] and

treatment of PD appears to diminish CVD risk or its progression [21]. The mechanisms behind the increased risk of CVD in patients with PD are multiple [22]-[48]. Invasion of pathogenic bacteria into the gingival tissue leads to local inflammation [22]. The inflamed gingival tissues allow oral bacteria to enter the blood stream, resulting in bacteremia [23]. Bacteremia may result from daily activities such as toothbrushing or flossing, as well as following interventions such as tooth polishing, tooth extraction and periodontal probing [24], [25]. There bacteria invade the arterial wall and initiate or worsen atherosclerosis [26]. A meta-analysis of 63 studies (1791 patients) confirmed the presence of oral bacteria in atherosclerotic plaques [27]. PD increases the risk of developing atherosclerosis by 2.52 times [28]. Oral bacteria have also been detected in cardiac tissue, and in biopsies from heart valves [29]. Oral bacteria and/or their DNA have also been detected in pericardial fluid and vascular thrombi in many studies [30], [31]. An association has been demonstrated between elevated anti-*P. gingivalis* antibody levels and several CVDs [32]-[34]. PD also induces systemic inflammation [35] and this is evidenced by elevated systemic inflammation markers including IL-1 $\beta$ , IL-8, IL-6 and tumour necrosis factor (TNF)- $\alpha$  [36]. C-reactive protein (CRP) level, another marker of inflammation, is also increased in PD patients [37]. Swallowed *P. gingivalis* may also cause gut epithelial alterations that may increase inflammation [35]. The increased inflammation seen in these patients leads to endothelial dysfunction [38]. There is also an increase in reactive oxygen species in PD patients, which enhances the inactivation of nitric oxide and this further worsens endothelial dysfunction [39]. Additionally, PD is often associated with smoking and diabetes mellitus which also cause endothelial dysfunction [40]. Endothelial dysfunction is a major factor behind the development of atherosclerosis [41]. PD also affects the lipid profile, with an elevation in serum total cholesterol levels, low-density lipoproteins (LDL), triglycerides, very-low-density lipoproteins,

oxidized LDL, and phospholipase A2 [42]. PD also reduces high-density lipoprotein levels (HDL) [42]. These lipid abnormalities further facilitate atherosclerosis [43]. PD patients have significantly higher levels of fibrinogen [44] and platelet activation markers [45], and both fibrinogen and aggregated platelets can induce thrombosis at the site of thin fibrous cap or fissure over a vulnerable lipid rich atherosclerotic lesion [46]. Genetic studies also indicate immunological commonalities between PD and CVDs [47], [48].

Regular dental hygiene and periodontal therapy helps reduce inflammatory markers [49], including CRP [50]. PD treatment also results in a significant decrease in fibrinogen levels [51] and platelet activation markers [52]. The lipid profile also improves [53]. Clinically, self-performed oral hygiene habits, dental prophylaxis, regular dental care utilization and periodontal treatment helps reduce primary acute CVD events [54]-[57]. Periodontal treatment (including tooth extractions, non-surgical and surgical periodontal therapy, and dental implant procedures) is generally safe in patients with CVD [58]. Individuals on single acetylsalicylic acid, clopidogrel, ticlopidine or ticagrelor therapy, do not have more bleeding events when compared to controls [59]. Dual antiplatelet therapy and anti-coagulants may increase bleeding, but usually this is manageable with local hemostatic measures [60], [61]. These medications are therefore not contraindicated for periodontal treatment and do not need to be discontinued. If doubt exists, and in patients with atrial fibrillation or with recent coronary stenting, consultation with the responsible medical professional is advisable [62], [63]. Further, antibiotic prophylaxis may be needed in certain cardiac patients with PD undergoing dental procedures to prevent infective endocarditis (IE) [64], [65].

### III. PERIODONTITIS AND HTN

Several observational studies have recognized an association between moderate-severe PD and HTN [66]. A study of almost 12,000 dentate adults conducted by NHANES III found that in middle aged individuals, there was a linear relationship between systolic blood pressure (BP) and severe PD [67]. PD is a major cause of tooth loss in the adults [68] and adults with missing teeth have higher blood pressures [69]. A recent study using Mendelian randomization found a causal relationship between PD and HTN [70]. PD patients exhibit significant inflammation and endothelial dysfunction, factors that contribute towards the development of HTN [71]. HTN and PD also share several risk factors, such as, smoking, stress, increased age, and socioeconomic factors, and they also have an independent association [72]. HTN is a contributing factor in almost 50% of the deaths due to CVDs [73]. Law et al in a meta-analysis reported that a 10-mmHg reduction in systolic and/or 5-mmHg reduction in diastolic BP resulted in a 25-30% reduction of major cardiovascular events [74]. Czesnikiewicz-Guzik et al. found a reduction in BP of  $7.5 \pm 10$  mmHg following intensive periodontal treatment [70].

### IV. PERIODONTITIS AND CAD/CHD

Dietrich and group, in a systemic review, found a robust association between PD and CAD/CHD [18]. Patients with PD have a higher rate of coronary artery events [75] and those with severe PD have the highest risk [76]. They also exhibit increased CHD mortality [77]. CAD is primarily due to atherosclerosis [78]. PD and atherosclerosis are strongly linked [79]. In a recent study of 72,630 patients with PD and a matched control group of 72,630 healthy patients, Tong and group found that male patients with chronic PD demonstrated a significantly higher risk of carotid atherosclerosis [80]. Carotid atherosclerosis is well known to be predictive of coronary atherosclerosis [81]. The latter can cause flow-limiting stenosis and plaque rupture, or an erosion can provoke atherothrombosis and vessel occlusion [82], leading to a myocardial infarction, or even death [83]. Besides endothelial dysfunction, inflammation and immune mediated responses, many other mechanisms are involved in the development and progression of atherosclerosis, including vascular lipid deposition [84]. Oral pathogens have been found in atherosclerotic plaques [85]. PD patients also exhibit harmful atheromatous plaque remodeling [86]. Plaque vulnerability may also be increased by PD related inflammation [87]. Oral bacteria such as *Streptococcus sanguis* are also known to increase platelet aggregation and increase the risk of thrombosis [88].

### V. PERIODONTITIS AND STROKE

There is considerable evidence from epidemiologic studies that a direct association exists between PD and CVBD [89]. A systematic review by Dietrich et al, confirmed this association [18]. In the ARIC study, patients with PD had more than double the risk of cardioembolic and thrombotic stroke compared with periodontally healthy individuals [90]. The higher CVD mortality seen with PD is in part due to an increase in CBVD seen in these patients [18].

### VI. PERIODONTITIS AND HEART FAILURE

PD and CHF frequently coexist [91]-[93]. Wood and Johnson noted that patients with PD tend to be at a higher CHF risk [91]. In a recent study, Aoyama and group found that enhanced antibody with high levels against *P. gingivalis* were associated with a high prevalence with greater of heart failure [92]. PD is also affected by heart failure [93]. The prevalence and severity of PD is higher in CHF patients than in the age-adjusted general population, regardless of the cause of CHF [94]. Periodontal disease is present in 47.2% of the general population [95]. A periodontal disease rate of 76% was found by Lessem and group and a rate of 69% detected by Schulze-Spate and group, in HF patients [96, [97]. The relationship between PD and heart failure therefore appears to be bidirectional [92], [97]. PD and CHF share several common risk factors such as smoking, diabetes mellitus, HTN, CAD, excessive alcohol consumption, and low socioeconomic status [98]. However, PD also independently induces inflammation, and inflammation of the cardiac tissue is not uncommon in HF patients with PD

[99]. Further, oral bacteria have also been noted in myocardial tissues [29].

#### VII. PERIODONTITIS AND ARRHYTHMIAS

Holm-Pederson et al, using a multivariate logistic regression analysis, reported that persons with three or more active root caries lesions had more than twice the odds of cardiac arrhythmias than persons without active root caries [100]. PD is a major cause of dental caries [101]. A study involving 22 adult mongrel canines of both sexes demonstrated that PD is associated with an inflammatory response in the atrial myocardium, which facilitates the development of AF [102]. A study using the Taiwanese National Health Insurance Research Database found that individuals with PD had a significantly higher incidence of AF or atrial flutter compared with the non-PD group [103]. Further, in patients with atrial fibrillation, PD is an independent predictor of major adverse cardiovascular events [104]. Dental scaling, which reduces the risk of PD, lowers the risk of AF [105]. Besides inflammation, PD likely affects the pathogenesis of AF by many other pathways including oral bacteria directly invading the heart and their toxins affecting the myocardium and deleterious effects on the autonomic nervous system [106].

#### VIII. PERIODONTITIS AND VALVULAR DISEASES

Dental infectious foci constitute a significant risk factor for infective endocarditis (IE) [107]. Bacteria from intra-dental foci have been found in the blood of 23.3% of patients with infective valvular endocarditis [107]. Bacteremia may occur after toothbrushing [108], and individuals with high levels of PD incur an almost eight-fold increased risk for bacteremia [109]. A recent study found fewer teeth and more advanced bone resorption in patients with IE, when compared to those without IE [110]. Further, preoperative periodontal treatment in patients undergoing cardiac valve surgery may help reduce postoperative infection [111].

#### IX. PERIODONTITIS AND PERICARDITIS

PD may be associated with pericarditis [112]. In one study, 63.6% of pericarditis were positive for endodontic-related bacteria and 36.4% were positive for PD-related bacteria in the pericardial fluid [112].

#### X. PERIODONTITIS AND CONGENITAL HEART DISEASE

PD during pregnancy has been linked to miscarriage, preeclampsia, preterm birth, and low birthweight [113], [114]. Dental problems are common in individuals born with congenital heart disease (CoHD) [115]. CoHD patients, especially those with cyanotic conditions, often develop enamel anomalies [116] and these are probably related to chronic hypoxia induced enamel hypo-mineralization [117]. Enamel anomalies impart a higher risk of caries in these children [118]. Franco and group found a higher incidence of untreated caries (in primary dentition) in CoHD children

when compared with other healthy children [116]. Untreated caries may often be a contra-indication for heart surgery, which these individuals often need [119]. PD may also increase the risk of IF endocarditis in patients with congenital cardiac defects [120].

#### XI. PERIODONTITIS AND HEART TRANSPLANT

Immunosuppressive drugs often used in heart transplant patients appear to increase the risk of gingival hyperplasia and periodontal conditions [121]. These patients often lead poor oral health-related behaviors such as infrequent toothbrushing and consumption of unhealthy snacks [122]. They may also not follow recommended professional dental evaluation, preventive interventions, and therapeutic care [123]. In a study of Chinese heart transplant patients, Cao and group reported poor periodontal health in heart transplant patients when compared with participants who had no such history [124]. Sezgin and Sezgin, in a more recent study, reported that when 40 heart transplant patients were compared with 40 healthy individuals, the former had higher mean probing depth, mean gingival recession, mean clinical attachment level, and mean plaque index scores on dental examination [122]. Poor oral health also further diminishes the quality of life in these patients [125].

#### XII. PERIODONTITIS AND PERIPHERAL ARTERY DISEASE

Mendez et al. noted that subjects with clinically significant PD at baseline had an increased risk of developing PAD [126]. Several subsequent studies have also noted a significant PD – PAD association [127]-[129]. Yang et al. did a meta-analysis of seven studies (total of 4307 participants) and confirmed a higher PAD risk in PD patients [129]. This increased risk is estimated to be five-fold [130]. Chen et al. also detected the presence of periodontopathic bacteria in 52% of the atherosclerotic specimens from patients with aorto-iliacal and femoro-popliteal PAD [130]. PD is a major cause of tooth loss [68] and PAD patients have been noted to have fewer teeth than control subjects [131], [132].

#### XIII. PERIODONTITIS AND ERECTILE DYSFUNCTION

ED is a multifactorial condition, and causes may be organic or psychological, or a combination of both [133]. Although vascular cause is the most common, in patients with PD it is usually a combination of vascular and psychological causes [134], [135]. Vasculogenic ED has been reported to have a higher incidence in PD patients in several studies [136]-[140]. A systemic review and meta-analysis by Liu and group confirmed a significant association between chronic PD and the risk of ED [141]. A more recent review of nine case-controlled studies and three meta-analysis further confirmed the significant association between these two conditions [142]. Wang et al, estimated that in patients with chronic PD, ED was increased approximately three-fold, when compared with non-PD controls [143]. Tooth lessness and oral mal odor related to PD, have adverse emotional and social effects, which may

also affect sexual performance [139], [144]. Further, these patients may suffer from poor nutrition, which may lead to systemic disorders, and further compromise socialization and sexual abilities [145]. PD treatment helps reduce erectile dysfunction [146].

#### XIV. PERIODONTITIS AND VENOUS THROMBO-EMBOLISM

PD is also associated with venous thromboembolism [147], [148]. Lippi et al found an increased risk of 1.9-fold of VTE in patients with severe PD when compared to those with no clinical signs of PD [148]. The increased risk climbed to 2.29-fold in patients who were edentulous [148]. In a prospective cohort study, using data from 8,092 participants in the Atherosclerosis Risk in Communities study to examine periodontal disease in 1996–1998 and incident VTE through 2011, Cowan et al found that self-reported tooth loss due to gum disease was associated with 30% higher VTE risk than no tooth loss due to gum disease, after elimination of confounding variables [149]. The major mechanism is systemic vascular inflammation [150]. Systemic inflammatory marker levels are effectively reduced by PD treatment, as reported in a meta-analysis of clinical trials [53].

#### XV. PERIODONTITIS AND OTHER CVD RISK FACTORS

Diabetes mellitus is a major risk factor for CVD and PD has a proven relationship with insulin resistance and diabetes [151], [152]. PD is also associated with lipid abnormalities, such as high triglyceride levels and low HDL cholesterol levels [153]. Obesity, another risk factor for CVD, is also common in patients with PD [153]. Smoking, stress, chronic obstructive pulmonary disease, and chronic kidney disease are also related with PD and are also major risk factors for CVDs [154]-[157].

#### XVI. CONCLUSION

Self-reported PD is often under-reported. PD once detected, is frequently untreated. The adverse effects of PD on cardiac health are irrefutable. Several mechanisms are responsible, but systemic vascular inflammation appears to be the main driver. Diligent oral health care is of paramount importance in reducing future CVDs. Even one additional toothbrushing per day is associated with a reduction in CVD events, while a professional dental cleaning reduces this risk even further. Prompt treatment of periodontal therapy also imparts a positive impact upon cardiovascular health. PD should be considered as a modifiable risk factor for CVD.

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