



## Periodontitis and Cardiovascular Diseases: The Nexus

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### Abstract

*Periodontal disease and cardiovascular disease are both multifactorial disease with a high prevalence worldwide. Cross-sectional and longitudinal prospective clinical studies show some evidence for a bidirectional relationship. Periodontitis and cardiovascular diseases share some common risk factors and there exist a mechanistic link between both. Earlier concepts of pathogenesis of cardiovascular events had lipid centric view of etiology. However, in recent years, there has been a shift towards importance of inflammatory processes in the body to be responsible for the disease. In spite of the rising prevalence of both diseases, many people remain unaware of their association with each other. Hence, this review article summarizes the potential link mechanisms in the association between periodontitis and cardiovascular diseases.*

**Keywords:** Cardiovascular diseases, Periodontitis, Infection, Inflammation, Risk factors, Atherosclerosis.

### Introduction

Periodontitis is a chronic inflammatory disease primarily caused by pathogenic microbiota of dental plaque and affects the supporting structures of the tooth. These microorganisms, particularly *Porphyromonas gingivalis* (*P.gingivalis*), produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host-mediated tissue destructive immune response.<sup>1</sup> Recent studies indicate that periodontal disease may have profound effects on systemic health. Subjects with periodontal disease may have a higher risk for cardiovascular disease when compared to subjects with a healthy periodontium.<sup>2</sup> International Classification of Diseases, 9th Revision defined diseases of the circulatory

system as follows: (1) Ischemic heart diseases, (2) cerebrovascular diseases, (3) diseases of arteries, arterioles and capillaries (known as peripheral vascular disease), arterial septal vascular disease (ASVD) affect the heart and blood vessels; which is a major component of the cardiovascular system (CVS).<sup>3</sup> Cardiovascular disease includes principally acute myocardial infarction and angina pectoris, and cardiovascular death and remains the leading cause of mortality in the United States since the 1950's and is becoming so worldwide. The World Health Organization (WHO) estimates that, in 2015, CVD was responsible for the deaths of 17.7 million people.<sup>4</sup>

The biological plausibility for a periodontal infection-systemic disease link can be briefly

explained as follows. Periodontal infection causes bacteraemia and endotoxaemia and promotes systemic inflammatory and immune responses that may roles in systemic disease. Periodontal pathogens express specific virulence factors that can affect atherogenic events. Finally, periodontal pathogens have also been isolated from non-oral tissues like atheromatous plaques.<sup>5</sup>

The consequence of these findings, recent researches have been focused the association of periodontal infection and systemic disease, and in this relationship in the alterations of lipid metabolism have been revealed as a potentially inductive factor.<sup>6</sup>

### Pathophysiology of Periodontitis

Three clinical parameters are typically recorded in epidemiological studies of periodontitis to assess its prevalence: (1) Bleeding on probing which reflects the presence of an inflammatory infiltrate in gingival tissue, (2) Pocket depth which describes the deepening of gingival sulcus from which dental plaque biofilm can propagate, and (3) Clinical attachment level, which reflects the amount of periodontal tissue loss. Bleeding on probing and increased pocket depth indicates current pathology, whereas attachment levels provide a cumulative measure of loss of support caused by aggregate effects of pathogenetic factors such as previous periodontal disease and trauma.

Markers of periodontitis include evaluation of subgingival microbial colonization by selected periodontal organism and level of serum immunoglobulin IgG and IgA antibodies to selected periodontal bacteria.<sup>7</sup> In some cases, high titres likely suggest the presence of a protective adaptive response, whereas, in others, they reflect the severity of periodontitis.<sup>8</sup>

### Microbiology of Periodontitis

A newly cleaned surface of the tooth is rapidly covered with a glycoprotein deposit referred as a pellicle. The microbial composition of dental plaque differs above and below the gingival

margin. Factors that influence the distinct pattern of microflora include specific local surface receptors for bacterial adherence. In the presence of gingivitis, Gram-negative anaerobic bacilli predominate in the subgingival flora. Subgingival microflora in gingivitis represents a transition between that associated with health and periodontitis.<sup>9</sup>

Initial (primary) supragingival colonizers have particularly affinity for constituents of pellicle. These colonizers include *Streptococcus sanguis*, *Streptococcus oralis*, *Streptococcus mutans*, *Actinomyces naeslundii*, and *Actinomyces odontolyticus*. The primary colonizer is followed by adherence of secondary colonizers such as *Fusobacterium nucleatum*, which in turn coaggregate with later colonizers. Within a short time complex communities of Gram-positive and Gram-negative bacilli and cocci become embedded in an extracellular matrix.<sup>10</sup>

### Risk Factors for Periodontitis and Cardiovascular Diseases

Risk factor associated with the development of periodontitis includes local, systemic, and genetic factors. Although several bacterial species are currently recognized as casually associated with periodontitis, mere colonization of the gingival niche by these species is not sufficient for disease to occur. Instead periodontitis is thought to be evolved from the stage of gingivitis, a local inflammatory process without loss of periodontal tissue support, that likely represent a stable, largely protective host response to periodontitis, a condition characterized by loss of connective tissue attachment and alveolar bone, influenced by environmental exposures and specific genetic predisposition.<sup>11</sup>

Contributors to cardiovascular diseases are similarly multifactorial and include a complex interplay between genetic, environment and lifestyle factors. Many prevalent risk factor with well-documented impact are shared by cardiovascular diseases and periodontitis and could confound a relationship between increasing

age, smoking, alcohol abuse, race/ethnicity, education and socioeconomic status, male sex, diabetes mellitus, and overweight are all factors associated with both CVD and periodontitis.<sup>12</sup> Although smoking is a major risk factor for both periodontal and CVD recent evidence seems to indicate that the observed association between PD and ASVD may be independent of smoking. It has been shown both in cross-sectional<sup>116</sup> and in longitudinal studies,<sup>13</sup> that periodontitis and CVD are associated in never smoker as well.

### **Potential Mechanisms in the Association Between Periodontitis and Cardiovascular Diseases:**<sup>14-19</sup>

Infection has been recognized as a risk factor for atherogenesis and thromboembolic events. Gram-negative bacteria or the associated lipopolysaccharide (endotoxin), when presented as a systemic challenge in animal models, can induce inflammatory cell infiltration into major blood vessels, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular coagulation. The remarkable similarities of bacterially induced vascular pathology, natural history of atherogenesis has led certain investigators to suggest that, in addition to genetic, lifestyle and dietary influences, infections of unknown origin may contribute to the observed cardiovascular pathology.

The chronic inflammatory burden of periodontal infection and the host response provide the bases for hypothetical model of the observed associations between periodontal disease and atherosclerosis, coronary heart disease and stroke. This model emphasizes that among certain individuals there may be an underlying hyperinflammatory trait in response to stimuli that is manifests by an excessive production of pro-inflammatory cytokine and lipid mediators by monocytes and other cell types.

Four potential mechanisms by which periodontal infections might contribute to the pathogenesis of CVD are: (1) Effects of Endotoxins in the circulation; (2) Role of heat shock proteins; (3)

Infection induced alterations in lipid profiles; (4) Formation of acute-phase reactants.

### **Effects of endotoxins in the circulation**

The microflora associated with periodontal infections is a rich source of endotoxins, which are lipopolysaccharide (LPS) components of the cell walls of all gram-negative bacteria. Entry of endotoxins into the circulation can occur from many sources including respiratory infections (*C. Pneumoniae*), gastric ulcers (*H. Pylori*), and periodontitis (*P. gingivalis*, *A. actinomycetemcomitans*, *B. forsythus*, etc).

Once endotoxins enter the circulation they present a considerable threat to the well-being of the host. They can directly injure endothelial cells, promote adhesion of monocytes to endothelium, induce macrophage foam cell formation and cause general endothelial dysfunction. All of these effects play a significant role in the initiation and development of atherosclerosis. One of the primary features of acute occlusion of vessels in CHD and stroke is the disruption of existing atherosclerotic plaques by macrophage-mediated inflammation.

### **Role of heat shock proteins**

Heat shock proteins (Hsp) are produced by a wide variety of bacteria and human cells under a variety of stressful or harsh conditions such as high temperature, infection, inflammation, and mechanical stress. It is well established that endothelial cells produce Hsp under stressful conditions such as exposure to endotoxins.

### **Infection-induced alterations in lipid profiles**

It is known from some studies that hyperlipidemia frequently accompanies many bacterial infections. Low doses of endotoxins cause a rapid rise in serum triglycerides due to an increase in triglyceride-rich very-low-density lipoprotein (VLDL). Hyperlipidemia may have negative effects such as promoting the release of proinflammatory cytokines from neutrophils. It is interesting to note that hyperlipidemia occurs

during periodontal infections. Cytokines like IL-1, IL-6, and TNF- have been implicated as risk factors for CHD and prolonged hyperlipidemia is likely to have deleterious clinical effects.

### **Formation of acute-phase reactants**

Acute phase reactants appear in the circulation in response to infections and tissue injury. C-reactive protein (CRP) is of particular interest since at "high -normal" levels it has been shown to be an important risk factor for CHD and is also elevated in patients with extensive periodontal disease. It remains to be determined if CRP elevations occurring during periodontal infections play a role in atherosclerosis.

### **Studies Establishing the Link between Periodontitis and Cardiovascular Disease**

#### **Case control studies**

In 1989, Kimmo Mattila and his co-workers in Finland conducted two separate case control studies totaling 100 patients with acute myocardial infarction and they compared these patients with 102 control subjects selected from the community. A dental examination was performed on all the patients and a dental index was computed. In this original report, subjects with evidence of oral infection were 30% more likely to present with myocardial infarction as against subjects without oral infections.

In a second case control report, Mattila and co-workers noted association between dental infections and degree of ATH. This study examined the same subjects as the first report with diagnostic coronary angiography. Accordingly the left main coronary artery, the circumflex artery, and the left anterior descending artery were assessed diagnostically and graded for the degree of occlusion on a 5-point scale. Again the total dental index score was used as a general score for dental caries, periapical lesions, and periodontal infections. In a multivariate analysis, significant associations were found between dental infections, age and triglycerides and severe coronary atheromatosis. These links remain significant even

after adjusting for other known risk factors like total cholesterol, HDL, smoking, hypertension, socioeconomic status, and body mass index. Mattila's provocative findings generated a great deal of interest in the scientific community.

The authors postulated that bacterial infections have profound effect on endothelial cells, monocytes-macrophages, thrombocytes and blood coagulation and lipid metabolism; and concluded that dental infections are the only risk factor outside the scope of classic coronary risk factors, which have shown independent association with the severity of adult coronary ATH in their multivariate assessment. Continuing to monitor for myocardial infarction among the cases in these first case control reports, Mattila *et al.* presented Cox proportional hazard models further implicating dental infections as a significant risk factor for new cardiovascular events.<sup>2,20</sup>

#### **Cohort Studies**

De Stefano and co-workers assessed the association between PD and CVD with National Health and Nutrition Examination survey (NHANES) I, which followed subjects for 14 years. This cohort study examined several potentially confounding variables including age, gender, race, education, marital status, systemic blood pressure, total cholesterol levels, body mass index, diabetes, physical activity, alcohol consumption, poverty and cigarette smoking. These investigators reported that among the 9760 subjects examined longitudinally, those with periodontitis has 25% increased risk of coronary heart disease related to those with minimal PD adjusted for the co-variables mentioned above. Interestingly, males younger than 50 years of age with periodontitis were 72% more likely to develop coronary heart disease compared to their periodontally healthy counterparts.<sup>21</sup>

Using data in the normative aging studies, Beck and co-workers evaluated 921 men aged between 21 and 80 years who were free of coronary heart disease at baseline. Over 18 years follow-up period, 207 men developed coronary heart disease,

59 died of coronary heart disease, and 40 had strokes. Odds ratio adjusted for age and established cardiovascular risks factors were 1.5, 1.9, and 2.8 for periodontal bone loss and total coronary heart disease, fatal coronary heart diseases and stroke, respectively. These data indicated that persons with radiographic evidence of periodontitis were 0.5–2.8 times more likely to develop coronary heart disease or suffer from a vascular event.<sup>22</sup>

In a larger six-year cohort study, Joshipura and co-workers studied 44, 119 men in the health professionals via mailed questionnaire with a self-reported history of PD and missing teeth. This study found no significant relation between self-reported history of PD and incidence of heart disease after adjusting for traditional risk factors (RR - 1.04). The study did however demonstrate that men with tooth loss and PD were 70% more likely to exhibit coronary heart disease.<sup>23</sup>

Genco and co-workers investigated the association between periodontal infections and risk of CVD in 1372 in Native Americans of Gila River Indian community, a group with high prevalence of diabetes mellitus. At baseline, alveolar bone level was measured and cardiovascular status was monitored for up to 10 years for electrocardiographic evidence of CVD using a pooling criteria. Among all age groups alveolar bone level was predictive for coronary heart disease, but did not remain significant in a multivariate analysis.[RR - 2.68 (95% CI 1.30–5.50)]. In contrast, for persons younger than 60 years of age, alveolar bone level was predictive of coronary heart disease (odds ratio of 2.68).<sup>24</sup>

### Cross-Sectional Studies

Arbes and colleagues<sup>25</sup> evaluated the link between PD and CHD in the NHANES III, and found that the odds of having history of heart attack increased with the severity of PD. The highest severity of PD in the population was associated with the odds ratio (OR) for 3.8 [95% CI (1.5–9.7)] compared with no PD; after adjusting for age, sex, race, poverty, smoking, diabetes,

hypertension, BMI, and serum cholesterol level. Thus this cross-sectional study confirmed the association and also showed a direct relationship between heart disease and increasing levels of PD. Genco and colleagues<sup>26</sup> assessed the association between specific subgingival periodontal organisms and MI. They compared 97 subjects with non-fatal MI with 233 control subjects. A panel of nine subgingival bacteria was evaluated, and subjects infected with one or more of these bacteria were compared with non-infected subjects. For MI the adjusted OR (95% C.I) was 2.99 (1.40–2.65) for the presence of *B. forsythus*, and 2.52 (1.35–4.70) for *P. gingivalis*; two periodontopathic bacteria. These findings support the notion that specific pathogenic bacteria found in cases of PD also may be associated with myocardial infarction.

### Meta-Analysis of Observational Studies

Janket *et al.*<sup>27</sup> performed a meta-analysis of nine cohort studies of PD as a risk factor for future cardiovascular and cerebrovascular events RR 1.19; (95% CI [1.08–1.32]) and found an overall 19% increased risk of such events in individuals with periodontitis. The increase in risk was greater (44%) in people under age 65.

Scannapieco *et al.*<sup>28</sup> concluded in an extensive systematic review that a moderate degree of evidence exists to support an association between PD and ATH, MI and CVD, but that causality is unclear. Results of another meta-analysis by Khader *et al* combining six cohort and two cross-sectional studies are lower RR 1.15; (95% CI [1.06–1.25]).

In 2009, a more promising and extensive meta-analysis of observational studies was conducted by Alessandra Blaizot *et al.*<sup>29</sup> in Toulouse, France, to examine the association between exposure to periodontitis and CVDs. Studies published between 1989 and 2007 (nearing two decades) were retrieved by electronic and manual search from seven databases. The included articles reported the results from observational studies and assessed the link between periodontal exposure

and CVDs as confirmed by one of the following criteria: diagnosed coronary artery disease, angina pectoris, myocardial infarction, mortality due to cardiac pathology. The study characteristics were abstracted by independent researchers following a standardized protocol. The MOOSE guidelines for meta-analysis for observational studies were followed.<sup>30</sup> From 215 epidemiological studies, 47 were observational; of which 29 articles could be combined by meta-analysis methodology. The pooled odds ratio calculated from 22 case control and cross-sectional studies was 2.35 (95% CI [1.87–2.96]);  $P < 0.0001$ ). The risk of developing CVD was found to be significantly (34%) higher in subjects with PD compared to those without PD (pooled relative risk from seven cohort studies was 1.34 (95% CI [1.27–1.4],  $P < 0.0001$ ). This result shows that subjects with PD have higher odds and higher risk of developing CVD.

### Interventional Studies

Noack and colleagues<sup>31</sup> demonstrated that C-reactive protein levels were highest in patients who were infected with periodontal pathogens where as CRP is an independent risk factor for CVD; however, detailed information is lacking about the mechanisms by which CRP participates in the pathogenesis of atheroma formation. C-reactive protein localizes the complement in human hearts during myocardial infarction, suggesting that CRP binds diseased muscle tissue, fixes complement and hence, triggers complement mediated inflammation that contributes to atheroma formation.

Recently in 2010, Cesar de Oliveira and colleagues<sup>32</sup> conducted Scottish Health Survey to examine if self-reported tooth brushing behavior is associated with CVD and markers of inflammation (C-reactive protein) and coagulation (fibrinogen). The database of the study drew 11,869 men and women from the population living in households in Scotland into the study. The results showed that there were a total of 555 CVD events over an average of 8.1 (SD 3.4) years of follow-up, of which 170 were fatal. In about

74% (411) of CVD events, the principal diagnosis was coronary heart disease. Participants who reported poor oral hygiene (never/rarely brushed their teeth) had an increased risk of CVD events (HR 1.7; 95% CI 1.3–2.3;  $P < 0.001$ ) in a fully adjusted model. They also had increased concentration of both C-reactive protein ( $\beta$  0.04, 0.01–0.08) and fibrinogen (0.08, -0.01–0.18).

Interventional studies conducted by Ebersole and colleagues<sup>33</sup> have shown that treating patients who have PD with scaling, root planing and flurbiprofen is associated with a trend towards reduced CRP levels one year after therapy.

There are also studies being designed to look at the effect of intervention on CVDs. David Paquette *et al.*, along with colleagues at Boston University; SUNY – Buffalo, University of Maryland and Oregon Health Science University (OHSU), have initiated plans for the “Periodontal Intervention and Vascular Events” (PAVE) pilot trial. This proposed multicentre study hopes to ultimately design and conduct a large clinical trial on periodontal therapy in patients at risk of cardiovascular events.<sup>34</sup>

### Conclusion

It is now clear from the epidemiologic studies that a potential link exists between periodontitis and CVD. Oral healthcare professionals can identify patients who are unaware of their risk of developing serious complications as a result of CVD and who are in need of medical intervention. Prospective interventional studies are required to determine the exact link between PD and CVD as well as to evaluate whether periodontal treatment may reduce the risk of developing CVD. Some studies which are in progress to evaluate the moderation of vascular disease (ATH) owing to interventional periodontal therapy and the extent to which it (ATH) is responsible for triggering cardiovascular events. However, the challenge remains whether PD can be considered one amongst the traditional risk factors for CVD as the link established from different studies is not limited to a recent CVD. Overall, PD seems to be

associated with no more than a modest increase (~20%) in cardiovascular risk in the general population.

As the ongoing studies report and confirm the strength of the association between PD and CVD, in the next two decades, the oral healthcare professionals and the medical professionals have to prepare for better planning of prevention programs. It seems from the scientific evidence gathered so far that interventional periodontal care remains invaluable not only for oral health but for general health as well.

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