REVIEW ARTICLE

Periodontitis and Cardiovascular Diseases – A Review on causality hypotheses

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Abstract

Over the past decade, mounting evidence has shown a link between chronic periodontitis and cardiovascular diseases. Alternate hypotheses which describe a causal relationship have been examined by various authors. These include the ability of periodontal pathogens to invade the endothelial and smooth muscle cells in the arteries and induce platelet aggregation and foam cell formation. This may also result in a systemic inflammatory response which favours the atherosclerotic process. This paper reviews the various possible linking mechanisms between periodontal disease and coronary artery disease.

Key Words: Cardiovascular diseases, Periodontal disease, Interleukins, Macrophages.

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Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both”.1

This destruction is brought about by interplay of bacterial products with the host’s immune system. Host response to periodontal infections result in the local production of cytokines and biological mediators including interleukins and prostaglandins as well as systemic responses such as induction of serum antibodies and acute phase proteins. The locally produced inflammatory mediators can spill over into the systemic circulation along with the microorganisms. This immunoinflammatory response of periodontal tissues and systemic vascular response can offer an explanation for shift in causality and directionality of oral and systemic associations.

Evidence emerging in the last decade has shed light on the relationship between oral health and various systemic conditions like coronary heart disease, stroke, adverse pregnancy outcomes, acute exacerbation of chronic obstructive pulmonary disease, aspiration pneumonia and diabetes.2

Coronary heart diseases form the leading cause of mortality and morbidity among the world population. The clinical manifestations and pathological correlates of coronary artery disease can be in the form of angina or myocardial infarction.

Myocardial Infarction is always due to the formation of an occlusive thrombus at the site of rupture of an atheromatous plaque in a coronary artery and can lead to sudden death. Main component of these atheromatous plaques are the foam cells. These are macrophages which have phagocytosed oxidized low density lipopolysaccharides (LDL). Besides these an atheroma also contains smooth muscle cells, leucocytes, extracellular matrix and lipids. Several host factors also increase the risk of coronary heart diseases and include diabetes, hypertension, smoking, abnormal serum lipids and age.3 The purpose of this report is to discuss the various hypotheses explaining the association between periodontitis and cardiovascular diseases.

Relationship between periodontal disease and coronary heart disease: Various studies have been done to assess the association between periodontal diseases and coronary heart diseases and to evaluate the biological framework that can potentially link the two diseases.

Perhaps one of the first indications that periodontal disease could be linked to cardiovascular disease or atherosclerosis came from an early study by MacKenzie and Mallard in 1965 who reported that 62% of the atherosclerotic group exhibited more periodontal bone loss than control.4

Evidence that oral health could predispose a patient to other thromboembolic disorders came from a case control study by Syjainen et al in 19895 of patients who had suffered ischemic cerebral infarction. Findings from this study suggested that in males less than 50 years old, severe chronic dental infection were an important type of infection associated with cerebral infarction.
Another series of studies together with follow up information came from Finland by Mattila et al. They reported that Dental health was significantly worse in patients with a recent history of acute myocardial infarction when compared with controls.

De Stafno et al in 1993 analyzed the data from the National Health and Nutrition Examination Study 1 (NHANES 1) in the United States. Subjects with periodontitis had a 25% increased risk of coronary heart disease (CHD) relative to those with minimal periodontal disease. Among those with periodontal disease, the relative risk of death from CHD was 2.86.

Beck et al in 1996 reported incidence data for coronary heart disease from the Normative Ageing Study. Multivariate incidence odds ratios for total CHD, fatal CHD and stroke according to the severity of alveolar bone loss were 1.5, 1.9, and 2.8 respectively. These odds ratios were adjusted for all the established risk factors for CHD.

Joshipura et al in 1996 in a 6 year survey of 44119 males found that those with <10 teeth were at an increased risk of CHD. Tooth loss may be associated with increased risk of CHD, primarily among those with a positive periodontal history. This study also had the advantage of being from a group of health professionals, which may limit the variability according to socio-economic status and perhaps even lifestyle.

Possible linking mechanisms between periodontal disease and cardiovascular disease
- Effect of bacterial lipopolysaccharides and inflammatory mediators
- Role of oral bacteria
- Increased fibrinogen and white blood cell counts
- Role of monocytes in periodontal disease and atherosclerosis
- Role of C-reactive protein
- Role of Heat Shock Proteins
- Shared risk factors.

Effect of bacterial lipopolysaccharides and inflammatory mediators: Lipopolysaccharides (LPS) are released as extracellular blebs from microorganisms with in the periodontal pocket and may enter the diseased periodontium. Bacteremia may also result in free lipopolysaccharides from periodontal organisms being present in plasma.

Intravascular infusion of LPS upregulates the expression of endothelial adhesion molecules, triggers the release of Interleukin 1β (IL-1β), Tumor Necrosis Factor α (TNF-α) and Thromboxane B2 (TxB2), initiates platelet aggregation and adhesion and promotes the formation of lipid–laden foam cells and deposition of cholesterol within the intima.

Lipopolysaccharides also serve to trigger endothelial expression of IL-1β, which favors coagulation and thrombosis while retarding fibrinolysis. These cytokines have been shown to enhance lipid accumulation within monocytes, especially cholesterol and cholesterol esters. Secondarily, monocyte cytokines such as IL-1β, transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) enhance smooth muscle proliferation leading to thickening of the vessel walls.

Bevilacqua et al demonstrated two major effects of IL-1 (Interleukin -1) on cultured human vascular endothelium:
1. IL-1 induces the biosynthesis and cell-surface expression of a tissue factor like procoagulant activity in endothelial cells, thus potentially making them actively thrombogenic
2. IL-1 dramatically and selectively induces endothelial adhesiveness for blood leukocytes

They proposed that endothelium which has been ‘activated’ by IL-1 in vivo, could mediate the development of intra vascular coagulation and/or promote localized adhesion of blood leukocytes at sites of inflammation.

Role of oral bacteria
Streptococcus sanguis is the most frequently isolated organism in dental plaque including subgingival sites. While not considered to be a periodontal pathogen, this organism enters the circulation by contact with chronically inflamed and ulcerated periodontal tissues.

The minimal platelet interactive domain of the platelet aggregation associated protein (PAAP) from S.sanguis is identical to the platelet interactive consensus sequence of Type I and III bovine and human collagens. This cell wall bound PAAP can induce the activation and aggregation of platelets.

In addition to S.sanguis, Porphyromonas gingivalis also expresses the Agg+ phenotype (aggregation-positive
phenotype) and a PAAP cross-reactive antigen and may contribute to both the chronic Lipopolysaccharide mediated and Agg+ mediated pathways to atherosclerosis and thrombosis.13 Harazathy and colleagues reported that 44% of the atheromas were positive for at least one of the target periodontal pathogens like Bacteroides forsythus, Porphyromonas gingivalis, Actinobacillus actinomycetem comitans and Prevotella intermedia. 14

Kuramitsu and colleagues showed that Porphyromonas gingivalis as well as its outer membrane vesicles (OMV) were able to induce foam cell formation. P. gingivalis is able to interact with the endothelial cells and induces the production of Monocyte Chemoattractant Protein-1 (MCP-1) and Intercellular Cell Adhesion Molecule 1 (ICAM-1) which enhance the recruitment of monocytes. Monocytes mature as macrophages in the subendothelial space and produce Reactive Oxygen Species (ROS) in response to microorganisms. ROS molecules oxidize LDL to the oxidized form (oxLDL), which is readily taken up by the macrophages to generate foam cells.15

Increased fibrinogen and white blood cell counts: Increased viscosity of blood may promote atherogenesis and thrombogenesis by increasing the risk of thrombus formation. Fibrinogen is probably the most important factor in promoting hypercoaguable state. Fibrinogen is the precursor of fibrin, which is a major determinant of platelet aggregation, and increased levels lead to increased blood viscosity.16

Multivariate analyses by Kweider et al, 1993 show that individuals with poorer Gingival index scores had higher fibrinogen scores (g/l) and white blood cell counts (×109/l). This probably may explain the increased susceptibility of periodontitis patients to atheroma formation.17

Role of monocytes in periodontal disease and atherosclerosis: Pocket is lined with ulcerated epithelium, which permits direct bacterial contact with both the subjacent connective tissue and the inflammatory cell infiltrate. Within the periodontium, the monocyte responds to the bacterial LPS (lipopolysaccharide, endotoxin) from these organisms by secreting three key proinflammatory mediators: Prostaglandin E2 (PGE2), IL-1β, and TNF-α. These paracrine in turn, have deleterious effects on the periodontium by eliciting vasodilation and increasing vasopermeability, inflammatory cell recruitment connective tissue degradation and bone destruction. The levels of these mediators within the affected periodontium can approach 1 to 3 µmol. Thus, the potential for the periodontium to serve as a concentrated reservoir of LPS and mediators, which may appear systemically, is extremely high.

Some individuals may respond to a microbial or LPS challenge with an abnormally high inflammatory response, as reflected in the release of high levels of proinflammatory mediators such as PGE2, IL-1β and TNF-α. Typically, peripheral blood monocytes from these Mφ phenotype (Hyper responsive monocytes) individuals secrete 3 to 10 fold greater amounts of these mediators in response to LPS in culture than those from normal MφN phenotype individuals.

Through action of TNF-α and IL-1β, exposure to endotoxin results in elevated levels of free fatty acids, LDL and Triglycerides. These elevations in serum are thought to arise from enhanced hepatic lipogenesis, increased adipose tissue lipolysis/blood flow, increased synthesis or reduced clearance of Triglycerides and reduced clearance of LDL due to reductions in lipoprotein lipase activity. Thus any condition producing elevations in serum IL-1β/TNF-α has potential to cause hyperlipidemia. In case of periodontitis elevations of these cytokines may be mediated by “systemic dumping” of locally produced IL-1β/TNF-α and/or low level asymptomatic bacteremia/endotoxinemia.18

Role of C-reactive protein
C Reactive Protein (CRP) may be considered as a primitive form of antibody specially interacting with cell membrane components of microorganisms, resulting in opsonization, enhanced phagocytosis and activation of the classical complement pathway. Serum CRP levels are greatly increased in patients with extensive periodontal pockets than in healthy adults.19

Moderately elevated levels of C-reactive protein are associated with greater risk of future myocardial infarction, stroke and symptomatic peripheral arterial disease. C-reactive protein enhances LDL aggregation and production of Vascular Cell Adhesion Molecule (VCAM) in cultured cells.20 Macrophages readily take up LDL bound to immobilized CRP
aggregates and this uptake induces the expression of adipophillin, a specific marker of cholesterol-laden macrophages. LDL particles phagocytized by sub endothelial macrophages leads to the formation of foam cells.21

Role of heat shock proteins (HSPs)

HSPs have been suggested to be important virulence factors in subgingival plaque. Elevated humoral immune response to HSP60 (Heat Shock Protein 60) family has been seen in periodontitis patients. Chronic oral infections stimulate high levels of HSP60 in subjects with cardiovascular risk. If antibodies directed against bacterial heat shock proteins cross react with HSPs expressed in the host tissue, especially if they are found in the lining of blood vessels, then there is a risk for an autoimmune reaction on the surface of the vessel. This could initiate the series of host responses which may contribute to the formation of atheromatous lesions in the presence of risk factors.22

Shared risk factors 23, 24, 25

Various environmental risk factors and indicators shared by periodontal disease and cardiovascular disease may also account for the significantly high prevalence of the two occurring together.

Diabetes: The increased risk of periodontitis in patients with either Type I or Type II diabetes has been confirmed in both cross sectional and longitudinal studies. The duration of diabetes and its metabolic control were found to influence the severity of periodontitis. Diabetes is also a major risk factor for CHD independent of other risk factors. Diabetes is associated with increased platelet activity and elevated plasma fibrinogen and plasminogen activator inhibitor 1 (PAI-1) levels. Endothelial dysfunction and erosion appear to be the dominant mechanism underlying coronary thrombosis in patients with diabetes. In the Framingham Heart Study, the presence of diabetes tripled the age adjusted risk for CHD in women and doubled in men.

Smoking: One of the strongest risk factors for the periodontitis is cigarette smoking. Several cross sectional and longitudinal studies have documented the increased prevalence of periodontitis in smokers compared to non smokers. Smokers are 2 to 6 times more likely than the non smokers to develop periodontitis. Grossi et al 26, 27 studied the association between the two adjusting for the known confounders and reported that the odds ratio for light and heavy smokers respectively, were 2.0 and 5.0 for clinical attachment loss and 3.3 and 7.3 for bone loss. Smoking also is a string risk factor for CHD among both males and females. The risk for CHD is 2 to 4 times greater among smokers than non-smokers. Smoking does not cause coronary atherosclerosis per se but rather increases the risk for thrombogenecity of plaques by upregulating tissue factor expression.28

Lipoproteins: Elevated serum total (and LDL) cholesterol and low serum High Density Lipoprotein (HDL) are major independent risk factors for CHD.

In periodontal disease, a number of cytokines are produced in response to systemic Gram-negative exposure. These cytokines mainly TNF-α and IL-1β exert effect on lipid metabolism by altering hemodynamics of various tissues involved in lipid metabolism, or modifying the hypothalamic-pituitary-adrenal axis increasing plasma concentration of adrenocorticotropic hormone, cortisol, adrenaline, nor-adrenaline and glucagons. Along with this there is an increase in hepatic lipogenesis and reduced clearance of LDL due to reduction in lipoprotein lipase activity.18 Recent studies also reported increased blood levels of cholesterol and LDL in periodontitis patients as compared to periodontally healthy subjects.29

Age: Age is suggested as a non modifiable risk factor for periodontitis. Several studies have shown that the severity and prevalence of periodontal loss is directly associated with age. This increased prevalence and severity of periodontitis may reflect a longstanding infection rather than a condition of the old age. The risk of coronary heart disease also increases with age in both males and females.30

Gender: In developed countries, males are more likely to develop periodontal disease than females. Findings from National Survey of Employed Adults and Seniors showed that that the male to female prevalence rate ratio for a probing depth greater than or equal to 5mm was 1.7:1 among adults 18 to 65 years of age. In parallel, CHD also is more common among males than females. It has been reported that males are 3 times more likely to develop chronic artery disease and 5 times more likely to die from heart disease than females.30
Conclusion

Substantial evidence documents a relationship between periodontal and cardiovascular disease. The interactions between dental and medical health are complex, multifactorial and involve so many common features that caution is needed before concluding that the associations are more than coincidental.

More research is required to confirm whether the risk for development of ischemic heart disease can be reduced by improvement in periodontal status of an individual.

It also signifies that the present day dentist should recognize the relevance of oral cavity in general health and well being of an individual and should also educate and motivate the patient about the same.

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