# Periodontitis as a Risk Factor for Cardiovascular Diseases- Hype or a Fact?

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## ABSTRACT

**Background:** The relationship between periodontitis and cardiovascular diseases has been a debatable topic since over a century, yet the debate is still ongoing. Periodontitis and coronary artery disease are both immuno- inflammatory in origin with many confounding risk factors associated with each other. Various epidemiological and interventional studies have been carried out to prove its biologic plausibility. There is however deficient literature on the exact pathophysiology of the spread of periodontal disease to cardiovascular disease. **Objective:** This review article aims to highlight on the most recent scientific evidence to substantiate on the causal relationship between the two diseases. **Results:** Various interventional and epidemiological studies suggest that there is a strong correlation between periodontitis and cardiovascular diseases, however there is a lacunae in literature in the in-vitro and long term clinical trials to support its exact biological mechanism. **Conclusion:** In the interest of public health, the cardiologists and the periodontists at large should be made to understand the role of maintaining good oral hygiene for general well being and refer to the specialist when necessary.

**Key words:** Cardiovascular Disease, Focal infection, Focal Sepsis, Heart Disease, Periodontitis.

## INTRODUCTION

Periodontitis is an inflammatory disease which is of microbial aetiology. It causes destruction of the periodontium- the attachment apparatus around the tooth which comprises of the gingiva, periodontal ligament and the alveolar bone. As a result of this, it causes the teeth to become mobile and fall off.

The infectious nature of periodontitis has been long studied. Socransky in 1977 gave the criteria to determine which microbe can be called as a periodontopathic pathogen.[1] According to this criterion, 6 organisms are presently considered as periodontopathic. They are *porphyromonas gingivalis (Pg), Treponema denticola (Td), Tannerella forsythia (Tf), Prevotella intermedia (Pi), Aggregatibacter actinomycetemcomitans (Aa), Capnocytophaga*.[2,3] Sockransky in 1998 examined over 13,000 subgingival plaque samples from 185 adult subjects using DNA hybridisation techniques. He proposed five complexes of bacteria which are the etiologic factors of periodontal diseases. The 5 complexes were named as red, orange, yellow, green and purple complex. Out of these groups of species, the yellow, green and purple complex are considered as early colonizers whereas the orange and the red complex are considered to be the major etiologic agents of periodontal diseases.[4] Interestingly, most of these microbes are also found in normal oral flora. The pathogenicity of these microbes depends on the number of microbes, their virulence features (adherence and invasion factors, capsules, endotoxins and exotoxins), the specific virulent strains (eg JP2 clone of Aa). The host response, immunity and genetic polymorphism of the host also play an important role in the pathogenicity of periodontal diseases. Environmental factors such as smoking, stress and systemic diseases plays an equally important role in the causation of periodontal diseases.

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### Focal Infection Theory

William Hunter in 1909, a British physician proposed that oral micro-organisms were responsible for a wide range of systemic diseases which were not easily recognised as infectious in nature.[5] He suggested to extract the teeth

rather than to restore. This lead to a widespread extraction of teeth in the 20th century. Focal infection theory in the 1950s fell into a major disrepute since widespread extraction of teeth did not improvise the systemic conditions of the individuals at large and Hunter's theory did not have any sound scientific evidence. The focal infection theory was revisited in 1951 by the American Dental Association and a confirmation of the link of periodontal diseases and systemic diseases was established.[6] Two major mechanisms were proposed for the spread of infection- either by the direct spread of the pathogen via blood stream causing septicaemia or by the spread of toxins to distant sites infect the surrounding tissues which may either infect the surrounding tissues or may produce a slow but progressive atrophy with replacement fibrosis in various organs of the body.[6]

## Atherosclerosis and Coronary Heart Disease

Atherosclerosis is an immuno-inflammatory disease which occurs mainly in the large and medium sized arteries. Endothelial injury is the prime step in the formation of atheroma. After endothelial injury, the surface adhesion molecules are increased and it leads to monocyte adhesion by the expression of monocyte chemoattractant protein-1 (MCP-1).[7] These monocytes are converted into tissue macrophages in the intima layer. The activated macrophages secrete various cytokines. Cytokines in turn stimulate the endothelial cells. Activated macrophages also have the property of capturing low density lipoproteins which undergo progressive oxidation and are no longer available for β oxidation of fatty acids to produce energy. Subsequently, there is a formation of lipid peroxidises and accumulation of cholesterol esters which leads to the formation of foam cells. Further accumulation of these cells by modified LDL leads to the formation of fatty streak which gets calcified to form atherosclerotic plaque. The features of atherosclerotic plaque include a lipid rich core with common focal calcification detected by the coronary calcium score, smooth muscle necrosis, neovascularisation and intra-plaque haemorrhage, vascular remodelling and luminal stenosis.[8]

## Periodontal Pathogens in Atheromatous Plaque

Since both periodontitis and atherosclerosis are immune-inflammatory diseases, a link was suspected as a causal relationship between the two diseases. Nested Polymerase Chain Reaction (PCR) of the bacterial DNA extracted from the atheromatous plaque from 42 endarterectomies of carotid arteries detected a fine number of periodontal pathogens. The most common bacterial species found were *Pg* (78.57%), *Aa* (66.67%), *Tf* (61.90%), *Eikenella corrodens* (54.76%), *Fusobacterium nucleatum* (50%), *Campylobacter rectus* (9.52%).[9] The major fimbriae of Pg FimA genotypic clone II has been implicated for its role in the adhesion to the endothelium and vascular tissues.[10] Studies by Schenkein *et al* in 2000 demonstrated that the invasion of Aa into the human vascular endothelial cells involves an interaction between bacterial phosphoryl choline and the platelet-activating factor receptor of the host cell.[11] *In vitro* studies on Pi Strain 17 and Tf has shown coronary invasion- both endothelial and smooth muscle cells through the invasion protein AdpC and BspA respectively belonging to the leucine rich repeat protein family.[12,13] Fifty one out of 53 patients with atherosclerosis have been reported to have periodontitis in Japanese population. PCR analysis revealed DNA specific for periodontal bacteria in 52% of the patients whereas 23% were detected in controls.[14] Indirect measurements by analysing the antibody plasma levels to periodontopathic bacteria has shown an association for the risk of coronary heart disease (CHD) in a case control study where a high tertile plasma antibody level (>184.9 U/mL) of Aa showed a higher risk of CHD with an OR of 4.64 at a CI of 95% when compared with low tertile level (<31.7 U/mL).[15] Also, C- Reactive Proteins, fibrinogen and white blood cells have shown a very high significant correlation with periodontal parameters as well as CHD.[16,17]

## The Link between Periodontits and CHD

One of the earliest benchmark longitudinal cohort by the National Health and Nutrition Examination Survey 1 in 1993 studied the outcome of CHD in 9,760 subjects with periodontitis. The study showed that periodontitis has 25% increased risk of CHD with a relative risk of 1.72.18 Mattila et al. in 1995 demonstrated statistically significant correlation between the total dental index and fatal and non fatal CHD in a 7 year follow up.[19] Beck *et al.* in 1996 evaluated the alveolar crestal bone loss and CHD in 1147 males and showed a causal relationship with a relative risk of 1.9.[20] Joshipura showed a relative risk of 1.67 in a study of 44119 male subjects who reported with periodontal disease and followed up for a period of 6 years to check for the occurrence of CHD.[21] Animals models have been used to study the link between periodontitis and CHD. Inbred mice when challenged orally or IV with invasive strains of Pg, has shown to increase the occurrence of aortic atherosclerosis. A systematic review and meta-analysis formulated of 7 cohorts in 2008 showed a relative risk estimates for different categories of periodontal disease ranging from 1.24 to 1.34 which suggests that periodontitis is an independent risk factor for CHD.[22] In 2009, a more promising meta analysis of 29 articles was compiled by Blaizot *et al* states that the

risk of developing cardiovascular diseases is 34% higher in patients with periodontitis when compared with patients without periodontitis.[23] Epidemiological evidence of 12 studies compiled by Dietrich *et al* in 2013 supports the notion that the incidence of CHD is higher in patients with worsened periodontal status.[24] Tonetti and Dyke in 2013 summarize the joint EFP/AAP consensus workshop and states that periodontal therapy does reduce the systemic inflammation as evidenced by decrease in the markers of systemic inflammation like C- reactive proteins but has no effects on lipid profiles.[25]

## DISCUSSION

The idea that the bacteria in the oral cavity can cause systemic diseases which was proposed a century ago still remains a debatable topic amongst clinicians at large. The exact pathogenesis of the causation is still a black hole in the literature. Also, there lack animal interventional studies of periodontitis induced animal models which when followed up for a long time eventually caused CHD. Consequently, based on the evidence we suggest that only certain pathogenic strains of the bacteria can lead to cardiovascular diseases. For example various strains of Pg induce varying responses in endothelial dysfunction which is the hallmark of CHD. Chou *et al* in 2005 demonstrated that Pg 381 (fimbriae type I) induces gene expression of GroA, GroE, IL- 6, IL-8, vascular cell adhesion molecule (VCAM)-1 and endothelial leukocyte adhesion molecule (ELAM)-1, which is a fimbriae dependent phenomenon.[26] More insight and detection of these pathogenic strains and chair side detection of these pathogens could be a goal for future to prevent occurrence of CHD. Modified Koch's postulates can be used as a model in animal experiments to substantiate the role of specific strains of periodontal pathogens in causing CHD.

Periodontitis and CHD are both of immune-inflammatory origin and there are confounding risk factors like smoking, age and other systemic diseases like diabetes. These factors need to be taken into account while evaluating the further studies to prevent independent occurrence of periodontitis and CHD due to such confounding risk factors.

## CONCLUSION

Although intervention studies and epidemiological data suggest that these is a strong correlation between periodontitis and CHD; *in vitro*, animal and long term clinical studies do not support the interaction and the exact biological mechanism of the pathogenesis of the spread of the disease. However in the interest of the patient's health, the cardiologists are advised to educate their patients on the role of maintaining oral health for general health and to refer to the periodontist when needed. At the same time the general dentists and the periodontists are advised to keep a check on the inflammation and maintain a zero tolerance for bleeding gums to prevent the percolation of septicaemia from oral tissues to distant sites.

## CONFLICT OF INTEREST

Authors declared no conflict of interest

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