

PERIODONTAL INFECTION – A RISK FOR CORONARY ARTERY DISEASE

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ABSTRACT

Over the years, advancement made in the field of scientific research has opened up new horizons in understanding the intricate aspects involved in the pathogenesis of various inflammatory human diseases including periodontitis. In recent times, there has been an increasing interest evinced in the areas relating to the impact of oral health especially periodontal infection on the cardiovascular system. With the advent of inflammation paradigm being considered in the coronary artery disease pathogenesis, research has focused on the role of chronic infections caused by oral pathogens on the endothelial

dysfunction and also the propagation of atherosclerotic lesions. Oral sepsis triggers the release of a plethora of inflammatory cytokines that travel their way into systemic circulation and exhibit their pro-inflammatory effects. The present review aims at highlighting the relationship between periodontal infection and coronary artery disease using various epidemiological studies and the underlying biologic plausibility that exists between them.

Key words : Inflammation, periodontitis, atherosclerosis, coronary artery disease

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INTRODUCTION

Inflammation referring to a protective tissue response to injury has been implicated in the pathogenesis of many human diseases. It plays a central role in complex multifactorial chronic inflammatory diseases including periodontitis and cardiovascular disease (CVD).

The word 'periodontium' means structures surrounding the teeth (i. e) 'peri'- 'around' and 'odontos'- teeth. It comprises of four tissues – gingiva (the investing tissue), periodontal ligament, cementum and alveolar bone (that constitute the attachment apparatus) (Fig 1). Periodontitis

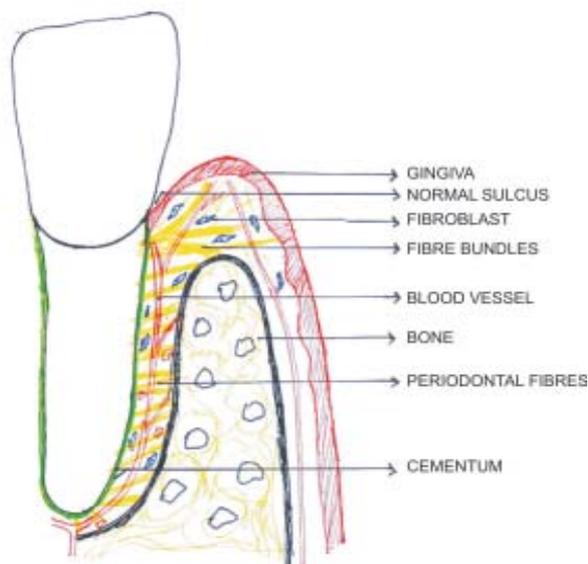


Fig. 1

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is a chronic 'infectious/inflammatory' disease of multifactorial etiology.^[1] Though it is initiated by dental plaque associated microorganisms, the inflammatory process is sustained by the host.

Atherosclerosis refers to a variable combination of changes of the intima of arteries consisting of a focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue, calcium deposits and associated medial changes. Ischemic heart disease (IHD) refers to a group of closely related syndromes that is caused by an imbalance between myocardial oxygen demand and blood supply. The most common cause of IHD is the narrowing of the lumen of the coronary arteries by atherosclerosis. Hence, IHD is often termed as coronary heart disease (CHD) or coronary artery disease (CAD). It has been suggested that inflammatory processes underlie all phases of atherosclerosis.^[2]

The probable link between oral and systemic disease dates back to 1900 when the concept of 'Oral sepsis' was put forward by a British physician, William Hunter.^[3] Subsequently in 1912, it was superseded by 'focal infection' by Frank Billings.^[3] Two major mechanisms of focal infection were proposed - an actual metastasis of organisms from a focus and the spread of toxins or toxic products from a remote focus to other tissues by the blood stream. Though the theory was accepted initially, it was later disregarded due to various reasons.

Over the last two decades, the whole concept of focal infection has resurfaced with the work done by Matilla et al., in 1989 who found a highly significant association between poor dental health and acute myocardial infarction.^[4] Of the various oral health related conditions, researchers have investigated the relationship between periodontitis and atherosclerotic cardiovascular disease and have thrown light on the underlying biologic plausibility that exists between them.

The purpose of the present review is to put forward the probable implication of periodontal infection on the cardiovascular system. Most of the scientific articles

published in the last decade studying the different aspects of periodontal disease and CAD indicate periodontitis as one of its risk factors. The reason for periodontitis being implicated could be attributed to the fact that there is a continuous bacteremia that poses a constant microbial challenge for a prolonged period. There is considerable global variation with periodontal disease in developing countries. However, the prevalence of severe generalized forms of the disease appears to be similar in most populations.^[5] The prevalence of periodontitis is reported to be between 20 and 50% in population worldwide.^[6] The information utilized for this review were searched on the internet with key words like atherosclerosis, focal infection, coronary artery disease, risk factor, periodontitis in pubmed and google websites.

PATHOBIOLOGY OF PERIODONTITIS

The inflammation begins in the gingiva initially and remains confined to it. Most of the time the condition is reversible. When allowed to progress, periodontal inflammation sets in with gradual destruction of the supporting tissues over time and the condition is characterized by irreversible loss of the supporting tissues of the teeth. Though periodontitis is initiated by microbes, the progression and destruction of the tissues is predominantly due to the reactive host response to microbial attack ('by stander damage'). Page and Kornman showed a new dimension depicting the central role of inflammation in the pathogenesis of periodontal disease.^[7]

When bacterial biofilms (initiating factor for gingivitis and periodontitis) on the teeth are not physically disrupted on a regular basis, it leads to the emergence of gram negative bacteria. As a result of chronic bacterial challenge, inflammation is triggered leading to a series of events and the condition perpetuating from a stage of gingivitis (confined to gingiva) to periodontitis. Bacteria and their toxins (especially endotoxin) stimulate a localized tissue response causing the release of various cytokines and other mediators of inflammation. Chronic damage of epithelial tissues and the underlying connective tissues due to periodontitis may induce the periodontal pocket (pathological deepening of the gingival sulcus) to ulcerate, allowing their access to the bloodstream.

All these processes can disrupt the homeostasis when toxins gain entry into the systemic circulation. The pro-inflammatory cytokines TNF- α (tumour necrosis factor-alpha), IL-1 β (interleukin-1 beta), gamma interferon and PGE2 (prostaglandin E2) reach a high tissue concentration in periodontitis. The periodontium thus serves as a renewing reservoir for these mediators, that is spilled over into systemic circulation thereby inducing and perpetuating the systemic effects (Fig 2). IL-1 β favors coagulation, thrombosis and retards fibrinolysis. Chemical mediators IL-1, TNF- α , and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells and deposition of cholesterol in the arteries.

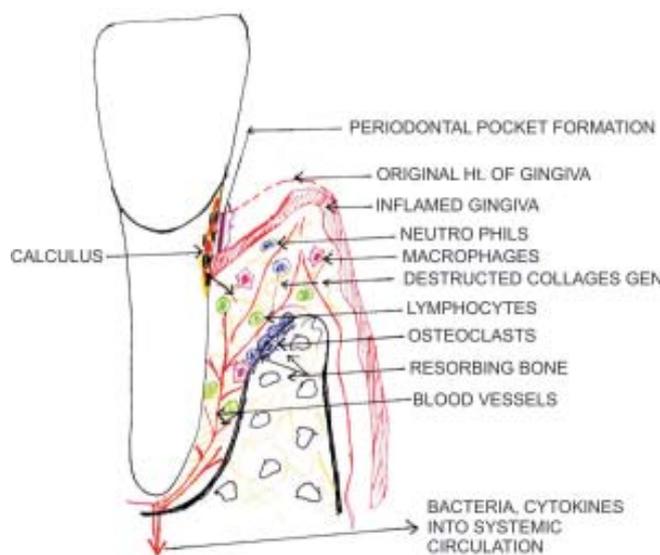


Fig. 2

One may debate that an individual may have other infections but why the specific association of periodontitis with coronary artery disease.^[1] The reason being the enormous bacterial load in diseased periodontium, a source for infection for continuous release into systemic circulation. The total surface area of the diseased pocket epithelium in contact with sub-gingival bacteria and their products in a patient with generalized moderate periodontitis has been estimated to be approximately the size of the palm of an adult hand with even larger areas of exposure in cases of more advanced periodontal destruction.^[8] They present a continually renewing reservoir of lipopolysacchride (LPS) and other gram-negative bacteria with ready access to the periodontal tissues and the circulation. When the surface area of dento-gingival epithelium exposed to bacterial invasion or infiltration of microbial antigenic components in periodontitis patients was calculated, the surface area of the inflamed portion was found to be ranging between 8 and 20 centimeter square.^[9]

Systemic challenge with predominantly gram-negative bacteria induce major vascular response that includes inflammatory cell infiltrate into the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular coagulation. In addition, LPS up regulates the expression of endothelial cell adhesion molecules.^[10]

Unique features of periodontal infection

Periodontal infection is considered unique for various reasons cited below.^[11, 12]

1. Periodontitis is a polymicrobial infection.
2. It is a longstanding chronic infection that is asymptomatic most of the times.
3. Normal daily activities like chewing, brushing and flossing can cause a transient bacteremia (in the process, cytokines and mediators are also pumped out into systemic circulation).

- Unusual anatomic feature – the tooth is partially exposed to the external environment and partially embedded within the periodontal connective tissue.
- The teeth are non-shedding surfaces unlike skin and provide a continuous microbial colonization that comes in contact with the supporting tissues of the teeth.
- The microorganisms that initiate periodontal disease reside within a protective environment (i. e) the biofilm.
- Presence of teeth enhances the complexity of the host-parasite relationship.

OVERVIEW OF THE STAGES IN THE DEVELOPMENT OF ATHEROSCLEROSIS

The stages in the development of atherosclerosis involves a series of events that include development of fatty streak, progression to complex plaque and plaque rupture.^[13]

During the stage of fatty streak – initially there is an accumulation of monocytes in the vessel intima which is an initial event in the development of early atherosclerotic lesion. There is adherence of monocytes to endothelium through the expression of MCP-1 (Monocyte chemoattractant protein-1). They migrate across the endothelial cells into the intima. They mature in to macrophages that express scavenger receptors and engulf modified lipoproteins. 'Foam cells' (i. e) lipid-laden macrophages are formed in the vessel intima. Macrophages multiply, release growth factors, cytokines that amplify and sustain the pro-inflammatory signals.^[13]

Next step features progression to complex plaque fixation with accumulation of fibrous tissue in vessel. Certain growth factors like platelet derived growth factor and cytokines like IL-1, transforming growth factor-beta from endothelial cells and monocytes stimulate smooth muscle cells to produce interstitial collagen.^[13]

One of the sequelae that occurs following complex plaque formation is plaque rupture. Thrombus formation results from the physical disruption of the plaque. In case of non-ruptured plaque, the fibrous cap protects blood from the lipid core of the plaque. When there is a fracture of fibrous cap, blood comes in contact with the lipid core and a thrombus gets formed. It is viewed that inflammation interferes with the integrity of the fibrous cap through blocking the creation of new collagen fibers and stimulating the destruction of existing collagen by the action of matrix metallo proteinases (MMPs).^[13]

THE PROPOSED SPECIFIC PATHWAYS LINKING PERIODONTITIS AND CARDIOVASCULAR DISEASE – BIOLOGIC PLAUSIBILITY

- Direct bacterial effects on platelets - Two oral bacteria *Porphyromonas gingivalis* and *Streptococcus sanguis* have been found to express virulence factor, collagen-

like platelet aggregation associated proteins (PAAP) that induce platelet aggregation in vitro and in vivo.^[14, 15]

- Invasion and/or uptake of bacteria in endothelial cells and macrophages -

Porphyromonas gingivalis (that is considered as one of the important putative periodontal pathogens) can invade aortic and heart endothelial cells via its fimbriae.^[16]

- Endocrine-like effects of pro-inflammatory mediators – there is an up regulation of mediators in vascular

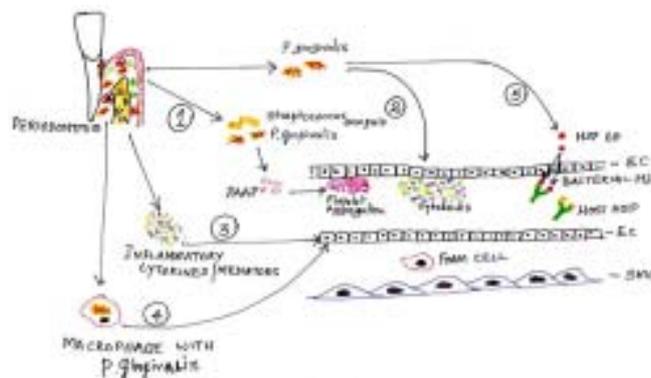


Fig. 2

tissues. C-reactive protein and fibrinogen levels are elevated.^[17, 18, 19]

- Macrophages incubated in vitro with *Porphyromonas gingivalis* and low density lipoprotein take up bacteria intracellularly and are capable of transforming into foam cells.^[20]
- Autoimmune response - Antibodies cross-react with periodontal bacteria and human

Heat Shock Proteins (HSPs).^[21,22] Antibodies developed against *Porphyromonas gingivalis* HSP 60 cross react with human HSP because of the structural homology that exists between the two (Fig 3).

Ever since Matilla et al published their observation regarding the relationship between acute coronary syndrome and oral hygiene, there has been a constant surge in the study linking periodontitis and atherosclerosis. Review of literature reveals several articles in regard to this. However, to draw conclusions relating to the cause(s) of disease, certain criterion have to be met. These criteria were put forward by Bradford Hill in 1965 and these include strength of association, dose-response effect, temporal consistency, biologic plausibility and specificity of association.^[23]

An overview on the various epidemiological studies carried out to determine the possible link between periodontitis & CVD is represented in Table 1, 2, 3.

TABLE 1 : Studies assessing the association between periodontitis and cardiovascular diseases

AUTHOR	STUDY DESIGN	FINDING
Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, et al., 1989 ^[4]	Case-control study	Acute Coronary Syndrome (ACS) cholesterol ($p < 0.001$) ACS-dental index ($p < 0.01$) ACS-smoking ($p < 0.01$) Odds Ratio – not calculated (after adjusting for smoking, socioeconomic class, serum lipids and diabetes)
Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S 1996 ^[24]	Cohort study	Odds Ratio = 1.5 95% Confidence Interval : 1.01-2.1 (after adjusting for age and cardio vascular disease risk factors)
Suresh, Thanikachalam, Ramesh, Manonmani 2000 ^[25]	Case-control study	Prevalence – 17% (seen in 140 patients with Ischemic Heart Disease)
Kiechl S, Egger G, Mayr M, Wiedermann CJ, Bonora E, Oberhollenzer F et al., 2001 ^[26]	Prospective study	Odds Ratio = 4.08 (adjusted to age and gender)
Sridhar, Byakod, Pudakalkatti, Patil 2001 ^[27]	Case-control study	No significant difference with respect to the lipid profile levels among the groups. Periodontitis in coronary heart disease patients did not seem to exacerbate the destruction of periodontal tissue
Lessem J, Driosko C, Greenwall H, Persson GR, Newman H, Smart G et al., 2002 ^[28]	Retrospective case series	76% of cases had periodontitis before heart transplantation
Nakib SA, Pankow JS, Beck JD, Offenbacher S, Evans GW, Desvarieux M et al. 2004 ^[29]	Epidemiological study	Odds Ratio = 1.595% Confidence interval : 0.5-4.2 Not statistically significant
Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR, Jr, Sacco RL., et al. 2005 ^[30]	INVEST (Oral infectious and Vascular disease Epidemiological Study) study	1000 subjects were studied without history of Myocardial infarction /stroke. Significant association demonstrated between bacterial load and sub-clinical atherosclerosis (after adjusting to the main risk factors for cardio vascular disease)
Beck JD, Eke P, Heiss G, Madianos P, Couper D, Lin D., et al. 2005 ^[31]	Cross-sectional study & a subset of participants in the Atherosclerosis Risk in Communities study	No association. Microbiologic data suggested significant odds ratios for some bacteria
Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand MJ 2008 ^[32]	Sub-group analysis of good quality studies	Independent association between periodontal disease and Coronary heart disease (with adjustment of all Framingham risk factors)
Balwant Rai, Kuldeep Singh Lallar, Simmi Kharb, 2008 ^[33]	Case-control study	Periodontal disease may show independent risk factors for coronary artery disease.

Most of the studies (using various epidemiological study designs) show periodontitis as a risk factor for CAD with different levels of Odds ratio. (Table 1) One of the recent and important studies on sub-group analysis of various studies by Humphrey et al., has found independent association between the two conditions after adjusting for all Framingham risk factors.^[32]

Table 2: Review of studies on the role of bacteria in periodontitis as a link to cardiovascular disease

AUTHOR	BACTERIA	TECHNIQUE EMPLOYED	RESULT
Haraszthy VI, Zambon JJ, Trevisan M, Zed M, Genco RJ. 2000 ^[34]	A. actinomycetemcomitans	Case series PCR analysis	61% - positive for bacteria; 36% were positive for P. gingivalis
Fiehn NE, Larsen T, Christiansen N, Holmstrup P, Schroeder TV. 2005 ^[35]	A. actinomycetemcomitans C. rectus, P. gingivalis, P. intermedia, P. nigrescens, T. forsythus, oral streptococci	PCR Technique	Viable oral bacteria could not be isolated from atheromas; DNA of periodontal pathogens was detected
Renvert S, Pettersson T, Ohlsson O, Persson GR. 2006 ^[36]	Subgingival pathogens were assayed	DNA-DNA hybridization	Oral bacterial load of S. intermedius, S. Sanguis, T. forsythia, T. denticola, P. gingivalis are concomitant risk factors in ACS
Pucar A, Milasin J, Lekovic V, Vukadinovic M, Ristic M, Putnik S et al., 2007 ^[37]	A. actinomycetemcomitans, C. pneumoniae, P. intermedia, P. gingivalis, T. forsythia, Cytomegalovirus	Clinical assessment of atherosclerotic degeneration were investigated	Absence of putative pathogenic bacteria in internal mammary arteries and they are present in higher percentage in coronary arteries

A review of studies depicted in Table 2 show the presence or absence of particular pathogens associated with periodontitis as a link to cardiovascular disease. Bacteria like oral Streptococci and other putative periodontal pathogens like Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Campylobacter rectus, Tannerella forsythus, Prevotella intermedia have been implicated.

Table 3: Review of studies on the role of infection and antibody titres in subjects with periodontitis in relation to CVD

AUTHOR	BACTERIA	RESULT
Furuichi Y, Shimotsu A, Ito H, Namariyama Y, Yotsumoto Y, Hino Y et al., 2003 ^[38]	A. actinomycetemcomitans, P. gingivalis	Significant association between antibody titre levels and risk markers for CVD
Pussinen PJ, Alfthan G, Tuomilehto J, Asikainen S, Jousilahti P 2004b ^[39]	A. actinomycetemcomitans, P. gingivalis	No association for IgA or IgG titres to A. actinomycetemcomitans and myocardial infarction found
Vilkuna-Rautiainen T, Pussinen PJ, Roivainen M, Petays T, Jousilahti P, Hovi T et al., 2006 ^[40]	Herpes simplex virus (HSV), A. actinomycetemcomitans, P. gingivalis	Combined HSV & P. gingivalis antibodies inversely correlated to high density lipoprotein (HDL)
Yamazaki K, Honda T, Domon H, Okui T, Kajita K, Amanuma R et al., 2007 ^[41]	12 different bacteria including P. gingivalis 381 & P. gingivalis SU63	High frequency of antibody positivity for P. gingivalis SU63 but not for P. gingivalis 381 disease subjects

Role of periodontal infection and estimated antibody titres in periodontitis subjects in relation to cardiovascular disease showed a varied pattern exhibiting high and low levels of antibody (Table 3).

INTERVENTIONAL STUDIES

Interventional studies have been undertaken after noting a strong association between periodontitis and coronary artery disease. Periodontitis may promote endothelial dysfunction as assessed by flow mediated dilatation of the artery.^[10] Studies have suggested that periodontal therapy may improve brachial artery flow rates in subjects with periodontitis but with no medically confirmed diagnosis of cardiovascular disease.^[42, 43, 44, 45, 46]

In a recent study, six months following non-surgical periodontal therapy with adjunct local antibiotics, no difference in plasminogen activator-inhibitor 1 was noticed.^[46] However, in another interventional study there was a decrease in plasminogen activator inhibitor and tissue plasminogen activator following tooth eradication.^[47, 48]

The association between periodontitis and intima media wall thickness (IMT) was put forward by Beck et al.^[49] The relationship between periodontal microbiology and

subclinical atherosclerosis (assessed by IMT) has been documented.^[30] No studies have assessed the result of periodontal intervention on the IMT.

REPORT ON META-ANALYSIS

Of all the epidemiological study designs, meta-analysis reports carry the highest weightage to draw conclusions about the research question. The findings of these meta-analysis with respect to the link between CAD and periodontitis have concluded the following:

1. Periodontal disease is a risk factor or marker independent of traditional CAD risk factors with relative risk estimates ranging from 1.24 to 1.35.^[32]
2. Significantly increased prevalence and incidence of CAD in patients with periodontitis raising the possibility that periodontitis independently predicts CAD.^[50]
3. Prospective and retrospective follow-up studies have shown that periodontal disease may only slightly increase the risk of CVD.^[51, 52]

SUMMARY : ASSOCIATION BETWEEN PERIODONTITIS AND CVD

1. The studies reported in literature have not shown that edentulous patients are at low risk for developing CVD.
2. The number of interventional studies carried out seem inadequate.
3. Studies on animals cannot be hundred percent extrapolated to humans owing to the varying environmental and genetic factors.
4. The confounding variables have not always been taken into consideration. (For example, both periodontitis and CVD are chronic diseases with common risk factors especially with tobacco smoking as this is significantly associated with both the diseases. Only studies with inappropriate adjustment to tobacco have found significant associations between periodontal disease and CVD).^[53]
5. The findings in various studies have not been consistent to prove the association.

As periodontitis continues to have a high prevalence within the population and the fact that CVD remains a major cause of human death in developed countries, in light of these associations we can legitimately based on evidence state that oral health has an influence on systemic health in general & in CVD in particular & therefore we should promote oral health in general periodontal health in particular as part of a healthy life style and hence as an important component in the prevention of CVD

Lot of interventional studies need to be carried out to reduce the risk as well as reverse the disease state. For further understanding, animal work should be translated to humans. Lastly, controlled prospective studies with large samples need to be conducted to possibly prove the association between periodontitis and systemic diseases.

A consensus report has been drafted jointly by the editors of The American Journal of Cardiology and the Journal of Periodontology and published simultaneously in both these journals.^[54,55] "Although the inflammation hypothesis provides a plausible and attractive explanation for the periodontitis-atherosclerosis relationship, further research is needed to define the mechanisms linking the two diseases and how patients with periodontitis should best be managed to reduce their risk for CVD".

A consensus document has also been put forward by the European workshop in periodontal health and cardiovascular disease.^[56] "Epidemiological studies have clearly shown a moderate but significant association between periodontitis and CVD. However, no compelling evidence suggest that preventive periodontal care or therapeutic intervention will influence cardiac health.

In conclusion, it could be asserted that in the years to come there would be a definite answer made possible through extensive research work and well established evidences to the eyebrow raising question "Periodontal infection – a real threat to cardio vascular disease!". There could be no doubt that this aspect gaining momentum would bring about the true causal rather than a casual relationship showing a remarkable breakthrough both in the fields of Medicine and Dentistry.

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