Role of Periodontal Infection in Cardiovascular Disease: a Current Perspective

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Abstract

Oral pathogens play a causal role in Cardiovascular Disease (CVD) that is largely driven by inflammation and host immune response. Clinico-epidemiological and animal studies provide a strong link between periodontal disease (PD) and CVD, both of which are highly prevalent, complex disease processes with common risk factors. Genes involved in inflammation, matrix degeneration and immune response have been implicated in the initiation and progression of both diseases. Recent studies have promoted the discovery of novel pathways and lead molecules thus providing opportunities for developing effective vaccine candidates to control disease progression. Following periodontal therapy, studies have shown reduction in the levels of pro-inflammatory cytokines and acute phase reactants, enhancement of endothelial function and lowered risk for future cardiovascular events. The above parallel provides a small yet important handle by which improvement in oral health can open up wider avenues for the overall betterment of systemic health.

Key words: oral pathogen, peridontal disease, cardiovascular disease, atherosclerosis, stroke.

Introduction

Over the last two decades, systematic epidemiological studies on humans and experimental animal models have shown irrefutable evidence of association between Cardiovascular Diseases (CVD) and chronic infections, oral pathogens being common among them [1-4]. Oral bacteria such as *Porphyromonas gingivalis* (Pg), *Aggregatibacter actinomycetemcomitans* (Aa), *Tannerella forsythia* (Tf), *Treponema denticola* (Td) and *Campylobacter rectus* (Cs) have been implicated in the aetiopathogenesis of Periodontal Disease (PD). A comprehensive list of some of the common oral pathogens implicated in PD is provided in Table I. Periodontal Disease causes tartar build up in the gums following infection by oral pathogens, while CVD involves the formation of plaque on the endothelial vessel wall due to lipid deposition, smooth muscle proliferation and tissue necrosis. This generates a chronic inflammatory and immune response, which contributes to the atheroma formation and the ensuing clinical complications. The extent of CVD risk has been equated to the 'pathogen burden' in an individual [5] and this concept has been extended to oral diseases. Periodontal disease is highly prevalent among older males, smokers and obese, diabetic individuals, suggesting that common risk factors tethered by an underlying inflammatory milieu

may link PD to atherosclerosis. The age-old belief of an association between chronic infection and vascular disease was re-established in 1989 in two concurrent reports that showed increased presence of surrogate markers of oral infection in patients with myocardial infarction (MI) [3] and poor oral health in patients who had had recent stroke events [6] as compared to healthy controls. This has provoked an intense debate on the causal vs. casual relationship between these two chronic diseases. The present review attempts to bring together an overview of our current knowledge on the role of oral pathogens in the aetiology of PD and CVD, obtained through clinico-epidemiological and experimental studies on humans and animal models. It also briefly summarizes the common genes and biomarkers, the underlying biological mechanism and the implications of therapeutics interventions.

Table I. List of common periodontal pathogens

S.No	Periodontal pathogen
Pathogens showing strong association with PD	
1	Porphyromonas gingivalis
2	Aggregatibacter actinomycetemcomitans
3	Tannerella forsythia
4	Treponema denticola
5	Campylobacter rectus
Pathogens showing weak association with PD	
6	Prevotella intermedia
7	Prevotella nigrescens
8	Micromonas micros
9	Fusobacterium nucleatum
10	Eikenella corrodens
11	Troponema socranskii
12	Bacteroides forsythus
13	Streptococcus sanguis
14	Peptostreptococcus micros
Pathogens associated with healthy periodontal conditions	
15	Veillonella parvula
16	Actinomyces naeslundii

Clinical and epidemiological studies that link periodontal disease and cardiovascular disease

Clinical manifestation of PD range from a mild form of gingivitis with swelling and bleeding of gums to severe forms that exhibit loss of gum attachment, gum recession and complete tooth loss, termed periodontitis. Matilla *et al*. published a pioneering report in 1989 that showed a significant association between oro-facial infections and myocardial infarction (MI) in Finnish men [3], that was subsequently confirmed through a follow-up survey of the same cohort [7]. Since then, large prospective studies [2, 7-10] and retrospective studies [11-13] on various populations have strengthened these initial findings. An overview of some of the key prospective cohort studies is provided in Table II. Studies have consisted of questionnaire-based surveys, popular observational retrospective analysis, and longitudinal follow-ups ranging from 6 to 21 years [2, 7, 10].

Table II. Overview of large cohort studies in relation to periodontal infection and CVD risk

Study [Reference]	Follow-up period [years]	Sample size	Association measure	Findings (95% CI)
NHANES I [2]	14	9760	RR 1.25 (1.06-1.48)	Significant association between dental disease and increased risk of CHD, particularly in men < 50 years
Finish Study [7]	7	214	RR 1.21 (1.08-1.36)	Increased risk of CHD in individuals with high TDI than those with low TDI
NHANES III [8]	–	5564	RR 1.4 (0.8-2.5) to RR 3.8 (1.5-9.7)	Significant increase in odds of heart attack with higher category of attachment loss
Nutrition Canada Survey [10]	21	10 368	RR 2.15 (1.25-3.72)	Poor dental health associated with increased risk of fatal CHD and CVD
Swedish population-based study [9]	–	4811	OR 1.57, $p = 0.0017$	Significant association between dental health and presence of CVD
Health Professionals follow-up study [20]	6	44 119	RR 1.04 (0.86-1.25)	No association between periodontal disease and CHD
NHANES I [19]	17	8032	HR 1.14 (0.96-1.36)	No strong evidence of causal association between Periodontitis and CHD
Physicians Health Study [21]	12.3	22,037	RR 1.13 (0.99-1.28)	Self reported periodontal disease was not an indepen dent predictor of Non fatal MI, stroke or CVD death

HR – hazard ratio, OR – odds ratio, RR – relative risk

While results gathered from questionnaires introduce recall bias, longitudinal studies of less than 10 years do not provide sufficient time for the clinical development of CHD [14]. In 1999, Offenbacher *et al*. coined the term 'periodontitis-atherosclerosis syndrome' in individuals with periodontitis who exhibited associated changes in cardiovascular pathology and proposed a model describing the possible mechanisms by which systemic inflammation and infectious challenge of periodontal origin may serve as potential modifiers of CVD [15]. A review of nine cohort studies published between 1980 and 2003 showed a combined relative risk (RR) of 1.9 (95% CI 1.08-1.32) for future CVD events and RR of 2.85 (95% CI 1.78-4.56) for stroke in individuals with PD as compared to controls [16]. In a recently published meta-analysis of seven large studies, Humphrey *et al*. opined that the RR estimate of CVD for different categories of PD ranged from 1.24 (1.01-1.51) to 1.34 (1.10-1.63), implying that oral disease could be an important marker for CHD independent of traditional risk factors [17]. A consensus report brought out at the 6th European Workshop on Periodontology in 2008 summarizes the current perspectives as follows: Lowered prevalence of periodontitis in recent years is related to improved oral hygiene; there is a positive association between PD and adverse pregnancy outcome; unanticipated diversity within pathogen species across ethnic groups complicates the interpretation of true positive associations; individuals with poorly controlled diabetes show greater disease severity; and finally, PD contributes to total infectious and inflammatory burden, which could progressively lead to a higher risk of CVD [18].

Two large-scale epidemiological studies, however, have shown contrasting findings (Table I) [19, 20]. In a 6-year follow-up by Joshipura *et al*., dental status was assessed by self-report of participants leading to an imprecise mode of oral health assessment. In the NHANES study, Hujoel *et al*. observed a non-significant increase in CHD risk among patients with periodontitis due to excessive adjustment for all potential confounders, which was corrected in the subsequent study by De Stefano *et al*. on the same cohort, wherein careful adjustment for confounders was done after close follow-up of disease progression for over 14 years [2]. Other large-scale studies involving over 12 years or more of follow-up have also shown that the association is largely dependent on common behavioural factors that can lead to false positive associations between oral health indicators and CHD [21, 22].

Dissection of unique predisposing environmental factors is critical for understanding the true relationship between PD and CHD. However, given that common confounding factors may enhance the risk of both diseases, it is important for dentists and cardiologists to create stringent classification criteria and yardsticks to methodically record clinical end-points and for epidemiologists to critically evaluate all potential confounding factors in parallel. The three disciplines must then work hand-in-hand to delineate the true association between these chronic diseases.

Experimental evidence of association

Experimental data from laboratories have shown a strong association between PD and CHD either through direct assessment and quantification of the oral microbiota in the subgingival plaque or measuring the systemic antibody levels against periodontal pathogens. In a comprehensive ten-year follow up of 6051 individuals from the FINRISK cohort, Pussinen *et al*. have shown a direct link between endotoxaemia induced by bacterial LPS and systemic inflammation leading to enhanced CVD risk [23]. Presence of Aa in both dental and atherosclerotic plaques has been obtained from the same subjects using a PCR based detection method [24]. Oral pathogens have been detected in atherosclerotic coronary tissue with comparable species in blood and atheroma samples [25, 26]. Species of *Streptococcus mutans* have been reported in dental vascular specimens in a recent Japanese study [27]. Some studies, however, failed to detect periodontal bacterial DNA in the atheromatous plaques [28, 29].

Sero-epidemiological evidence of an association between high antibody titres to Pg and risk of MI has been shown in a 10-year longitudinal study on the Kuopio ischaemic heart disease cohort, with the odds of MI increasing with increasing quartiles of IgA-class antibody titres from 2.47 to 3.99 when compared to the 1st quartile group [30]. High serum antibody titres to both Pg and Aa were associated with all stages of CHD ranging from subclinical CIMT measures to incident and future events of CHD [23], and with high plasma CRP levels in the NHANES II study [31]. Strong evidence of pathogen-induced CAD has been shown through the association of seropositivity to hepatitis C virus with 2- or 3-vessel obstructive CAD [32] as well as accelerated course of atherosclerotic vascular disease in familial Mediterranean fever [33]. Thus, there is ample support from experimental and clinical observations for the direct and indirect role of pathogens in the aetiopathology of both PD and CVD.

Periodontal disease in Stroke and other co-morbidities

Of the various modifiable factors that have been implicated in stroke risk, chronic infections through oral pathogens have evoked great interest in recent times. There have been several reports on the

association of periodontitis with ischaemic stroke in men and young adults [34], carotid atherosclerosis [35], incident stroke [23], as well as with peripheral arterial disease (PAD) [36]. Periodontal pathogens have been identified in carotid plaques [37]. Acute periodontal bone loss has been associated with a nearly 4-fold increased risk of carotid artery plaque (adjusted odds ratio 3.64, CI 1.37 to 9.65) [35]. Systemic exposure to Pg showed increased stroke risk in a longitudinal Finnish study on 6950 subjects between 45 and 64 years of age who were followed up for 13 years. They showed that the 109 subjects who were healthy at recruitment and had subsequently developed a stroke event had higher baseline antibody titres to Pg than the controls [38]. High serum levels of IgG titres to Cr and presence of pathogen in carotid plaques have been associated with increased mean CIMT in females [39, 40].

A strong association was observed between incident tooth loss and PAD in a 12-year follow-up of over 45,000 healthy men [36]. Periodontal disease contributed to over 20% enhanced risk of CVD, while the relative risk for stroke varied from 1.74 (95% CI 1.08-2.81) to 2.85 (95% CI 1.78-4.56) and that of peripheral vascular disease from 1.41 (CI 1.12-1.77) to 2.27 (CI 1.32-3.90), respectively, in a meta-analysis of studies published until 2003 [41]. Periodontitis was associated with 5-fold increase in risk of PAD after adjusting for potential confounders, which was attributed to the elevated levels of inflammatory cytokines [42].

Epidemiological studies have shown the impact of PD on other systemic conditions such as diabetes [43], obesity [44], metabolic syndrome [45] and adverse pregnancy outcomes [46, 47]. These studies provide supporting evidence of the intimate relationship that exists between PD and the traditional co-morbidities of CHD. Cardiologists and dentists are now coming together to address the growing concern of poor oral hygiene leading to increased CVD morbidity.

Table III. Genes and biomarkers belonging to pathways commonly associated with PD and CVD

Metabolic pathway	Genes	Biomarkers
Periodontal disease		
Inflammation	IL-1 [50], IL-4 [52], IL-4, IL-13 [49], IL-6 [53, 55], IL-10 [54], TNF-α, TGF-β1 [48], Cox-2 [51]	CRP, IL 6 [79]
Immunity	TLR 2, TLR 4 [56, 57]	TLR 2, TLR 5 [86], TLR 1-10 [85]
Matrix metalloproteinase	MMP 1 [59], MMP 1, MMP 3 [58]	MMP 9 [94], MMP 2, 8, 9 [93]
Prothrombotic factors	PAI-1 [70, 72]	PAI-1 [70, 96]
Growth factors	VDR [71, 73, 74]	Vitamin D [98]
Atherosclerotic disease		
Inflammation	IL-1β [63], IL-6 [64], TNF-α [62], Cox-2 [60, 78]	IL-6 [82], IL-6, hsCRP [83, 84], TNF-α [80, 81]
Immunity	TLRs [66], TLR 4 [69] TLR 9 [67]	TLRs [87-89]
Matrix metalloproteinase	MMPs [68], MMP 3 [65]	MMP 1 [91], MMP 3 [95], MMP 7 [92], MMP 9 [90]
Prothrombotic factors	PAI-1 [75, 76]	PAI-1 [75]
Growth factors	Vit. D [77]	Vit. D [97]

Cox-2 – cycloxygenase-2, CRP – C-reactive protein, IL – interleukin, MMP – matrix metalloproteinase, PAI-1 – plasminogen activator inhibitor-1, TNF-α – tumor necrosis factor-α, TGF-β1 – transforming growth factor-β1, VDR – vitamin D receptor, Vit. D – vitamin D, TLR – Toll-like receptor

Common genes implicated in periodontal disease and cardiovascular disease

Genetic factors that regulate basic biological processes represent one of the key mechanisms that link PD and CVD. In the last decade, a multitude of research articles ranging from small, cross-sectional studies involving less than 100 cases with PD and healthy controls to large population-based, prospective studies involving more than 2000 healthy volunteers followed up for nearly 15 years have identified several putative candidate genes and polymorphisms associated with chronic and aggressive periodontitis. These studies have shown that the disease phenotype is largely dependent on exposure to specific microbial and environmental agents, lifestyle factors and their interaction with the various genes that initiate and modulate the progression of disease. Table III lists some of the common genes and associated biomarkers implicated in both PD and CVD. The reported candidate genes associated with chronic, aggressive periodontitis code for proteins that play a role in inflammation [48-55], innate immune response [56, 57] and matrix degeneration [58, 59]. Involvement of similar pathways has been implicated in the aetiopathogenesis of CVD [60-69]. Other metabolic pathways involving coagulation and growth have been associated with PD [70-74] as well as CAD [75-77]. The above findings provide strong evidence of the prevailing complex interactions between the pathogens residing in the periodontal tissues and the host genome, which form the basis of susceptibility to PD that eventually impacts on other chronic disease states such as diabetes, metabolic syndrome and CVD.

The below examples showcase the common aetiopathological mechanisms that underlie PD and CVD. The cycloxygenase-2 (COX-2) gene on chromosome 1q25.2-q25.3 codes for cycloxygenase enzyme that catalyses the formation of prosta-

glandin E, a pro-atherogenic factor. A genetic variant, –765 G>C, in the promoter region of the COX-2 gene, has been associated with reduced risk of aggressive periodontitis in a recent Taiwanese study [51], lowered risk of MI and stroke in an Italian cross-sectional study [60] and lowered risk of cerebrovascular ischaemia in yet another independent Italian study [61]. In subjects with hypercholesterolaemia, a population that carries a high risk of developing CVD, a similar protective effect of the –765 G>C SNP was shown, where the 'C' allele was found to be associated with reduced CIMT scoring and lower CRP, IL6 and vWF levels [78]. This commonality in the underlying genotype-phenotype interactions throws open unique opportunities for developing common therapeutic targets that can control both diseases.

Biomarkers and other systemic conditions associated with periodontal disease

The association of periodontitis with CVD is mediated through markers of endothelial dysfunction and dyslipidaemia as indicated in the Health Professional Follow-Up Study [79]. Table III provides a brief list of some of the common biomarkers associated with PD and CVD. These biomarkers belong to pathways relating to inflammation [79-84], immune response [85-89], matrix degeneration [90-95], prothrombotic factors [70, 75, 96] and factors relating to growth [97, 98]. High prevalence of CVD has been shown in individuals in whom periodontitis coexists with elevated CRP levels, indicating that PD may be a risk factor for CVD in subjects who react to the presence of infection with a strong systemic, inflammatory and immune response [99]. The utility of CRP as a biomarker for enhanced risk prediction in CVD has been reiterated in a recent review by Packard and Libby [100].

Periodontitis has been shown to be negatively associated with serum levels of antioxidants such as vitamin C, bilirubin and total antioxidants [101]. In an interesting correlation between 8-hydroxydeoxyguanosine (8-OhdG) and oral pathogen load, Sawamoto *et al*. have shown that 8-OhdG could serve as a useful biomarker for accurately predicting the periodontal status and evaluating the efficacy of periodontal treatment [102]. Yet another study has shown a significant association of salivary cyclic nucleotide (cGMP and cAMP) levels with severity of PD along with other markers of oxidative stress [103]. Studies have shown that Pg is capable of stimulating low-density lipoprotein oxidation [104], foam cell formation [105], de-regulation of lipid metabolism [106] and rupture of atherosclerotic plaque through induction of matrix metalloproteinases [107]. Presence of high vascular endothelial growth factor (VEGF) levels was detected in the gingival cervical fluid in chronic periodontitis cases from India as compared to gingivitis patients and normal individuals [108]. In yet another recent study, plasma surfactant protein, which belongs to a class of humoral molecules of innate immunity, showed a strong association with chronic periodontitis [109].

Although many biomarkers have been detected to date in the circulation among patients with PD, they probably reflect an association derived as a consequence of disease progression rather than initiation. Further work based on large prospective studies with periodical, clinical and biomarker assessment may bring greater clarity in this regard.

Animal studies

Experiments on animal models of atherosclerosis and periodontitis have served as an ideal medium for testing hypotheses emanating from clinical studies. While the atherosclerotic mouse models such as the apo E knock-out (apoE $^{-/-}$) mice have shown that periodontal infections induce and exacerbate atherosclerosis, mouse models of PD have fostered our understanding of periodontal biology. Prolonged challenge with intravenous inoculation of live Pg promotes plaque progression in heterozygous apoE $^{-/-}$ mice [110, 111] and in hypercholesterolaemic pigs [112] as well as inducing intimal hyperplasia in iliac arteries of balloon-injured rabbit models [113]. In a study on drug-induced reactions in the oral cavity, a small Iranian study has shown that nifedipine, a commonly prescribed calcium channel blocker for CAD patients, induces gingival hyperplasia and subsequent salivary gland dysfunction in rats which can be controlled by activation of the NO protective mechanism via the cGMP-dependent positive signal transduction [114]. Lipid peroxidation has been shown to play a critical role in the induction of both periodontitis and atherosclerosis in rat models [115].

Exacerbation of PD has been shown to be mediated through IL-1 receptor (IL-1R) signalling [116] and the Toll-like receptor (TLR) pathway [117]. Pg has been shown to induce oral inflammatory bone loss in mice in the presence of TLR2, as well as accelerating atherosclerosis in hyperlipidaemic mice with elevated expression of TLR2 and TLR4 in the lesion, which provides novel targets for developing intervention strategies [118]. These studies suggest that Pg mediated PD and atherosclerosis are disparate diseases with commonalities in pathogenesis through the TLRs [119].

Mechanistic evidence for an association between oral pathogens and cardiovascular disease

Several hypotheses have been postulated to explain the underlying disease mechanisms, including common susceptibility factors, systemic inflammation

with increased circulating cytokines, direct infection and cross-reactivity or molecular mimicry between bacterial antigens and self-antigens.

Toll-like receptors

Up-regulation of TLR expression by endothelial and macrophage cells present in atherosclerotic lesions in response to invading pathogens is mediated through the nuclear factor-kappa B (NF-κB) receptor pathway and constitutes an important step by which innate signalling mechanisms operate to counter infections [120]. According to the cytokine theory, inflammatory mediators that are released by the immune cells in response to bacterial LPS play a key role in inducing damage of the endothelial vessel wall. The role of TLRs in mediating intracellular signalling has been independently demonstrated in several studies [121, 122]. This signalling triggers the transcription of pro-inflammatory and pro--aggregative cytokines such as PGE-2, IL-1, IL-12 and TNF-α, followed by the release of prothrombotic agents by the leukocytes and platelets. These compounds promote foam cell formation through monocyte chemotaxis and adhesion to the endothelial cell surface followed by lipid accumulation. TLR agonists of oral origin elicit a similar response as shown by the Pg fimbria induced TLR-dependent activation of NF-κB and up-regulation of the cytokines, chemokines and other pathogen recognition receptors (CD14, CD11b/CD18) in monocytic cells [121]. Gibson *et al*. have opined that engagement of the cell-specific inflammatory signalling pathway in Pg infections influences the localized innate immune signalling, leading to chronic inflammation and systemic involvement [123].

Other immune mechanisms

Pathogens manipulate the innate immune system of the host to promote their own adaptive fitness. The virulence of a pathogen is primarily contributed by its fimbria, which expresses native minor proteins, FimCDE [124]. The FimCDE allow Pg to exploit the TLR2/complement receptor 3 pathways for intracellular entry, inhibit IL-12 p70 and persist in the macrophages, while such a response is lacking in the mutant form [124]. Invasion of Pg on the endothelial surface triggers the humoral immune cross-reaction of antibodies to heat shock proteins (HSPs) derived from both bacterial mHSP65 and human endothelial HSP60, resulting in vascular endothelial injury [125]. Cross-reaction and T-cell specific response to Pg HSPs has been reported in CHD subjects with common T and/or B cell epitope specificity and in the peripheral blood of patients with atherosclerosis as well as in the atherosclerotic plaques [126, 127]. Recent studies involving IL-17, produced by a new class of T-helper subset Th-17, have been implicated in autoimmune disorders such as diabetes, CHD and periodontitis [128]. The IL-17 mediates adaptive immune processes through cooperation with TLR ligands, IL-1β and TNF-α, thereby enhancing the inflammatory reaction in defence against the invading microbes [129]. The IL-17 signalling pathway provides a potential therapeutic target to mitigate the inflammatory component of these chronic diseases [130].

In an eloquent dissection of the plausible causes of the association between oral pathogens and CVD, Haynes and Stanford proposed that common confounders, innate inflammatory mechanisms that predispose certain subsets of genetically susceptible individuals to inflammation driven disease conditions, shared humoral and cell mediated immunity and inoculation of oral pathogens into atherosclerotic plaque, resulting in plaque instability and subsequent rupture, may link these two diseases [131].

Cardiovascular health benefits of periodontal therapy

Non-surgical and surgical treatment of PD have been shown to not only improve oral health but also reduce the levels of CRP and IL6 and improve endothelial function [132, 133], which could translate into long-term benefits of reduced cardiovascular events. Reduction in serum E selectin levels has been shown in patients undergoing treatment for aggressive periodontitis [134]. Diabetic patients with periodontitis showed improved glycaemic control and reduced tendency of monocyte/ macrophage-driven inflammation following periodontal therapy, which could have a potential impact on atherosclerosis-related complications [135, 136]. Mechanisms that prevent binding of ligands to TLR4, block the interaction between TLR4 and signalling adaptors, and that block enzymes on one hand and cause immune stimulation with vaccine adjuvant on the other, have been considered as attractive therapy for atherosclerosis [137]. Immunization through the mucosal route raises the possibilities of developing effective and safe vaccines, given the recent advances in mucosal immunology in experimental animal models [138, 139]. Treatment with natural and synthetic forms of collagenase inhibitors such as matrix metalloproteinase inhibitor (MMPI) provides fresh hope for reducing CVD and stroke risk [140].

In summary, strong evidence of an association between pathogen-induced PD and CVD has been obtained through clinical and experimental studies. Close cooperation between the medical and research disciplines can generate a stringent clinical definition of PD and CHD, while well-planned longitudinal studies can help in the proper evaluation

of confounding factors so as to accurately assess the true association between PD and CVD. Preliminary studies on animal models have identified novel inflammatory and immune pathways that could be effectively used to improve risk prediction beyond traditional and well-established risk factors. A positive effect of periodontal therapy on cardiovascular health provides us with a potential alternative of redressing the global burden of CVD in the near future.

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