European Heart Journal Supplements (2010) **12** (Supplement B), B3–B12
doi:10.1093/eurheartj/suq003

# European workshop in periodontal health and cardiovascular disease—scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature

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**KEYWORDS**
Periodontal diseases;
Cardiovascular disease;
Oral health;
Systemic inflammation;
Cardiovascular events;
Periodontal pathogens

In the last 10 years, a rising number of epidemiological investigations have studied the possible association between chronic oral infections and cardiovascular diseases (CVD). These studies were based on the hypothesis that periodontal diseases (PD), may confer an independent risk for CVD. There is, however, still controversy whether these associations are causal or whether there are common aetiological factors common to both diseases (residual confounding). The objective of this paper was to review the possible association between PD and CVD on both the epidemiological association and the possible preventive and treatment implications.

Although the reported epidemiological studies have shown a significant, albeit week associations, we still lack properly designed clinical trials demonstrating that these chronic infections are independent factors of cardiovascular risk. The use of surrogate variables assessing the infective load and measures of subclinical atherosclerosis have clearly shown, not only a significant pathogenic relationship, but also a significant impact after periodontal therapy.

From a public health perspective, if further studies consistently identify PD as a risk factor for CHD and treatment studies show benefit, the implications are significant, since PD is mostly avoidable and treatable when not prevented. In addition, good preventive dental care has multiple other benefits, particularly on quality of life. Furthermore, identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate treatment of risk factors known to decrease CHD events in high-risk individuals and this might be significant given the high prevalence of PD in the population and the common problem of CHD.

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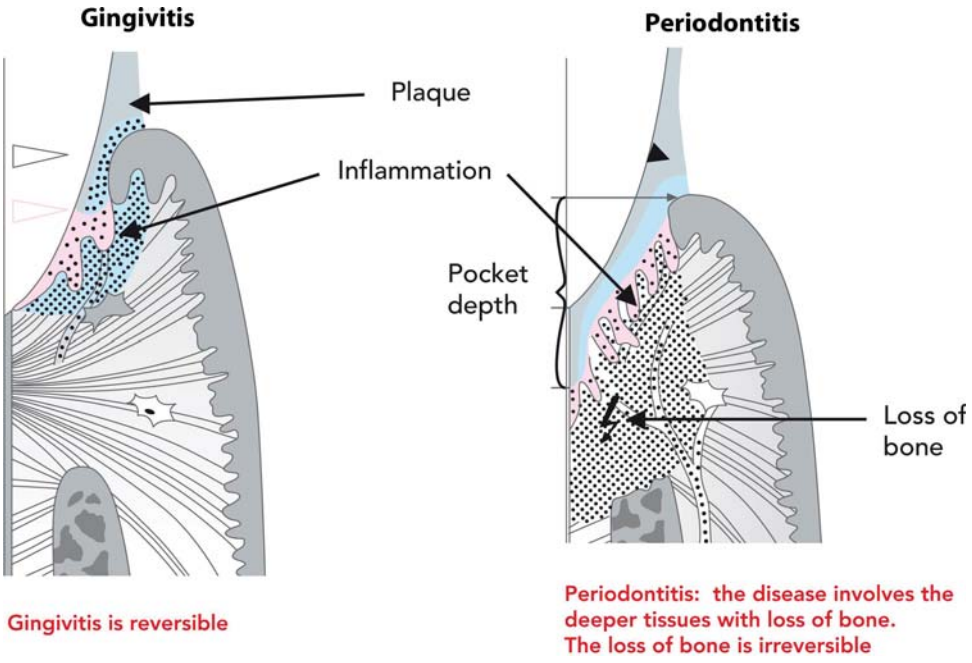


**Figure 1** Gingivitis is a chronic inflammatory condition affecting the supraalveolar periodontal tissues (gingival). It is characterized by the presence of an inflammatory infiltrate below the gingival margin. Its symptoms are reddening and bleeding of the gum line. It is a fully reversible condition, if the dental plaque causing the inflammation is removed. Periodontitis is a chronic inflammatory condition affecting deeper periodontal tissues (connective tissue attachment and bone). The destruction of the tooth attachment apparatus is usually irreversible. Its symptoms depend on the amount of periodontal destruction, often leading to pain, tooth drifting, and mobility.

## Introduction

In the last 10 years, a rising number of epidemiological investigations have studied the possible association between chronic oral infections and cardiovascular diseases (CVD). These studies were based on the hypothesis that oral infections, including periodontitis may confer an independent risk for CVD. As periodontal diseases (PDs) are among the most prevalent chronic infections in humans, there is a mounting scientific interest and public awareness of these possible interactions, mainly due to the likely public health implications if these associations were shown to be significant and clinically relevant. In fact, the World Health Organization (WHO) in its latest world assembly advocated the integration in the preventive and health promotion policies between oral and general health.[1] In a similar manner, the European Union has developed a program of future health promotion policies in chronic diseases including the most common oral diseases.[2] In USA, the General Surgeon '*Oral Health in America*' clearly emphasizes this approach of oral health as a fundamental part of general health.[3]

There is, however, still controversy whether these associations are causal or whether there are common aetiological factors common to both diseases (residual confounding). Nevertheless in the last 5 years, numerous publications have provided support to the hypothesis of a causal association, mostly through the evidence that bacterial pathogens derived from the sub-gingival biofilm are directly or indirectly, through the resulting host response, involved in the pathogenesis of the atheroma plaque formation. It is therefore, the objective of this paper to review the possible association between PDs and CVD on both the epidemiological association and the possible preventive and treatment implications.

## Periodontitis

Periodontal diseases comprise a large group of disorders of the periodontal tissues of a predominant infectious/inflammatory origin. Gingivitis, the most common form of gingival inflammation is a reversible inflammatory reaction of the dento-gingival tissues to bacterial plaque accumulation which resolves soon after the dental bacterial biofilm is disrupted.[4] Periodontitis, in contrast to gingivitis, is a chronic inflammatory reaction of the same compartment involving not only superficial gingival tissues but also periodontal ligament and the alveolar bone (*Figure 1*). It is a rather symptomless condition with gingival bleeding and swelling representing the most common reported symptoms. Gingival recession, drifting of teeth, mobility, and suppuration are instead, signs often associated with an advanced form of periodontitis due to progressive destruction of the dental supporting tissues. This is because if left untreated, periodontitis results in a progressive deepening of the gingival sulcus associated to alveolar bone destruction up to the apex of the tooth which eventually ends with its loss (tooth exfoliation).[5]

### Pathophysiology

Periodontitis diagnosis is predominantly based on clinical and radiographic measures. Accurate assessment of the dento-gingival condition is often performed by a trained

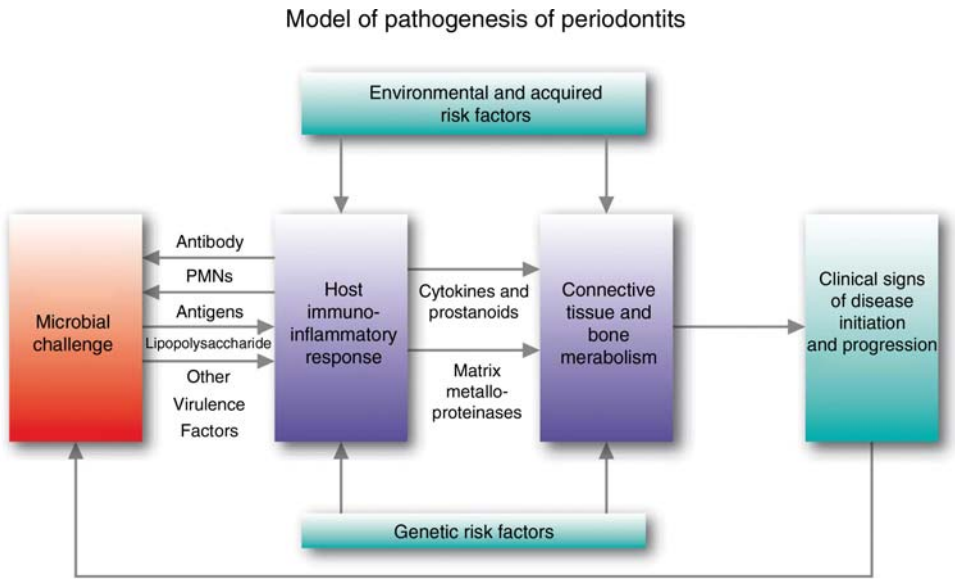


**Figure 2** Model of pathogenesis of periodontitis (adapted from Kornman *et al*. Journal of Periodontology 2008). Although the bacteria are the main aetiological agents, most of the tissue destruction occurs as a consequence of the host immuno-inflammatory response against the microbial challenge. This response is modulated by both genetic and environmental risk factors.

examiner including recording of the depth of the gingival sulcus around each tooth, presence of gingival bleeding. This is then confirmed by radiographic assessment of the alveolar bone levels of all dentition.

The prevalence of periodontitis is reported to be between 20 and 50% of the worldwide population.[6] The lack of a unique case definition for periodontitis is most probably responsible for the lack of more precise estimates in prevalence among different populations and countries.[7] In Europe, the prevalence estimates seem not to differ from those reported in the USA with the more severe forms of periodontitis (aggressive) limited to a small proportion ($<$10%) of the population.[8,9]

Periodontitis is a chronic 'infectious/inflammatory' disease of multifactorial aetiology.[10] Although bacterial accumulation and organization in the dental biofilm is the initiator, the host-mediated cell-mediated immune response in the gingival produces the destruction of the deeper periodontal tissues. Activated leucocytes in the gingival tissues are responsible for the generation of disproportionate amounts of inflammatory mediators including cytokines–chemokines and matrix-metalloproteinases promoting soft and hard tissue destruction[11] (*Figure* 2).

A number of potential risk indicators that could be associated with PD but are not proven to be causative have been identified, such as (i) increasing age,[12] (ii) specific periodontal pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Fusobacterium nucleatum*,[13,14] (iii) ethnic minorities,[15] (iv) low socio-economic status,[16] (v) male gender,[17,18] and (vi) stress.[19,20] Recent evidence suggests that common cardio-metabolic risk factors including body weight,[21,22] dyslipidaemia,[23] and hypertension[24] as individual components or clustered in the metabolic syndrome are also associated with increased odds of prevalence of periodontitis.[25]

In terms of periodontitis-associated true risk factors (not including dental plaque accumulation), significant evidence exists on the role of cigarette smoking[26–28] and diabetes mellitus.[12,29]

Current cigarette smokers exhibit some degree of alteration in the gingival microcirculation[30] and alteration of immune local defences including increased adhesion molecules production, neutrophil counts, and local inflammatory mediators.[31] Nicotine might directly affect inflammatory host cells as well as fibroblasts cell structure and function and wound healing processes.[32]

Prevalence and severity of PDs are overrepresented in people with diabetes mellitus.[33] Metabolic control of diabetic individuals directly influences the severity and extent of periodontitis.[29] Animal experimental models have shown that glycation products of proteins can stimulate an inflammatory response.[34] Blockage of these products has also been associated with a reduced periodontal destruction.[35] Independent epidemiological surveys have demonstrated that the incidence[36] and prevalence[29,37] of type 2 diabetes is at least doubled in subjects with periodontitis when compared with unaffected populations. Severe periodontitis was associated with an increased risk of diabetic complications (nephropathy) and morbid mortality.[38] There appears to be, however, no conclusive evidence suggesting that effective periodontal therapy will predictably improve metabolic control.[39]

Genetic factors might play the most important role in the expression of periodontitis. Evidence from twins studies suggested that genetic factors explained a substantial proportion (almost 59%) of the variation in the severity and extent of periodontitis.[40–42] Mutations of the cathepsin C gene have been clearly associated with early onset periodontitis and premature loss of the deciduous and permanent dentitions.[43–45] Furthermore, genetic variants in the pro-inflammatory [i.e. interleukin

(IL)-1, IL-6, and tumour necrosis factor (TNF)-α] genes have been identified as potential risk factors for periodontal destruction.[46]

### Treatment

The combination of supra- and sub-gingival root debridement with oral hygiene instructions is the most effective therapy in eradicating periodontal infection and control gingival inflammation.[47–49] After a period of healing, if residual periodontal infection is found, then localized periodontal surgery may be required to gain access for removal of bacterial deposits and biofilm on the root surfaces. Sometimes tissue regeneration procedures could be combined at this stage to attempt re-establishment of some of the lost periodontal tissues.

Use of systemic antibiotics has proven to be effective in eradicating specific pathogenic periodontal bacteria[50,51] and being associated with greater reductions in clinical periodontal parameters in combination with mechanical periodontal therapy.[52,53] Clinicians, however, limit their use only to those patients who have not responded to the mechanical therapy alone or in the most aggressive form of the disease.[54,55]

The recognition of the important role of the host in the pathogenesis of periodontitis and its response to therapy has created the opportunity to explore the impact of adjunctive use of host modulation treatments with mechanical periodontal therapy.[56] Targeting the arachidonic acid metabolites cascade with non-steroidal anti-inflammatory drugs has been shown to reduce gingival inflammation and PD progression.[57] Similarly sub-antimicrobial long-term (3 months) doxycycline administration, known to downregulate collagenase activity without generation of microbial resistance, has been associated with greater improvements in clinical periodontal parameters.[58–60]

Successful periodontal therapy is, however, ultimately achieved only when resolution of the gingival inflammation is maintained over a long period of time. Supportive periodontal therapy phase is usually tailored to patients' needs and usually consists of continuous reinforcement of oral hygiene, repetitive scaling and root planning, and control of risk factors at regular intervals (3–4 months).[61]

## Periodontitis and cardiovascular diseases

Cardiovascular diseases are the main cause of death in the world, being responsible of 16% of these deaths in developing and 50% in developed countries. More than 70 million North American have CVD, including 7 million with coronary heart disease (CHD) and more than 5 million suffering from stroke. The scientific community constantly search for novel pathobiological mechanisms in the development of the atheroma lesion in particular to those related to inflammation. Indeed inflammation is the initiating process of the atheroma formation and chronic infections including periodontitis might influence both systemic or vascular inflammation processes. This may also help understanding the complex interplay between recognized (i.e. age, gender, lipids, obesity, diabetes, cigarettes smoking) and novel cardiovascular risk factors.[62]

One of the biological mechanisms under investigation is the possible role of chronic infections in CVD.[63] Under this hypothesis, chronic infections and their associated inflammatory processes can directly influence the physiopathology of atherosclerosis and thus alter CVD risk. Kiechl *et al*.[64] showed in a population-based prospective study that the presence of various chronic infections amplified significantly the risk of aortic atherosclerosis progression (OR: 4.08 adjusted to age and gender; IC: 2.42–6.85).

The source of bacterial pathogens responsible for the most prevalent chronic infections affecting humans, caries, and PDs, derives from the adhered bacterial populations to the tooth surfaces consisting on biofilms with a bacterial density of about $10^{11}$ UFCs/mg. These bacterial communities are among the most complex existing in nature, due in part to the non-shedding nature of tooth surfaces that allow the development of a persistent bacterial colonization and, to the rather complex ecosystems that exist in the oral cavity, mostly in the periodontal environment. Within this biofilm, there is a dynamic co-existence between pathogenic and commensal bacteria, both being well protected from the physical and chemical natural barriers, as well as the host cell defences.[65] In close vicinity with these biofilms lies the epithelial component of the gingival sulcus wall or periodontal pocket in patients with periodontitis. This well-defined anatomical compartment, so called gingivodental interface, is an area especially prone for bacterial dissemination into the systemic circulation. In fact, Hujoel *et al*.[66] have calculated in patients with periodontitis the surface area of the dento-gingival epithelium exposed to bacterial invasion or infiltration of microbial antigenic components, which could be an area ranging between 8 and 20 $cm^2$.

Transient bacteraemia has been reported in clinical trials after different preventive and therapeutic dental procedures, such as after scaling and root planing, periodontal surgery, and dental extractions.[67] Although the focus has been mainly on therapeutic procedures as the cause of bacteraemia, recent studies have suggested that everyday events such as chewing and tooth brushing contribute more significantly to the cumulative exposure of the vascular system to the oral bacteria.[68] Although most of the bacteraemias are transient, it has long been recognized that bacteria in the blood stream may cause distant site infections. Several studies have demonstrated the presence of certain oral bacteria in atherosclerotic plaques and abdominal aortal aneurysms, in particular species implicated in the pathogenesis of periodontitis.[69–71] Recently, prospective studies have also provided serological evidence that infections caused by major periodontal pathogens like *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* are associated with future stroke,[72] increased risk of myocardial infarction,[73,74] and acute coronary syndrome (ACS).[75]

These bacteria may not only colonize distant sites, but also their components will elicit a host-tissue response characterized locally by a dense infiltrate of neutrophils,

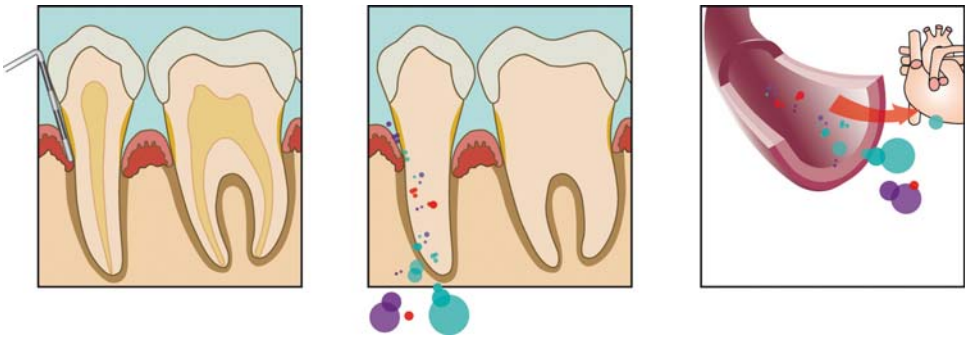

**Figure 3** Model of pathogenesis of periodontitis—ischaemic cardiovascular diseases. Bacteria residing at the subgingival biofilm–gingival interface may disseminate systemically and influence directly or indirectly the atheroma pathophysiology. Lipopolysaccharides and other products from Gram-negative bacteria may stimulate systemic inflammation that would eventually act directly and/or indirectly on the vascular walls inducing a state of endothelial dysfunction. Bacteria themselves, once in the blood stream may cause distant site infections. Several studies have demonstrated the presence of certain oral bacteria in atherosclerotic plaques and abdominal aortal aneurysms.

macrophages, and different lymphoid cells. These cells together with the adjacent host-tissue cells will subsequently elicit an immune–inflammatory response with the release of different cytokines and prostanoids, such as IL-1, IL-6, IL-8, TNF-$\alpha$, prostaglandin E2, and different matrix metaloproteinases, which play a pivotal role in the connective tissue and bone destruction occurring in the periodontal lesion. These bacteria and released metabolites beyond this potential local pathogenicity may disseminate systemically and influence directly or indirectly the atheroma pathophysiology (*Figure 3*). In fact, lipopolysaccharides and other products from Gram-negative bacteria may stimulate cytokine production, hypercoagulability, monocyte activation, and liver activation by releasing acute phase proteins, such as C-reactive protein. This repeated systemic exposure of orally derived bacteria, bacterial endotoxins, and systemic inflammation would eventually act directly and/or indirectly on the vascular walls inducing a state of endothelial dysfunction. Considerable *in vitro* and animal model evidence supports a plausible set of mechanisms by which periodontal bacteria may contribute to CVD. It includes blood-platelet aggregation, enhanced low-density lipoprotein and cholesterol deposition in the arterial wall, as well as direct invasion of the cardiac and carotid endothelium.[69,76,77]

## Epidemiological association

In the last 20 years, an important number of clinical studies, mainly cross-sectional and case–control have shown positive associations between PD severity and CVD. In the last 5-years, several systematic and narrative reviews have gathered and synthesized this evidence linking PDs and CVD.[78–83]

Bahekar *et al.*[78] in a recent systematic review included studies defining cases as subjects with fatal or non-fatal CHD and exposure as subjects with PD defined either by clinical assessment of oral health or self-reported PD. They identified five prospective cohort studies (follow-up >6 years), five case–control studies, and five cross-sectional studies that were eligible for meta-analysis. Meta-analysis of the five prospective cohort studies (86 092 patients) indicated that individuals with PD had a 1.14 times higher risk of developing CHD than the controls (relative risk 1.14, 95% CI 1.074–1.213, $P < 0.001$). The case–control studies (1423 patients) showed an even greater risk of developing CHD (OR 2.22, 95% CI 1.59–3.117, $P < 0.001$). The prevalence of CHD in the cross-sectional studies (17 724 patients) was significantly greater among individuals with PD than in those without PD (OR 1.59, 95% CI 1.329–1.907, $P < .001$).

Humphrey *et al.*[80] also published recently a systematic review selecting only prospective cohort studies (seven) that assessed PD, Framingham risk factors, and CHD incidence in the general adult population without known CHD and carried out meta-analysis. Summary relative risk estimates for different categories of PD (including periodontitis, tooth loss, gingivitis, and bone loss) ranged from 1.24 (95% CI 1.01–1.51) to 1.34 (95% CI 1.10–1.63).

It is notable that results from both meta-analysis are similar and also consistent with older meta-analyses that have shown summary relative risks in the 1.15–1.19 range,[81] showing that PD is an independent, though relatively weak, risk factor for CHD conferring approximately a 24–35% increase in risk of CHD.

One of the main weaknesses identified by these authors in the available clinical evidence is the exposure misclassification that may result in underestimation of the true risk associated with PD. In fact, identified three levels of quality dependent from the appropriateness in the reporting of the exposure (assessment of PD), the measurement of outcome (cardiovascular event) and other quality criteria.[84] This critical appraisal would significantly limit the available evidence, as very few studies have assessed adequately the degree of exposure (PD severity) and in most of them the sample size was small and these investigations did not assess properly drop-out rates or did not updated regularly the degree of exposure throughout the study.

Another limitation is incomplete adjustment for all Framingham risk factors in some of these studies. In spite of this, Humphrey *et al.*[80] performed a subgroup analysis of the good quality studies with adjustment for all Framingham risk factors, and an independent association between PD and CHD was identified. This matter is, however, still controversial, because both periodontal

and CVD are chronic diseases with common risk factors. This fact is especially relevant to tobacco consumption, as this risk factor is significantly associated in both disease processes. In fact Hujoel *et al*.[85] have stated that only studies with inappropriate adjustment to tobacco have found significant associations between periodontal and CVD. More recent studies, however, adjusting both to dosage and time, have again showed significant associations between periodontitis and CVD.[86,87]

Periodontal diseases have also been implicated as a risk factor for stroke as well as carotid atherosclerosis. In the two meta-analysis including these outcomes,[81,88] results were slightly greater than for coronary artery disease, with mean estimations of risk ranging between 1.54 for stroke and 1.5 for peripheral arterial disease, although the number of studies is small.

Longitudinal studies with standardized measures of PD and careful follow-up and adjustment to known confounders will be the ultimate step to clarify the link between CVD and PDs.

## Use of surrogated variables

Braunwald *et al*.[89] studied the surrogated variables with highest predictive value for future cardiovascular events with the purpose of their use as markers of cardiovascular risk in clinical trials and preventive programs. These markers are mainly serum proteins involved in the pathophysiology of atherosclerosis such as: C-reactive protein, homocysteine, plasma fibrinogen, factor VII, plasminogen activator inhibitor-1, D-dimers, and lipoproteins. Among these, C-reactive protein has been the most studied and has been the focus of attention as a key marker of atherosclerosis risk with elevated levels (e.g. $\geq$2.1 mg/L) demonstrating a significant risk predictor for CVD.[90] Danesh *et al*.[91] carried out a systematic review and meta-analysis with all published studies evaluating the levels of C-reactive protein and its relationship with future cardiovascular events, demonstrating a significant association with a mean risk estimate of 1.9 (IC 1.5–2.3).

Elevated levels of this protein are also significantly associated with PD severity[92,93] and with the presence of periodontal pathogens in patients with severe periodontitis.[94] A recent systematic review investigated the association between plasma/serum levels of C-reactive protein and destructive PD.[95] It included both cross-sectional (case–control) studies in humans (plasma/serum C-reactive protein levels in periodontitis patients and control subjects) and longitudinal (treatment) studies: randomized-controlled trials and controlled clinical trials (C-reactive protein levels before and after periodontal therapy) resulting in 18 suitable papers. The majority of the studies showed that C-reactive protein levels are consistently higher ($>$2.1 mg/L) in periodontitis patients than in healthy or gingivitis controls. The meta-analysis of 10 cross-sectional studies showed that the weighted mean difference (WMD) of C-reactive protein between patients and controls was 1.56 mg/L ($P < 0.00001$). Evidence from available treatment studies[6] showed lower levels of C-reactive protein after periodontal therapy with a WMD of reductions of C-reactive protein after therapy of 0.50 mg/L (95% CI 0.08–0.93) ($P = 0.02$).

Using this marker (C-reactive protein $\geq$ 3 mg/L) in patients with periodontitits, Ajwani *et al*.[96] showed a highly significant association (odds ratio of 3.80, IC 2.84–15.94) with a future CVD event, once adjusted for all Framingham risk factors. Results with this marker, however, have not been so clear in other studies and because it is a risk marker for both disease processes it is not obvious whether to use it as a marker of exposure or a marker of outcome.[97]

As a clear marker of exposure and based on the hypothesis that the periodontal pathogens from the subgingival biofilm once they invade the tissues may disseminate systemically and influence atherogenesis, some authors have used the infective load at the subgingival biofilm, assessing either the presence and quantity of periodontopathogenic bacteria or indirectly by evaluating the host-tissue response through the assessment of the antibody levels against these putative bacteria.

Renvert *et al*.[75] assessed the total bacterial load and the presence of periodontal pathogens, demonstrating a significant association in patients with ACS. Similarly, Spahr *et al*.[98] measuring the log 10 of all pathogens as a measure of the total bacterial load, found a positive association with CHD (OR 1.92; IC 1.34–2.74). When assessing specifically the amount of *A. actinomycetemcomitans*, the degree of association raised (OR 2.70; IC 1.79–4.07).

The most frequently used surrogate variable for exposure has not been, however, the measurement of infection, but rather the immunological host response against the main periodontal pathogens, thus demonstrating the systemic exposure of these bacteria. Pussinen *et al*. has reported significant associations between elevated levels of antibodies (IgA and IgG) against *P. gingivalis* and cardiovascular events (MI) (OR 3.3)[73] and between elevated levels of antibodies (IgA and IgG) against *A. actinomycetemcomitans* and cardiovascular events (MI) (OR 2.4).[99] Recently, these authors have reported a significant association between these elevated antibody levels (*Pg*) and stroke.[72]

A systematic review has recently evaluated all studies (including both cross-sectional and prospective cohort) that have used surrogate variables of periodontal bacterial exposure on future risk of CVD events.[83] Fourteen studies were selected, where in seven CHD was the outcome measurement, four stroke, and three subclinical atherosclerosis by measuring the carotid intimae media thickness (IMT). The meta-analysis resulted in a significant association between PD, as assessed by measures of bacterial exposure, and CVD with a mean risk estimate of OD 1.75 (IC 1.32–2.34).

Similarly, surrogate markers of subclinical atherosclerosis have been employed in several clinical trials proving the beneficial effect of various intervention including cholesterol-lowering drugs on progression of atherosclerosis. The most used marker has been the carotid arterial wall thickness. As this artery is easily

accessible for its study by high-resolution ultrasounds and the assessment of the intimae-media reliably reflects subclinical atherosclerosis when its width reaches a pre-established threshold ($\geq$1 mm) (IMT). Using this variable of outcome, several studies have shown significant associations with both periodontitis,[100] tooth loss[101,102] and with the presence of a systemic exposure of periodontal pathogens.[103]

In the INVEST study (Oral Infectious and Vascuar Disease Epidemiology Study*)*,[97] more than 1000 subjects without a history of stroke or MI were studied by the evaluation of periodontal pathogens from subgingival plaque samples and by assessing subclinical atherosclerosis through high resolution B-mode ultrasounds and systemic inflammatory markers in serum. After adjusting to the main risk factors for CVD, a significant association was demonstrated between bacterial load and subclinical atherosclerosis, being these associations specific and demonstrating a dose–response relationship between the upper tertile of the aetiological bacterial load (periodontal pathogens) and the upper level of IMT.

## Intervention studies

Proving a causal link between PD and CHD will require large randomized controlled trials in which individuals are randomized to treatment vs. usual care of PD and followed carefully for CHD events. However, there are important ethical considerations as well as feasibility issues related to a randomized trial of an intervention known to be of benefit for reasons other than the question under study. Data from a secondary prevention trial termed PAVE (Periodontitis and Vascular Events) on a cohort of individuals with prevalent CHD and has been recently reported.[104,105] This multicentre study carried out in five clinical centres has recruited subjects with documented history of CHD and PD. These patients were randomized to receive either non-surgical periodontal therapy (experimental group) or basic oral primary care (control group). These preliminary results report adverse effects and cardiovascular events at 3 and 6 months. There were 15 adverse effects with a non-significant higher percentage in the primary care (control) (6.6 vs. 3.3%). These results are, therefore, very preliminary and do not allow for any valid conclusion.

In order to overcome some of the difficulties that make these intervention clinical trials almost unfeasible, some authors have used surrogate variables as outcome variables after periodontal therapy, indicating a likely less risk of a CVD event or an improvement in the systemic inflammatory status or an improved vascular response. As a measure of improved systemic inflammatory status, different authors have studied the reductions of C-reactive protein after periodontal therapy. Several clinical trials have shown a significant reduction of C-reactive protein levels and other inflammatory markers in serum after periodontal therapy[106–109] and after total tooth extraction.[110,111]

As marker of vascular response some authors have used the evaluation of the endothelial function by physical means. This test is a reliable assessment of vascular function and it is carried out in the brachial artery after its flow-mediated dilation (FMD) and assessment by ultrasounds. Clinical trials using this outcome measurement have demonstrated that the vascular response significantly improves after periodontal therapy.[112–115] It is especially relevant the clinical trial recently published by Tonetti *et al*.[115] where 120 subjects were selected on the basis of a severe periodontitis diagnosis. They were then randomly assigned to receive either an intense periodontal therapy, including full mouth subgingival debridement and locally delivered antibiotics, or primary periodontal care. As outcome measurements, they studied at different intervals, up to 6 months post-therapy: periodontal outcomes in order to evaluate the efficacy of periodontal therapy, vascular outcomes by means of FMD and inflammatory and coagulation biomarkers in serum. Immediately after treatment (24 h), the vascular response was significantly worsened in the intensive periodontal treatment group, compared with the control and serum levels of C-reactive protein, IL6, soluble E-selectin, and Von Willebrand factor were significantly higher in this experimental group. Throughout the study, however, the FMD values improved and beyond 60 days they were significantly higher than the control group. The degree of improvement in vascular function was significantly correlated to the degree of improvement in the periodontal parameters ($r = 0.29$ in Spearman rank test, $P = 0.003$), which in the intensive treatment group were significantly better than in the primary care group. This study clearly shows that periodontal treatment causes an acute bout of systemic inflammation, followed by a significant improvement in endothelial function. Just recently an uncontrolled clinical trial has also proposed a positive effect of periodontal therapy on the progression of atherosclerosis as assessed by IMT. Indeed a reduction of IMT was observed and 12 months after periodontal therapy.[116]

## Conclusions

A bulk of evidence has emerged in these last 10 years revealing the possible associations between periodontal infections and CVDs. Although the reported epidemiological studies have shown a significant, albeit week associations, we still lack properly designed clinical trials demonstrating that these chronic infections are independent factors of cardiovascular risk. The use of surrogate variables assessing the infective load and measures of subclinical atherosclerosis have clearly shown, not only a significant pathogenic relationship, but also a significant impact after periodontal therapy.

From a public health perspective, if further studies consistently identify PD as a risk factor for CHD and treatment studies show benefit, the implications are significant, since PD is mostly avoidable and treatable when not prevented. In addition, good preventive dental care has multiple other benefits, particularly on quality of life. Furthermore, identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate treatment of risk factors known to decrease

CHD events in high-risk individuals and this might be significant given the high prevalence of PD in the population and the common problem of CHD.

**Conflict of interest**: none declared.

## Funding

This workshop has been made possible by an unrestricted grant from Colgate Palmolive Europe.

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