EXPERT REVIEWS

Why should a doctor be interested in oral disease?

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Oral health has been implicated in systemic disease throughout the ages; however, the understanding of the relationship between oral disease and systemic diseases such as cardiovascular disease and Type 2 diabetes mellitus is still emerging today. Chronic periodontal disease is widespread in the general population and a significant proportion of adults suffer from the most severe form of the disease. Dental plaque biofilm is necessary for the development of chronic periodontal disease with genetic and environmental factors contributing towards the pathogenesis. The putative biological mechanisms of the association between oral disease and atherogenesis are discussed, although there is insufficient evidence to establish causality at this time. Regardless of a direct causal relationship between oral disease and cardiovascular disease, treatment of oral disease leads to both a reduction in the systemic inflammatory burden as reflected in inflammatory markers and an improvement in endothelial function and hence improved overall health outcomes. A brief overview of periodontal disease including etiology, pathogenesis, screening and therapeutic implications is presented.

Keywords: cardiovascular disease • inflammation • molecular mimicry • periodontal disease

In 1965, an article published in the *American Heart Journal* entitled 'The necessity for effective dental health service in cardiology' opened with the following statement: "In almost all ailments of the heart caused by bacteria the source of the infection is known to be the pathologic and infected environment of the teeth" [1].

Although this paper by Bass was directed towards the prevention of infective endocarditis, the sentiments regarding the importance of dental health by meticulous oral hygiene in preventing infection in susceptible patients are as relevant today as they were at that time. He went on to make the following comment: "I believe that, at some time in the future, leading cardiologists will wonder, in retrospect, how information so greatly needed by many of their patients could have been overlooked or neglected for so long."

More than four decades later, this wisdom has been realized. It is now widely accepted among the medical and dental literature that oral disease is associated with systemic illnesses including atherogenic cardiovascular diseases (CVDs), Type 2 diabetes mellitus and diabetic nephropathy [2–8]. Research into the putative biological mechanisms of these relationships is now being carried out around the globe and these mechanisms will be discussed in this article. With CVD imposing major personal and economic burden and being the number one cause of death in many societies [101], it is of particular relevance that this research continues and appropriate preventive and therapeutic protocols are developed.

The aim of this article is to highlight the link between periodontal disease and CVD, including a brief overview of the putative biological mechanisms, to raise awareness of this and its therapeutic implications among medical practitioners. It is not the intention to provide a detailed review of specific mechanisms that are available elsewhere (for review see [9]), but rather to add an additional facet that is key to the long-term prevention of the chronic disease burden.

A schema that outlines the proposed links between oral and systemic disease is shown in Figure 1.

What is periodontal disease?

Periodontal disease is the term given to a disease process affecting the supporting tissues of the teeth, including gingivae, periodontal ligament, cementum and alveolar bone. The majority of the pathology found in the periodontal tissues is caused by the dental plaque biofilm resulting in the disease entities gingivitis and periodontitis. Accumulation of dental plaque around and beneath the gingival margins of teeth results in

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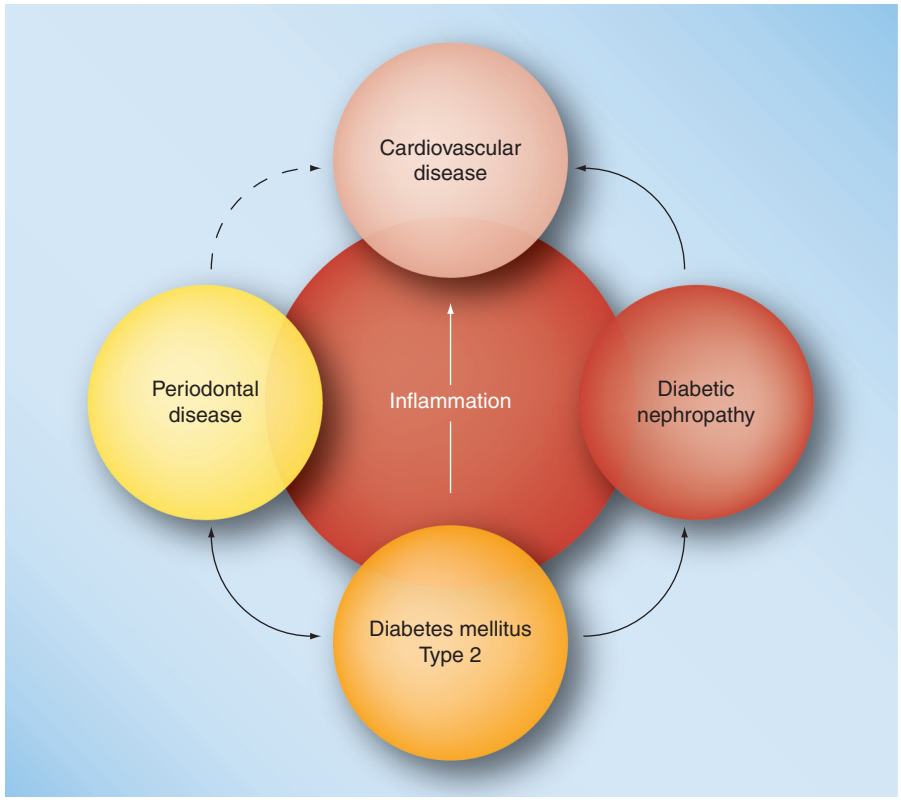

Figure 1. Inflammation as the link between oral and systemic diseases. The association between oral disease and systemic diseases such as cardiovascular disease and Type 2 diabetes mellitus is centered around systemic inflammation.

an inflammatory reaction called gingivitis. Gingivitis is characterized by the classic signs of inflammation – redness, swelling and increased vascularity. The clinical picture of gingivitis shows red, swollen gums that bleed easily when brushed or probed (Figure 2A). This contrasts sharply with healthy gingival tissues which are pink, firm, do not bleed and are closely contoured to the cervical region of the teeth (Figure 2B). Many individuals can suffer from gingivitis for long periods of time and be unaware of its presence as it is largely asymptomatic, with bleeding on brushing being the most evident sign. However, if gingivitis is ignored it can progress to periodontitis in some individuals. Chronic periodontitis or periodontal disease is a more serious and damaging condition that causes destruction of the tooth-supporting tissues – periodontal ligament and alveolar bone – and can ultimately result in tooth loss. Periodontitis is characterized by loss of attachment of the supporting structures resulting in gingival recession, pocket formation, tooth mobility and migration (Figure 2C). Periodontitis is irreversible and in susceptible individuals it can progress to tooth loss. Genetic and environmental factors such as smoking and stress also contribute to an individual's susceptibility to chronic periodontitis (Figure 3).

Reported prevalence rates for periodontitis vary considerably around the world depending on the population and age group studied and the disease criteria used; however, they indicate that mild to moderate forms of periodontitis occur most commonly, with prevalence rates of 13–57% [10]. Severe periodontitis is generally believed to be less common; however, recent studies across all age groups in Europe, Australia, the USA and Brazil have reported prevalence rates of 4–43% [11].

Etiology & pathogenesis of chronic periodontitis

The importance of the dental plaque biofilm in the etiology and pathogenesis of chronic periodontitis is now recognized. Indeed, while it is estimated that over 700 different bacterial species can occur in the human mouth, it is recognized that specific complexes of these bacteria are responsible for periodontal disease. These Gram-negative anaerobic complexes generally include *Porphyromonas gingivalis, Tannerella forsythia*, *Fusobacterium nucleatum* and *Treponema denticola*. With the recent application of second-generation high-throughput pyrosequencing it is likely that numerous other potential pathogens will also be identified. The communal nature of the microbial plaque and the role of the less pathogenic but early-colonizing bacteria is also being recognized and is better understood. These less harmful bacteria form the initial network on which the putative pathogens can later colonize and the degree to which this happens is largely dependent on environmental factors and host susceptibility. The complexity of microbial interactions and communication within the biofilm and with the host is a focus of current research. As the biofilm matures, bacterial enzymes and metabolic end products increase the permeability of the periodontal tissues and this in turn begins the cascade of the immune responses and the development of inflammation.

The role of host susceptibility is recognized to be central to the pathogenesis of periodontal disease but it remains less well understood than the microbiological factors. This was eloquently demonstrated by Cullinan *et al.* in a 5-year longitudinal study showing that there is a high variability amongst individuals in the acquisition and loss of periodontal pathogens over time [12]. The study further showed that subjects carrying the pathogenic microorganisms did not always manifest the disease, thereby implicating host susceptibility in pathogenesis. It is well established that gingivitis is primarily a cell-mediated immune response while chronic periodontitis is dominated by B cells and antibody-producing plasma cells. In this context current research is aimed at determining the immunoregulatory control mechanisms that result in the development of the destructive periodontitis lesion in some people. In recent years it has been demonstrated that this immunoregulatory control rests with the balance between the Th1 and Th2 cell populations and the mechanisms that control this balance. In this context, the nature of the innate immune

system and the role of Toll-like receptors (TLRs) has been extensively studied (for review see [13]). TLRs are expressed on polymorphonuclear neutrophils (PMNs), monocyte/macrophages and dendritic cells. Furthermore, there is evidence to suggest that the lipopolysaccharide (LPS) of *P. gingivalis* is recognized by TLR-2 and -6, which in turn promote a Th2-type response. Other mechanisms that control the Th1/Th2 balance include the nature of the antigen-presenting cell, the nature of the antigen(s) and T-cell receptor affinity [14]. In recent years the role of the Treg/Th17 axis has been a major focus [15]. With the addition of environmental factors such as cigarette smoking, obesity (which impairs immune function) and stress, which are confounding factors for systemic diseases, the current teachings of the pathogenesis of periodontal disease have become much more complex in recent times than their simplistic beginnings of the late 19th Century.

The relationship between periodontitis & CVD

Cardiovascular disease is the leading cause of death in Western societies [101]. It accounts for an estimated 40% of all deaths worldwide with atherosclerosis being the underlying etiology in the vast majority of cases. Risk factors are the key to prevention and even a modest change in risk can lead to a significant change in disease burden. The importance of the role of infection and inflammation in the initiation and progression of atherosclerosis is now widely accepted [16–22]. Chronic periodontitis is among the most common chronic infections worldwide with, as noted previously, a prevalence of between 13 and 57% for mild to moderate disease and 4–43% for severe disease. Over the past 20 years numerous studies, particularly in the dental literature, have reported that individuals with severe chronic periodontitis have a significantly increased risk of developing CVD including atherosclerosis, myocardial infarction and stroke after adjusting for many of the traditional risk factors [2,17,23–28]. For example, in a subgroup of men in the Normative Aging Study (NAS) in Boston, periodontal disease increased the odds of coronary heart disease (CHD) by 1.5 and stroke by 2.8, while controlling for the effect of age, smoking, diabetes mellitus, family history and education [25]. This odds ratio (2.8) was larger than the odds ratio for smoking (1.6). Although still a controversial topic, there have in fact been over 50 studies investigating the relationship between periodontal disease and CVD with the majority showing a significant, albeit modest, positive association even after adjusting for confounders. Of these studies relatively few have been longitudinal but nevertheless a number have shown a positive relationship [2–4,28] while others have failed to do so [29–32]. As a result the association between periodontal disease and CVD has been questioned [32]. Hujoel *et al.*, using the first National Health and Nutritional Examination Survey Epidemiologic Follow-up Study (NHANES 1) data set and adjusting for confounders, were unable to find convincing evidence for a causal relationship between periodontal disease and CHD [32]. This retrospective study has itself been criticized on the basis that it overcorrects for socioeconomic level, excludes subjects who had evidence of CVD and uses aggregate data, which is a poor indicator of periodontal disease status [32]. Notwithstanding this, meta-analyses have also concluded that periodontal disease and CVD are significantly related [33,34]; however, the risk was not strong [35]. Therefore, care must be taken in interpreting all of these studies and, as pointed out by Hujoel *et al.*, longitudinal intervention and pathogenic mechanism studies are urgently required [32].

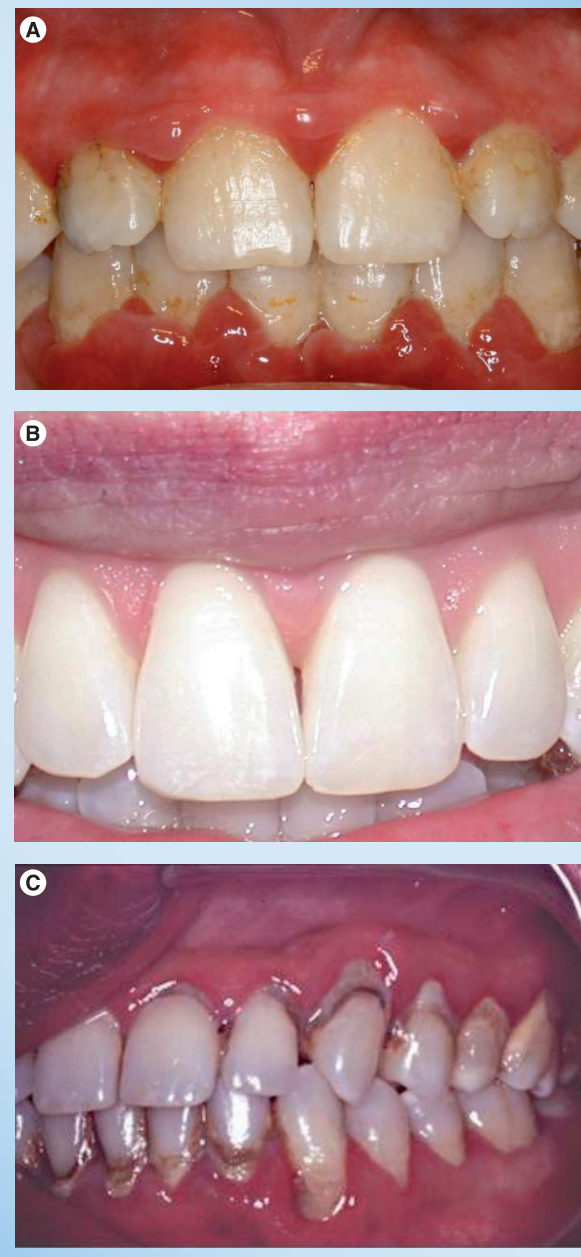

Figure 2. Clinical appearance of the gingival tissues.
(A) Gingivitis – illustrating the clinical signs of redness and swelling of the gingival tissues. **(B)** Healthy periodontal tissues – illustrated by the firm, pink, stippled gingivae that closely contour the cervical region of the tooth. **(C)** Periodontitis – characterized by inflammation, gingival recession and periodontal pocket formation.
Photograph in **(A)** courtesy of Edward J Ohlrich.

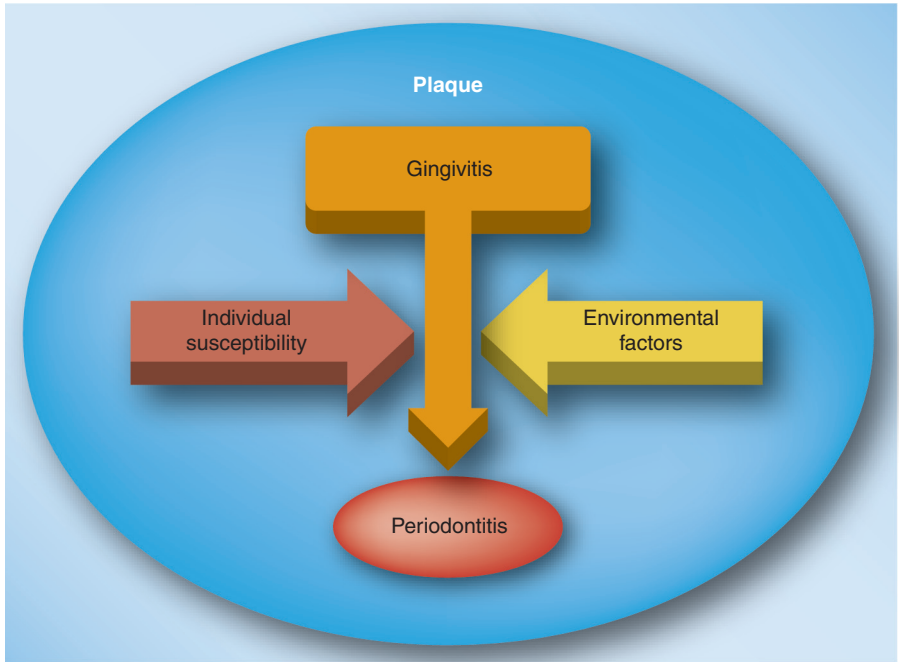

Figure 3. Dental plaque biofilm is the causative factor of chronic periodontal disease, being necessary for the development of both gingivitis and chronic periodontitis. Periodontitis is widespread in the general adult population. The factors that determine the progression from gingivitis to periodontitis are both environmental (e.g., cigarette smoking) and individual susceptibility factors (e.g., immune response).

Conclusive support for a causal relationship would come from intervention studies where treatment of periodontal disease resulted in a reduction in coronary or cerebrovascular events. Taylor *et al.* found that tooth extraction in patients with severe periodontal disease reduced systemic inflammatory markers of risk [36]; however, Hujoel *et al.* found that removal of all teeth, and thus any chronic infection, did not mitigate the risk of a CVD event [37]. This finding, however, would be expected if the underlying mechanism involved immunological memory. While to date there is no evidence that treating periodontal disease reduces the risk of a cardiovascular event, a number of studies have shown that periodontal treatment leads not only to a reduction in systemic inflammation but also to an improvement in endothelial function [38,39]. The lack of long-term interventional studies is primarily due to the scale of such studies and the costs involved.

Nevertheless, it should be noted that there are strong data supporting the role of molecular mimicry as a possible underlying biological mechanism to explain the association [9,40,41].

Putative biological mechanisms

As noted previously there is much evidence to support the role of infection, particularly chronic infection and inflammation, in the initiation and progression of atherosclerosis (Figure 4). Two organisms responsible for common chronic infections in humans are *Chlamydia pneumoniae*, a ubiquitous respiratory tract pathogen, and *Porphyromonas gingivalis*, a bacterium involved in chronic periodontal disease [42]. *C. pneumoniae* causes respiratory tract infections, which range from asymptomatic infection to severe pneumonia, persistent infection and possibly asthma [43]. This organism is responsible for approximately 10% of community-acquired pneumonia and 5% of pharyngitis, bronchitis and sinusitis [44]. *P. gingivalis* belongs to a small group of bacteria that reside in the complex biofilm of dental plaque and which have been associated with periodontal disease progression [45].

Epidemiological studies have repeatedly shown that these infections are associated with an increased risk of developing CVD even after adjusting for traditional risk factors [23,46]. *C. pneumoniae* and *P. gingivalis* have also been identified in the atherosclerotic lesions themselves [47] and in association with activated inflammatory cells [40]. An inherent problem with human studies is the presence of confounding variables since periodontitis and CVD share common risk factors. These include diet, lifestyle, infection history and genetic background. Studies using the atherosclerosis-susceptible apolipoprotein E (apoE)-deficient mice are therefore useful and have provided further support for this association, demonstrating that inoculation with *C. pneumoniae* [48] or *P. gingivalis* [41,49,50] resulted in atherosclerotic lesions that were more advanced and developed more rapidly than in control mice.

While great advances have been made in the treatment and prevention of CVD, the burden of this disease continues to increase. Clearly, further understanding of the pathogenesis of atherosclerosis is required so that additional risk factors such as chlamydial and periodontal infections can be addressed.

Molecular mimicry as a mechanism for atherosclerosis

It is now recognized that immune responses are central to atherogenesis [51] and a mechanism by which infection may initiate and facilitate the progression of atherosclerosis can be explained in terms of the immune response to bacterial heat shock proteins (HSPs; termed GroEL for some bacteria, including *P. gingivalis*). All cells express HSPs on exposure to various forms of stress including temperature, oxidative injury and infection [52]. HSPs are highly conserved throughout nature and many pathogens bear antigens that are homologous to human HSP (hHSP) [53]. During infection, bacterial HSPs are highly immunogenic [54]. Factors such as bacterial LPS, cytokines and mechanical stress may induce the expression of host protective hHSP60 on endothelial cells. Cross-reactivity of the immune response to bacterial HSP with hHSP60 on endothelial cells may subsequently result in endothelial dysfunction and the development of atherosclerosis [55]. The presence of risk factors such as high blood LDL-cholesterol would enhance the expression of hHSP60 and adhesion molecules by endothelial cells and result in progression from early fatty streak lesions to severe and irreversible atherosclerotic alterations. Studies

have shown an association between anti-HSP60 antibody levels and the presence and severity of CVD [56,57]. These antibodies were cross-reactive with other bacterial HSPs and were able to lyse stressed but not unstressed endothelial cells [58]. Elevated hHSP60 levels have been found in patients with increased carotid stiffness [59] and borderline hypertension, and have also been associated with early atherosclerosis [60].

GroEL proteins have been reported to be major antigens in several pathogenic bacteria [61]. GroEL of the periodontopathic bacteria *P. gingivalis*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* [62] was recognized by serum antibodies in patients with periodontal disease [63]. Patients with periodontal disease were shown to have higher antibody responses to hHSP60 and *P. gingivalis* GroEL than periodontally healthy controls. In addition, these antibodies were cross-reactive [64]. Similarly, the HSP60 of *C. pneumoniae* is an important immunogenic protein that is substantially upregulated during the infective developmental cycle of the organism [65]. Antichlamydial HSP60 antibodies have been shown to cross-react with host HSP60 and this has been proposed as a mechanism for immune damage during chronic infection [66].

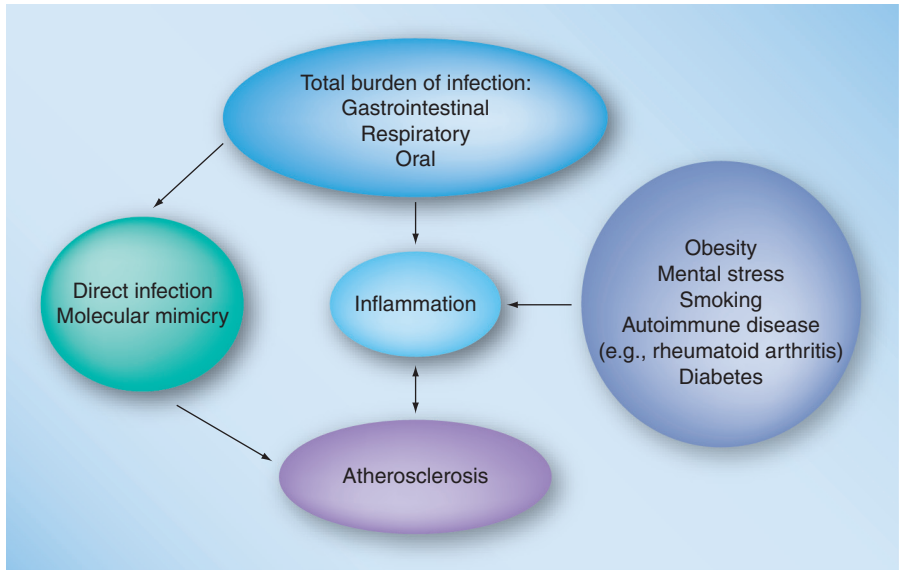

Figure 4. Proposed interaction between infection and the pathogenesis of atherosclerosis. Oral disease is a major contributor to the total burden of systemic infection and the resultant inflammation.

Chronic infections including those caused by *P. gingivalis* and *C. pneumoniae* have therefore been associated with atherosclerosis possibly due to cross-reactivity of the immune response to bacterial HSPs with hHSP60. This cross-reactivity is likely to occur as a result of the structural similarity or 'molecular mimicry' of these antigens. Studies evaluating the effect of antimicrobial therapy on CVD have demonstrated little or no benefit [67]. This may be due in part to the difficulty of eradicating chronic *P. gingivalis* and *C. pneumoniae* infections. In addition, immune cross-reactivity would continue to occur following elimination of the pathogen due to the presence of long-lived cross-reactive T cells.

Murine models have also provided evidence for the role of HSP immunity in atherosclerosis. Immunization of C57BL/6 mice fed a cholesterol-rich diet with recombinant HSP has been shown to increase the development of atherosclerosis [68,69]. Gene targeting has led to the development of apoE-deficient mice that exhibit hyperlipidemia and develop atherosclerosis (comparable to human lesion development and structure) even when fed a normal diet [70]. Along with the animal studies described previously in this article, the results strongly support the hypothesis that cross-reactivity between *P. gingivalis* and *C. pneumoniae* HSPs and hHSP60 is a mechanism explaining the link between periodontal and chlamydial infections and CVD. This model can now be used to investigate this mechanism in more specific terms using experiments not possible in human studies. From this background, defined questions are now able to be posed to determine whether molecular mimicry involving the HSP60 of *P. gingivalis* and *C. pneumoniae* contributes to atherogenesis in mice. This mouse model is ideally suited to provide answers to these questions since the atherogenic effect of the immune response to specific antigens can be studied in isolation from the other risk factors and infections that make interpretation of human studies so complex.

Figure 5 is a schematic representation of the concept of molecular mimicry.

Induction of tolerance to bacterial HSP60: an important new therapy for CVD?

It has been recognized that orally administered antigen induces peripheral immune tolerance [71]. This state of oral tolerance prevents hypersensitivity to food and commensal bacterial antigens. Induction of oral tolerance to specific autoantigens including HSPs has been used to suppress autoimmune responses in murine models of uveitis, diabetes, arthritis and transplantation. Clinical trials, however, have had limited success and further investigations are required into factors modulating tolerization, such as route of administration and adjuvant type [72]. Tolerance induction via sublingual administration shows promise as a more efficient route than oral (intragastric) administration [71] and has shown positive results in early human trials to treat allergic rhinitis [73]. Furthermore, coupling of antigens to cholera toxin B subunit (CTB) has been shown to enhance their ability to induce peripheral tolerance, possibly by facilitating uptake and processing in the mucosal lymphoid tissue [74,75]. The mechanisms underlying mucosal tolerance are dependent on antigen dose. High doses of antigen can lead to anergy or deletion of Th1/Th2 cells whereas low-dose antigen can lead to the activation of Treg cells, which are immunosuppressive. This immune cell subset is expanded following sublingual administration of low-dose antigen [71]. There is recent evidence for a Th17/Treg imbalance in acute coronary

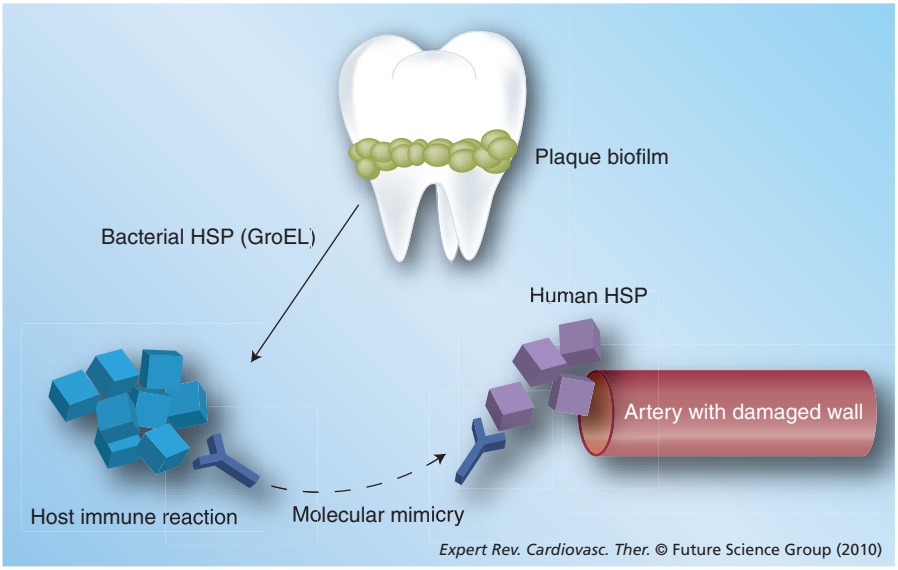

Figure 5. Molecular mimicry as the link between periodontal and cardiovascular diseases. The immune response mounted to the bacterial HSP (GroEL) cross-reacts with human HSP found on damaged arterial walls.
HSP: Heat-shock protein.

syndrome. Th17 cells and associated cytokines (IL-17, IL-23 and IL-6) were higher and Treg cells and cytokines (IL-10 and TGF-β) were decreased in patients compared with healthy controls [76].

Other possible mechanisms for infection-induced atherosclerosis

It has been postulated that multiple pathogens are involved in atherogenesis and that 'pathogen burden', or the aggregate pathogen load, is a more significant risk factor than any single infection [77]. It is likely that molecular mimicry is one of several mechanisms that occur in pathogen-induced atherosclerosis. Innate immune responses may also be implicated. In addition to stimulating specific humoral and cellular immune defences, bacterial HSP60 is recognized by the innate immune system by means of TLRs. TLRs allow recognition of structurally conserved pathogen-associated microbial products such as LPS, fimbriae and HSPs. Ligation of these receptors triggers signal transduction pathways leading to rapid innate inflammatory responses and facilitation of antigen-specific acquired immunity [78]. ApoE mice orally inoculated with *P. gingivalis* showed upregulation of TLR2 and 4 in aortic tissue [79] and TLR2-deficient mice inoculated with *P. gingivalis* had reduced atherosclerosis [80]. TLR4 expression in lesions is enhanced by the presence of oxidized LDL, suggesting that inflammation due to pathogens may act synergistically with hypercholesterolemia to promote atherosclerosis [81]. It has also been reported that direct bacterial invasion of the arterial wall could be a mechanism for atherosclerosis development since wild-type *P. gingivalis* but not a fimbriae-deficient mutant strain upregulated aortic TLR2 and TLR4 expression and accelerated atherosclerosis in apoE mice [82].

At present there is evidence for infection as a risk factor for atherosclerosis, although the mechanisms are still unknown. Much work has been done to address the conventional cardiovascular risk factors such as high cholesterol and hypertension; however, the burden of this disease is enormous and is becoming more associated with chronic disabling illness. Therefore, in addition to the conventional risk factors it is important to understand other risk factors such as infection if morbidity and mortality are to be reduced.

Clinical implications of periodontal disease for doctors

As the evidence linking oral disease and atherogenic CVD continues to emerge, it is incumbent upon health professionals to increase public awareness of this relationship. Unlike many of the other risk factors (e.g., obesity and cigarette smoking) and CVD symptoms (e.g., angina and shortness of breath), chronic periodontal disease is largely asymptomatic and most often progresses without individuals being aware of its presence. Although the diagnosis and management of periodontal disease has improved over time there is still much work to be done in raising public awareness about the importance of oral health and its possible impact on systemic health.

Identification of risk factors is the key to prevention of atherogenic CVD on a community level. Important modifiable risk factors include elevated cholesterol levels, cigarette smoking, hypertension and diabetes mellitus. Strategies that improve the control of these risk factors have all been shown to improve cardiovascular outcomes. The role of inflammation as a modifiable cardiovascular risk factor is less clear. C-reactive protein as a blood marker of inflammation has been found to be an independent risk factor for CVD in some studies but not in others [83]. To date the hypothesis that chronic inflammation is an independent risk factor for CVD and that efforts to reduce markers of inflammation lead to improved cardiovascular outcomes has not been proven.

Chronic periodontal disease is an inflammatory disease that is widespread in the community [10]. It is also a preventable and treatable disease that has the potential to be a modifiable cardiovascular risk factor. As such, both doctors undertaking primary and secondary CVD treatment and dentists should assess patients' oral health status and make appropriate referrals where necessary. Doctors should assess the oral cavity as part of their examination. Where there are signs of oral inflammation, patients should be screened for periodontal disease and referred for thorough oral examination, diagnosis and treatment where appropriate. The screening questions for periodontal disease found in Box 1 have been found to provide useful levels of prediction and low rates of nonresponse in a population-based national oral health survey [84]. These questions may be a useful adjunctive tool for doctors in their periodontal disease screening of patients. Dentists should also screen their patients for the risk factors of CVD. Patients with CVD risk factors should be referred for assessment

by a medical doctor, and given appropriate advice and education on oral hygiene and effective management of periodontal disease. Those dental patients with diagnosed systemic disease including CVD and diabetes mellitus must be managed effectively to optimize their oral health and lower the burden of any additional risk.

Therapeutic implications

The recognition of the relationship between oral and systemic disease has resulted in approaches to encourage better oral health both by publicly funded schemes and private health insurances. In Australia, there is government funding through Medicare Australia for the dental treatment of patients with chronic systemic disease, such as diabetes and existent CVD [102]. Despite difficulties in the administration and delivery of this program the concept is a step in the right direction. Some private health insurance funds will cover some dental costs. In the USA a number of private health funds have commenced programs to improve their members' oral health as they are aware that the prevention and treatment of oral disease leads to improvements in systemic health and a resultant decrease in the medical cost burden [103,104].

Without question, prevention is the ideal strategy to lower the systemic illness burden in the community. This preventive strategy should be aimed at all the recognized risk factors. In the case of CVD, these preventive strategies should be aimed at the promotion of healthy eating and exercise regimens, cessation of cigarette smoking and oral health education. Medical and dental professionals should work together to plan and execute effective community-based programs with the common goal of promoting healthy lifestyles which encompass diet, exercise, smoking cessation and oral health.

To ensure the inflammatory burden is controlled, patients with existing CVD should receive appropriate oral diagnosis and treatment. Diagnosis involves clinical and radiographic examination of the oral cavity. The fundamental principle of treatment for periodontal disease is removal of the bacterial load. This can be achieved mechanically by scaling and root-planing teeth and educating patients to achieve good plaque control at home. In severe periodontal disease where there is deep periodontal pocket formation and loss of alveolar bone support, surgical intervention is often required for effective debridement and recontouring to allow adequate home care. Regular monitoring is necessary for prevention of disease recurrence or to enable early intervention.

The preventive measures patients perform at home between dental visits are of vital importance in the long-term management of chronic periodontal disease. The adjunctive use of home products in addition to the traditional mechanical plaque removal methods of toothbrushing and flossing can be of much benefit.

Box 1. Periodontal screening questions.

Question 1
- Do you think that you have gum disease?

Question 2
- Has a dental professional ever told you that you have lost bone around your teeth?

Question 3
- Have you ever had scaling, root planing, surgery or other treatment for gum disease?

Question 4
- Have you ever had any teeth that have become loose by themselves without some injury (not baby teeth)?

Affirmative answers to the above questions are positive predictors of a clinical diagnosis of moderate/severe periodontitis and, in addition to signs of oral inflammation, may assist doctors in periodontal disease screening [84].

Box 2. Summary of periodontal disease including signs, symptoms, diagnosis, management and maintenance.

Signs
- Inflammation of periodontal tissues
- Periodontal pocket formation
- Alveolar bone loss
- Tooth mobility and migration
- Tooth loss

Symptoms
- Bad breath
- Bleeding on brushing
- Tooth mobility and migration
- Tooth loss

Diagnosis
- Clinical examination including periodontal charting
- Radiographic examination

Management
- Patient education
  - Oral hygiene instruction
  - Smoking cessation
- Mechanical therapy
  - Scaling and root planing ± surgical periodontal therapy
- Chemotherapeutic therapy
  - Toothpaste
  - Mouthrinse
  - Local and systemic antibiotics

Maintenance
- Regular review with periodontal charting ± radiographs
- Patient motivation – good oral hygiene and smoking cessation
- Ongoing mechanical and/or chemotherapeutic therapy as required

Therapeutic products that have been used as mouth rinses to some benefit for periodontal health include chlorhexidine, essential oils and cetylpyridinium chloride [85–91]. These types of mouth rinses offer different levels of antimicrobial activity, alcohol content and side effects which need to be assessed on an individual patient basis depending on diagnosis, length of time to be used and specific needs. Antimicrobial toothpastes containing triclosan have been extensively tested and found to provide antiplaque and antigingivitis benefits with twice-daily unsupervized home use [92–94]. Of particular interest, triclosan/copolymer appears to exert anti-inflammatory properties, which may provide further benefits to periodontal patients, although confirmatory research in this area is required.

The main goal of periodontal therapy is establishing a healthy oral environment; however, the long-term maintenance of this is critical. Not only does regular review serve to reinforce patients' home plaque control, but monitoring of periodontal parameters detects any changes in disease activity and risk status and facilitates early interception when required. Studies analyzing the efficacy of periodontal maintenance therapy show that patients who undergo a regular program of review suffer from less recurrent disease, slower progression of disease and less tooth loss [95–97]. **Box 2** summarizes the key points of periodontal disease including signs, symptoms, diagnosis, management and maintenance.

Expert commentary & five-year view

Although we have come a long way in the past two decades with regard to our understanding of how oral health and systemic health are related there are still many questions to answer. Further knowledge and confirmation of the mechanisms of the relationship linking periodontal disease and CVD are needed. This would require cohort studies in populations with minimal CVD risk factors and with CVD events as an outcome. Such research would answer the question of whether periodontal disease is a risk factor for atherosclerotic disease in its own right or whether the two conditions share common genetic or environmental risk factors.

Further intervention studies are also required in order to assess the effect of periodontal therapy on cardiac outcomes for patients with and without existing CVD. A pilot study to a large multicentered randomized controlled trial on the secondary prevention of CVD among those with existing CVD has recently been published [98], but an extension of this study that reaches greater statistical validity with regard to periodontal treatment effects is awaited.

Finally, continued study into the biological mechanisms is warranted to confirm and further elucidate the currently accepted theory of molecular mimicry.

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Key issues

- Studies have linked poor oral health with systemic diseases such as cardiovascular disease and Type 2 diabetes mellitus.
- Several putative biological mechanisms have been proposed to explain the relationship between oral and systemic disease but at this stage there is insufficient evidence to establish causality.
- Chronic periodontal disease is very common among the adult population.
- Prevention and management of periodontal disease should be undertaken at both the individual and community levels as it may reduce the risk of chronic systemic disease.
- Medical and dental professionals should work together to raise public awareness and promote good oral health as part of the healthy lifestyles message.

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•• of considerable interest

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