

REVIEW

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## Chronic Periodontitis as a Risk Marker for Systemic Diseases with Reference to Cardiometabolic Disorders: Common Pathways in their Progression

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**Abstract:** Periodontitis, an inflammatory condition of the supporting structures of teeth resulting from dental plaque biofilm attached to tooth surfaces is potentially an important nidus of systemic inflammation and its sequelae. Relevant risk markers common to periodontitis co-existing with coronary heart disease and diabetes mellitus play an important role in their pathogenesis and abate in response to treatment. An over-exuberant host-response to periodontal pathogen-mediated inflammation, triggers a cycle of events which is not dissimilar to an autoimmune response in a cohort of susceptible individuals. Some variation in documented findings regarding correlations with co-morbidities and periodontitis could be explained by the lack of uniformity in studies with regard to stipulation of periodontal inflammatory status in the context of risk factors examined. There are several genetic and environmental factors which influence the progression of inflammatory periodontitis in response to plaque biofilm, also relevant to associated cardiometabolic disorders in the same subject. Some common mechanisms in the pathogenesis of periodontitis and cardiometabolic disorders based on regulation of inflammation are addressed in this review. There is some evidence of an improved systemic inflammatory profile in response to periodontal treatment which emphasizes the importance of periodontal management for systemic health in relevant cases.

**Keywords:** periodontitis, cardiometabolic disease, dyslipidaemia, cytokines, risk markers

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## Introduction

### The inflammatory nidus in periodontitis

Periodontal disease is initiated by bacterial plaque biofilm attached to tooth surfaces and results in damage to supporting structures comprising root cementum, periodontal ligament and bone with ultimate tooth loss. Products of periodontal pathogens consisting of enzymes, toxins and lipopolysaccharide (LPS), from gram negative periodontal pathogens induce an inflammatory response in the host.<sup>1</sup> An uncontrolled, over-exuberant inflammatory response in chronic periodontitis associated with an oxidative stress-induced inflammatory pathogenesis,<sup>2</sup> has links with systemic diseases such as cardiovascular disease,<sup>3,4</sup> diabetes mellitus (DM)<sup>5-7</sup> and rheumatoid arthritis<sup>8,9</sup> to name a few in a cluster of associated disorders including carcinogenesis.<sup>10</sup> An oxidative stress-enhancing cycle of events with release of reactive oxygen species (ROS) in periodontal tissues could mediate insulin resistance.<sup>11,12</sup> Reversal of the cyclical pro-inflammatory profile in response to LPS, advanced glycaemic end products and nicotine<sup>13,14</sup> by antioxidants improves insulin resistance in mice and humans.<sup>15,16</sup>

Multiple virulence factors generated by surface proteins, capsules and fimbriae of the periodontal pathogens *Porphyromonas gingivalis* (*Pg*), *Aggregatibacter actinomycetemcomitans* (*Aa*) and others trigger an inflammatory response in the host.<sup>17</sup> The inflammatory infiltrate from gingival tissue initiates destruction of connective tissue and alveolar bone via activation of pro-inflammatory cytokines including IL-1, IL-6 and TNF- $\alpha$ . Multiple signals modulate the activation and binding of receptor activator of nuclear factor kappa B ligand (RANKL) to its cognate receptor RANK essential for osteoclastogenesis, modulated by the soluble decoy receptor osteoprotegerin produced by osteoblasts; this inhibits the RANKL/RANK interaction and has potential therapeutic implications in the management of diseases characterized by progressive bone loss. These inflammatory agents and markers of progressive periodontal disease such as C-reactive protein (CRP) have important parallels with systemic inflammatory markers of cardiometabolic events.

### Relevance of periodontal inflammatory status for correlation with systemic co-morbidities

In epidemiological studies a range of classifications is used for periodontitis as a risk factor for other diseases, seldom quantifying the amount of inflamed periodontal tissue. This is required to quantify the amount of inflammatory burden imposed by chronic periodontitis. A spreadsheet for calculation of periodontal inflamed surface area (PISA) was developed by using clinical attachment levels, recession and bleeding on probing (BOP), reflecting bleeding pocket epithelium in square millimeters which would quantify inflamed periodontal tissues. It could be applied readily to broader applications.<sup>18</sup> The underlying bacterial aetiology of inflammation as a risk factor for cardiometabolic disorders is customarily represented by parameters of periodontal inflammation which do not directly correlate with bacterial burden.

In order to assess this correlation, a study was conducted amongst 706 men and women aged 55 y or greater. Standard values for the periodontal pathogens *Aa*, *Pg*, *Treponema denticola* (*Td*) and *Tannerella forsythia* (*Tf*) were averaged in sub-gingival biofilms using DNA-DNA checkerboard hybridization and summed to represent bacterial burden for correlation with clinical parameters.<sup>19</sup> Clinical periodontal constructs which demonstrated the best correlation with bacterial burden were the percentage of sites with bleeding on probing and relatively shallow sites of periodontal pocketing, also demonstrated by others.<sup>20</sup> Associations with cardiovascular disease markers are optimized in low threshold definitions of clinical periodontitis.<sup>21</sup> This emphasizes the importance of clinical specifications that include less severe periodontal disease of relevance as a model of infection for systemic inflammatory loading, in clinical epidemiological studies. Elevated levels of selected populations of periodontal pathogens are associated with increased thickness of the carotid artery intima-media<sup>22</sup> and increased prevalence of coronary artery disease.<sup>23</sup>

### Concept of the host-response in inflammatory periodontitis

The complexity of the aetiopathogenesis of periodontal disease arises from the host-response to bacterial



challenge, rather than the presence of virulent pathogens alone; considering the variation in disease presentation and progression between individuals who harbour the same periodontal pathogens. Given microbial factors, a range of genetic, systemic and environmental factors predispose to periodontal diseases in susceptible individuals.<sup>24</sup> Inflammation is strongly associated with dyslipidaemia, raised levels of CRP, cardiovascular events and morbidity.<sup>25</sup> Adipose tissue could function as an endocrine organ contributing to significant levels of cytokines. This source of inflammation is less amenable to treatment.

### An overview of adipose tissue as a risk factor in periodontal and cardiometabolic disorders

Metabolic events in adipose tissue have adverse consequences such as increased oxidative stress, endothelial dysfunction and damaging effects on the periodontium as a result of raised levels of cytokines. Obesity is a significant risk factor for periodontitis. The interface between obesity and periodontitis has been analysed elucidating the relevance of resultant oxidative stress and the host-response.<sup>26</sup> The role of oral bacteria as a contributory factor in obesity was investigated.<sup>27</sup> Analysis of salivary microbiological composition showed that 98.4% of overweight women were identified by the presence of *Selenomonas noxia* at levels greater than 1.05% of total salivary bacteria. There was also a median percentage difference of greater than 2% in 7 of 40 bacterial species measured in the saliva of overweight women. These bacterial species could serve as salivary biological markers of the onset of obesity and possible indicators of involvement in the pathogenic process.

Host-mediated inflammatory responses to periodontal pathogens in chronic periodontitis with associated release of matrix metalloproteinases (MMPs) and products of lipid metabolism could be contributory risk factors for atherogenesis and DM in periodontal patients. In this context it was hypothesized that periodontal treatment complemented with preventive measures targeting hypertension, dyslipidaemia, DM and obesity could reduce morbidity and mortality from cardiovascular disease.<sup>28</sup> There is evidence for this hypothesis in recent documentation. This review addresses the

consequences of periodontal disease progression, causal mechanisms of risk factors associated with cardiometabolic co-morbidities and potential targets for reversal of their pathogenesises.

## Pathobiology of Periodontal Disease Progression

### Microbial initiation and interaction with the host-response

The initiation of chronic periodontitis by plaque pathogens such as *Pg*, *Aa* and its progression as a result of the host-response could result in an over-exuberant, uncontrolled immune response with an autoimmune element leading to cyclical episodes of tissue damage.<sup>17</sup> Along with other inflammatory diseases, in periodontitis there is an imbalance in the levels of MMPs and their inhibitors.<sup>29</sup> Activated osteoclasts play an important role in bone destruction via cytokine-mediated inflammatory pathways, such as those initiated by IL-1 $\beta$  and TNF- $\alpha$ .<sup>30,31</sup> An example of the multiple inflammatory signals affecting osteoclastogenesis are those that modulate RANKL, RANK or osteoprotegerin which constitute the TNF-ligand and receptor-superfamily.<sup>32,33</sup> The soluble decoy receptor osteoprotegerin inhibits RANK/RANKL interactions and shows promise for the treatment of bone destructive diseases such as chronic periodontitis. TNF blockade inhibits osteoclastogenesis and is a target for therapeutic development<sup>34</sup> also relevant to rheumatoid arthritis and periodontal disease.

In the presence of periodontal pathogens such as *Aa*, CD4+ T lymphocytes display enhanced expression of RANKL, stimulating the activation of osteoclasts leading to bone loss, similar to mechanisms found in rheumatoid arthritis and osteoporotic bone destruction.<sup>35,36</sup> Several enzymes specially MMP-8 play an important role in collagen degradation. MMP-8-deficient and wild-type mice were used to investigate *Pg*-induced periodontitis.<sup>37</sup> *Pg*-infected mice in both categories showed accelerated bone loss, being most severe in the MMP-8-negative group and it was unusual that MMP-8 significantly attenuated site-specific bone loss. The MMP-8-negative mice showed smaller particle size of the lipoproteins HDL and VLDL (high density and very low density), increasing in size during inflammation. The protective effect of MMP-8 against *Pg*-mediated periodontal

destruction could be mediated by anti-inflammatory cytokines and chemokines.

Inflammation mediated by IL-6 has implications on several disease entities including atherosclerosis, type 2 DM, arthritis, cancer and periodontal disease. Statins and biphosphonates inhibit IL-6-mediated inflammation by inhibiting cholesterol synthesis and isoprenoid depletion.<sup>38</sup> There is further coverage in the next section on toll-like receptor (TLR)-signalling, an integral component of the pathology of periodontitis.

### TLR-signalling in periodontitis and systemic inflammation

TLR-signalling plays an important role during microbial infections, as TLRs are pathogen-associated molecular pattern receptors. They are up-regulated during infection and inflammation of particular significance in periodontitis and atherosclerosis. Specific periodontal pathogens such as *Pg*, implicated in the initiation and progression of chronic periodontitis, show a link with progression of atherosclerosis. *Pg* resides in the walls of atherosclerotic vessels and there is evidence of an association between pathogen-specific antibody levels and atherosclerotic changes in vessel walls.<sup>39</sup> Focal and distant signalling pathways would have an impact on disease progression locally and with systemic impact. TLR2 is required for *Pg*-mediated inflammatory bone loss in mice. Hyperlipidaemic mice demonstrating accelerated atherosclerosis in response to infection with *Pg* show a concurrent increase in expression of TLR2 and TLR4 in atherosclerotic lesions. Immunization has been shown to be effective in controlling pathogen-accelerated atherosclerosis. This is a new therapeutic target for pathogen associated atherosclerosis based on the inflammatory sequelae that are triggered.

A secretory cell surface protein (BspA) associated with the gram-negative periodontal pathogen *Tf* is an important virulence factor in the pathogenesis of periodontitis. This multifunctional protein interacts with monocytes which respond through TLR-signalling. The response of gingival epithelial cells to BspA challenge and the role of TLRs in BspA recognition as well as BspA domains involved in activation of cells were investigated.<sup>40</sup> It was demonstrated that BspA binds to TLR2 and that BspA-mediated

release of IL-8 from human epithelial cells is dependent on TLR2, confirming their interplay in cytokine-mediated host-modulatory responses, in conjunction with TLR1. Secretion of BspA has implications on inflammatory activity at sites distant from bacterial colonization. This is of relevance to the pathogenesis of co-morbidities associated with periodontitis.

In principle most inflammatory responses could become destructive when de-regulated due to their magnitude.<sup>41</sup> *Pg* could enhance TLR2-mediated inflammatory osteoclastogenesis.<sup>42</sup> There is extensive documentation to indicate that periodontal bacteria preferentially activate immune and non-immune cells via the TLR2 pathway.<sup>43–45</sup> Stimulation of TLR2, independent of simultaneous stimulation of TLR4 favours the development of a T-helper 2-type of immune response,<sup>46,47</sup> characteristically associated with the progressive periodontal lesion.<sup>48</sup> It would be logical to assume that periodontal pathogens preferentially stimulate TLR2 activity thereby contributing to a T helper type-2 trend in the immune response, perpetuating chronic inflammatory progression of the periodontal lesion.

Infection inflammation and atherogenesis are potentially linked by TLR activity in response to pathogen mediated pro-inflammatory stimuli<sup>49</sup> relevant to progression of uncontrolled DM in periodontitis patients. Host-derived ligands are also recognized by TLRs indicating a role in the progression of non-infectious inflammatory diseases. It is relevant that oxidized lipoproteins function as TLR-ligands in the presence of an inflammatory process instigated by hyperlipidaemia, in the absence of infection. In hyper-lipidaemic mice TLR2-mediated activation of cells in response to endogenous and exogenous agents is pro-atherogenic. These pathways are relevant to dyslipidaemic subjects presenting with periodontal disease and co-existing cardiometabolic disorders, in view of pathogen-mediated TLR2 activity seen in periodontitis.

### Metabolic Syndrome and Periodontal Disease

Metabolic syndrome is diagnosed in individuals with a risk of cardiovascular disease,<sup>50</sup> comprising a cluster of abdominal obesity, hypertension, impaired glucose tolerance, hyper-insulinaemia and



dyslipidaemia.<sup>51</sup> A significant relationship between oxidative stress and metabolic syndrome has been demonstrated in humans when compared with normo-lipidaemic subjects. Systemic oxidative stress and insulin resistance have been shown to correlate with attenuated antioxidant capacity.<sup>52,53</sup> Several cytokines are involved in the mediation of insulin resistance, TNF- $\alpha$  in particular.<sup>54</sup> In the context of substances derived from oxidative damage, plasma lipid peroxidation plays an important role in the diabetic periodontal patient<sup>55</sup> with decreased lipid peroxidation following periodontal therapy. The pathogenesis and progression of periodontal disease is escalated by advanced glycaemic end products AGE,<sup>56</sup> receptor for AGE (RAGE) which is highly expressed in periodontal tissues<sup>57</sup> and AGE/RAGE interactions in uncontrolled diabetics.

Periodontitis is characteristically associated with increased levels of LDL-cholesterol and triglyceride with concurrent decreased levels of HDL-cholesterol. This emphasizes the relevance of oxidative stress in the pathogenesis of metabolic syndrome and periodontal disease with correlations between clinical periodontitis and plasma levels of anti-oxidised LDL-cholesterol antibodies.<sup>58</sup> Adiponectin has important implications in metabolic syndrome. It is usually maintained at fairly constant levels<sup>59</sup> but shown to decrease in obesity, cardiovascular disease, insulin resistance and DM,<sup>60</sup> preceding these conditions and have been used to predict their onset.<sup>61</sup> In the context of periodontitis it is relevant that adiponectin is potent in its negative regulation of osteoclast formation induced by LPS of the periodontal pathogen *Aa* and could therefore contribute to attenuation of the disease process.<sup>62</sup> Studies in humans have demonstrated decreased levels of serum adiponectin in periodontitis,<sup>63</sup> although not significantly so. Periodontitis is associated with significant levels of oxidative stress markers<sup>58,64</sup> and reduced antioxidant capacity<sup>65-67</sup> with clear indications of mechanisms for progression and remission associated with parameters of metabolic syndrome in periodontitis patients.

It is relevant that metabolic syndrome and periodontal disease have an increasingly significant prevalence globally with some association with regard to their aetiopathogenesis. This association was surveyed in a nationally representative sample of

non-institutionalised civilians in the United States.<sup>68</sup> A population of 13,994 males and females aged 17 y or older who received a periodontal examination were investigated for association of parameters of severity of periodontal disease with metabolic syndrome and its individual components comprising central obesity, hyper-triglyceridaemia, LDL/HDL-cholesterol, hypertension and insulin resistance. After adjustment for confounders, those of >45 y of age with severe periodontitis were 2.3 times more likely to have metabolic syndrome than unaffected individuals, indicating an association between severe periodontitis and metabolic syndrome in middle-aged subjects. Potential bi-directional responses to treatment require further exploration.

Infections predispose to atherosclerotic risk and the potential mechanisms linking periodontal disease with atherosclerosis have been reviewed.<sup>69</sup> Focal accumulation of lipids arising from inflammatory cytokine-mediated metabolic responses initiates atherosclerotic plaque. The link between periodontal disease and impaired lipid metabolism is well documented.<sup>70,71</sup> Metabolic syndrome is a combination of obesity, hypertension, dyslipidaemia, hyperinsulinaemia and impaired glucose tolerance. An association between some of these parameters and periodontal disease has been reported based on oxidative stress-inducing mechanisms and the release of adipocytokines amongst others which could influence redox modulation bi-directionally.<sup>12,72</sup>

The adipokines resistin and adiponectin formed in adipose tissue have opposing functions in insulin resistance and inflammation. Large amounts of resistin have been detected in macrophages suggestive of their important role in inflammation. Serum levels of adipokines in women with periodontitis have been studied.<sup>63</sup> The prevalence of periodontitis was significantly associated with raised levels of resistin. Association of periodontitis with decreased levels of adiponectin did not reach statistical significance. It was concluded that an increased level of serum resistin could influence systemic health in middle aged Japanese women.

Although insulin resistance is considered to be a unifying factor in the logical progression of metabolic syndrome, epidemiological studies show that it may not be the case in a significant proportion of

patients with metabolic syndrome. The relationship between insulin resistance and the strategic components of metabolic syndrome (hyperglycaemia, dyslipidaemia, hypertension and obesity) have been reviewed.<sup>73</sup> Again although obesity could contribute to the equation, it is not prevalent in all cases of metabolic syndrome and not all obese patients have metabolic abnormalities.

### **Associations of Periodontal Disease with Coronary Heart Disease**

A possible association of periodontal disease with coronary heart disease (CHD) has received attention in the literature, demonstrating a raised antibody titre to periodontopathic bacteria in CHD patients compared with healthy controls. When serum antibody levels in response to 12 periodontal pathogens were investigated amongst patients with CHD and moderate to severe periodontitis, the antibody response was most prevalent for *Pg* a major causative pathogen implicated in CHD as well as periodontitis.<sup>74</sup> When the antibody response to two different strains *Pg* FDC381 and Su63 was analysed, periodontal patients were positive for both strains while CHD patients showed an elevated response to *Pg* Su63 but not for the *Pg* FDC381 strain. These findings demonstrate that periodontal pathogens with high virulence may affect atherogenesis; knowledge of the virulence factors of *Pg* Su63 could open new therapeutic modalities for *Pg*-associated atherosclerotic changes.

### **Epidemiological overview of periodontitis and coronary heart disease**

Inflammation constitutes a common pathway in the progression of periodontal and cardiovascular disease, in the context of common risk factors. Screening for periodontal disease has potential in identifying those at risk of coronary heart disease. Self-reported health status and its independent association with inflammatory risk markers and the application of oral health assessment for cardiovascular screening without conventional cardiovascular risk factors were investigated.<sup>75</sup> Baseline analysis of 421 participants in a family intervention trial for heart health without CVD or DM, consisted of oral health, lifestyle, CVD risk factors and markers such as high sensitivity-CRP and lipoprotein associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>).

Statistical analyses for associations between oral health, risk factors and inflammatory markers were adjusted for effects of life style and potential confounders by logistic regression. History of periodontal disease was reported in 24% of non-overweight, non-hypertensive, non-hyper-cholesterolaemic subjects; 34% demonstrated elevated high sensitivity-CRP or Lp-PLA<sub>2</sub>. It was concluded that self-reported periodontitis was found to be independently associated with inflammatory risk markers and prevalent amongst subjects without traditional CVD risk factors. Periodontal health screening could be a valuable asset in detecting susceptibility to cardiovascular disease.

The association between periodontitis/tooth loss and levels of CRP was investigated in a 60–70 year old male population enrolled in a cohort study of cardiovascular disease. They were screened at baseline and in 10 years when a periodontal examination was completed. Fasting blood levels of high sensitivity-CRP were measured. Models were devised to depict CRP as the outcome variable and high or low threshold periodontitis as predictor variables. Socioeconomic status, body mass index, age, smoking, cardiovascular risk factors and diabetes were incorporated in the analysis as confounders.<sup>76</sup> The unadjusted odds ratio for an association between severe periodontitis and elevated levels of CRP was 3.62 and remained significant although relatively attenuated after accounting for confounders. There was also an association between elevated CRP levels and tooth loss in the population studied.

Chronic inflammatory episodes applicable to periodontal disease could predispose to cardiovascular disease. The association of periodontal disease and tooth loss with sub-clinical atherosclerosis was investigated.<sup>77</sup> 711 subjects with a mean age of 66 y and no history of stroke or myocardial infarction were examined in the Oral Infections and Vascular Disease Epidemiology study. Comprehensive periodontal examination was carried out, together with cardiovascular risk parameters and a carotid scan. Prevalence of carotid artery plaque was 46% amongst those with 0–9 teeth missing and 60% in those with >10 missing teeth. Tooth loss being a marker of past periodontal disease in the population studied correlated with sub-clinical atherosclerosis, indicating a plausible link between coronary heart disease and progressive periodontal disease.



## Risk markers and their relevance to periodontitis and coronary heart disease

High sensitivity-CRP used as a risk marker for cardiovascular disease has low specificity. A method of prediction of risk for cardiovascular disease was investigated.<sup>78</sup> The association between high sensitivity-CRP and osteoarthritis was evaluated for application as a risk marker for cardiovascular disease amongst 662 patients. In this group, factors comprising obesity, ethnicity, gender and co-morbidities appeared to confound the prediction of risk for CVD.

The effect of comprehensive periodontal therapy on the levels of multiple systemic inflammatory markers was investigated. Periodontal therapy was carried out on 30 patients with severe periodontitis over a 6 week period.<sup>79</sup> On completion of treatment certain parameters such as integrins, MMP-9, myeloperoxidase and a composite summary inflammatory score were significantly reduced. However at 4 weeks after completion of treatment sustained reduction was seen only in certain parameters such as sE-selectin, s-ICAM and serum amyloid P. One possible explanation is that results of periodontal treatment manifest over a longer period following completion of treatment and more work along these lines could clarify the significance of parameters used.

The implications of periodontal disease as a risk factor for cardiovascular disease was investigated in age and sex matched New Zealand White rabbits fed on a lipid inducing diet for 13 weeks as a model for atherogenesis.<sup>80</sup> Silk ligatures impregnated with *Pg* were applied around mandibular premolars to initiate periodontitis. At 14 weeks, there were significantly greater deposits of lipid in the aorta of animals with experimentally induced-periodontitis than in non-periodontitis animals, with a positive correlation between periodontal disease severity and the extent of lipid deposition. This investigation provides direct evidence of periodontitis being a risk factor for atherogenesis, supporting the concept of a remote inflammatory nidus being able to influence atherogenesis.

## An Overview of Periodontitis and DM

There are associations between diabetic and periodontal parameters such as gingivitis, clinical attachment loss and alveolar bone loss.<sup>81</sup> Evidence of a direct

association between DM and periodontitis has been reviewed in the literature.<sup>82</sup> Significant correlations between periodontal disease parameters and poor glycaemic control have been demonstrated<sup>83,84</sup> and other reports of a reciprocal relationship between periodontal disease and glycaemic control.<sup>85,86</sup> Cross sectional studies on Pima Indians representing uncontrolled disease displayed the highest global prevalence of type 2 DM demonstrating an odds ratio of 2.8 to 3.4 for developing periodontal disease in type 2 DM compared with non-diabetic controls.<sup>87</sup> Other longitudinal studies demonstrate these concepts; poorly controlled diabetics do not respond to periodontal therapy as well as controlled diabetics or non-diabetics.<sup>88,89</sup>

Genetic factors play an important role in susceptibility to periodontal disease<sup>90–92</sup> as well as to systemic diseases. The impact of a poorly regulated immune response in fuelling the progression of periodontal destruction secondary to bacterial plaque is well documented.<sup>93</sup> The mechanisms involved include primed neutrophils, IL-1 gene polymorphisms and their genotypes associated with periodontal pathogens<sup>94</sup> and increased risk of severity of periodontal disease. Other studies demonstrate a lack of association between IL-1 genotype and periodontal disease in non-smokers;<sup>95</sup> while a possible relationship between IL-1 genotype and periodontal disease in diabetics has been reported.<sup>83</sup> Genetic and environmental factors could influence the severity and progression of chronic periodontitis.

Case definition of the status of periodontal inflammation could have some bearing on the results of clinical studies. A meta-analysis of 10 intervention studies was done to quantify the effects of periodontal treatment on HbA1c levels among diabetic patients.<sup>96</sup> Data sources were MEDLINE (January 1980–January 2005), EBMR, Cochrane Register and bibliographies of the published papers. The weighted average reduction in HbA1c level was 0.38% when all studies were considered, 0.66% when restricted to type 2 DM patients and 0.71% if antibiotics were used; however there was no statistical significance. This degree of improvement in glycaemic control could be beneficial to certain patients but the evidence was not strong enough to be conclusive about the benefits of periodontal treatment on diabetes control.



This could be partly due to lack of definition of the severity and extent of periodontal disease in the subjects examined. Adjustment needs to be made for environmental factors such as smoking, BMI and diet which could affect levels of cytokines and acute phase reactants such as TNF- $\alpha$  and CRP. Case definition related to disease aggression and distribution would potentially contribute to more significant inflammatory burden which in turn could affect disease parameters for DM, after treatment of the periodontal condition.

### Mechanisms involved in the link between uncontrolled DM and periodontitis

An over-exuberant immune response could have a synergistic effect in periodontal patients with co-existing DM.<sup>97</sup> Effective treatment of periodontitis could improve diabetic parameters such as glycated haemoglobin.<sup>98</sup> Non-enzymatic glycation of amino acids could result in the formation of AGE which alters tissues and modifies cell-signalling, affecting physiological functions and wound healing. Hyperglycaemia induces oxidative stress via protein kinase-dependent activation of enzymes that catalyse the generation of reactive oxygen species. These actions have a direct bearing on periodontitis in uncontrolled diabetics.<sup>99</sup>

Fundamental mechanisms associated with an over-exuberant host-response are synergized in diabetic and pre-diabetic obese subjects prone to severe periodontal disease.<sup>100</sup> Severe periodontitis has been reported to be a predictor of cardiorenal death in type 2 diabetic Pima Indians.<sup>101</sup> Prevention and management of progressive periodontal disease has important implications in subjects who may harbour co-morbidities which could escalate in the absence of disease control.

The potential role of  $\alpha$ -defensins in dyslipidaemia and vascular dysfunction in humans has been investigated,<sup>102</sup> based on the hypothesis that  $\alpha$ -defensins 1–3 (DEFA1–3) synthesized by neutrophils are associated with modulation of cholesterol metabolism and vascular function in humans. A group of 113 healthy white males was assessed for lipid profiles, insulin sensitivity and non-stressed circulating DEFA1–3 using ELISA. Subjects in the highest quartile for serum levels of DFA1–3 were

significantly more sensitive to insulin with reduced total and LDL-cholesterol in comparison with subjects in the lowest quartile for circulating DEFA1–3. This study indicates that  $\alpha$ -defensins could have clinical implications in modulating vascular dysfunction or hyper-cholesterolaemia. Increased body weight and smoking decreased circulating levels of  $\alpha$ -defensins 1–3 in apparently-healthy males with elevated levels of total and LDL-cholesterol, suggestive of potential for therapeutic targeting in this context.

There is substantial documentation regarding the link between periodontal disease severity and systemic diseases. This raises the question of morbidity and mortality in the absence of periodontal treatment and the implications of reducing risk associated with systemic inflammatory loading by treating periodontal disease.<sup>103</sup> This has been shown to improve glycaemic control in diabetics and improve serum levels of surrogate markers of coronary heart disease. There is increasing documentation of a close relationship between periodontitis and DM which has been reviewed recently.<sup>104</sup> Cohort studies in Japan indicate a significant association of obesity and metabolic syndrome with periodontal diseases. More work is required to prove direct associations of glycaemic control in response to periodontal treatment.

Infection and inflammation are risk factors for type 2 DM. It was hypothesized that chronic inflammatory periodontal disease is related to A1C progression in DM-free subjects.<sup>105</sup> A population Study of Health in Pomerania (SHIP) was conducted including 2973 diabetes-free participants aged 20–81 years. Participants were characterized into 4 groups of ascending values of periodontal attachment loss (of >5 mm). Mean absolute changes in A1C were regressed across to periodontal categories. There were approximately five-fold increases in the absolute difference in Delta A1C when dentate subjects in the range of periodontal categories were compared and correlated well with levels of high sensitivity-CRP > or equal to 1 mg/l. The difference in Delta A1C values between periodontitis- and non-periodontitis subjects and progressive longitudinal deterioration was also significant. It was concluded that periodontal disease was associated with progression of A1C over 5 years; and this





association was similar to that observed for a 2-SD increase in either waist-to-hip ratio or age in this group of subjects.

Factors that predispose to alveolar bone dehiscence were investigated in a model model of metabolic syndrome with type 2 DM.<sup>106</sup> The effect of administering the antioxidant N-acetylcysteine on alveolar bone loss, expression of endothelial nitric oxide synthase in keratinocytes and hydrogen peroxide concentrations in plasma were assessed in this animal model. The expression of endothelial nitric oxide synthase was decreased in gingival keratinocytes of test versus control mice. This was restored by administration of N-acetylcysteine with reduced alveolar bone loss and decreased plasma levels of hydrogen peroxide. There was no significant improvement in obesity or diabetes. Reactive oxygen species such as hydrogen peroxide and resultant oxidative damage are responsible for the above changes. It was concluded that oxidative stress and its sequelae are highlighted in their role in contributing to periodontal bone loss secondary to diabetic complications.

Microbial metabolites play an important role in interspecies and host-modulated inflammatory responses. Oral microbial dynamics with specific relevance to *Pg* and its genome scale metabolic network was investigated using a stoichiometric model encompassing 679 metabolic reactions.<sup>107</sup> To provide further clarification of metabolic functions, knockout of the LPS biosynthetic pathway was studied and 8 putative targets were identified. Further refinement of this model could prove useful in defining microbiome-dynamics relevant to biomedical applications.

### Connections that unify links between periodontitis and DM

Complications of DM affect most organ systems and the periodontium. Insulin resistant states in the absence of DM have been reported in conjunction with increased inflammation, raised levels of inflammatory markers such as cytokines, CRP and plasminogen activator inhibitor-1.<sup>108</sup> Monocytes could be initiated to secrete inflammatory cytokines in response to lipids, fatty acids and various adipokines which could contribute to insulin resistance.

An inflammatory nidus of adipose tissue metabolism and type 2 DM could contribute to periodontal disease progression in the susceptible individual via a progressive inflammatory pathology. Further clarification is required regarding correlations in the aetiopathogenesis of DM, microvascular diseases and chronic periodontitis. Adipocytokines play an important role in the mechanisms governing correlations between obesity and periodontitis.<sup>70,71</sup>

Obesity and resultant chronic inflammation function as a common denominator in the documented association between periodontitis and type 2 DM. A rat model system that simulates human obesity and type 2 DM was used to investigate the effect of periodontal disease and diet on the onset of insulin resistance and type 2 DM.<sup>109</sup> Twenty-eight, 5 week old female Zucker diabetic fatty rats were set up in 4 experimental groups of high-fat or low-fat diet with or without ligature-induced periodontitis. At week 13, rats with periodontitis fed on a high-fat diet developed significantly more severe insulin resistance than any of the other three categories; with a more rapid onset of insulin resistance and hyperglycaemia in comparison with high-fat controls. The low-fat groups showed no significant change. The level of TNF- $\alpha$  was significantly higher in high-fat periodontitis-rats when compared with high-fat controls. It was concluded that periodontitis significantly enhanced the onset of insulin resistance and impaired glucose homeostasis in Zucker diabetic rats on a high-fat diet.

### Evidence for Effects of Periodontal Treatment on Parameters of Insulin Resistance and Coronary Heart Disease

There is documented evidence of greater severity of periodontal disease in poorly controlled diabetics than in healthy subjects. Monocytes and macrophages have been implicated in the damaging inflammatory changes seen in diabetic periodontal patients by producing higher levels of inflammatory cytokines. The underlying mechanisms have been investigated recently using histiocytes cultured in normoglycaemic (5 mM) and hyperglycaemic (25 mM) media in the presence of 100 ng/ml of LPS for 24 h.<sup>110</sup> Histiocytes cultured in hyperglycaemic



conditions showed significantly greater secretion of pro-inflammatory cytokines in response to LPS than normoglycaemic cells. This hyper-inflammatory response in histiocytes was associated with increased mRNA expression. LPS seems to act synergistically with high glucose concentrations in stimulating the secretion of inflammatory cytokines. This response was inhibited by simvastatin which has applications in the adjunctive management of severe periodontitis fuelled by DM.

The anti-inflammatory properties of statins which are used to treat hypercholesterolaemia, hyperglycaemia and hypertriglyceridaemia in diabetic subjects have been addressed by other workers.<sup>111,112,7</sup> They are effective in inhibiting high glucose-enhanced TNF- $\alpha$ , IL-1 and IL-6 to significantly low levels and also inhibit their expression as well as that of MMP-1. The anti-inflammatory effects of atorvastatin in type 2 DM patients include reduced levels of CRP,<sup>113,114</sup> decreased inflammatory activation of endothelium and improved endothelial function<sup>115</sup> in addition to improving hypercholesterolaemia. The results of these studies highlight potential applications of statins in reducing periodontal inflammation as well as dyslipidaemic control<sup>116,117</sup> and also the importance of reducing periodontal inflammation with active initial phase periodontal treatment in controlling DM, emphasizing a bi-directional relationship in the progression of both diseases.<sup>118,119</sup>

Periodontal disease has been shown to overcome the beneficial effects of antimicrobials in preventing coronary events. Its link with coronary heart disease is well documented. Very few pathogens including *Chlamydophila (Chlamydia) pneumoniae* have been targeted in the context of coronary events. A recent pilot study showed that long-term clarithromycin treatment was effective in reducing recurrent cardiovascular events in non-periodontitis subjects but failed to do so in subjects with periodontitis.<sup>120</sup> Periodontitis could contribute to the failure of antibiotics in preventing coronary events and underscores the importance of the systemic effects of uncontrolled periodontitis and the relevance of periodontal stabilization particularly in those at risk of coronary events. The effects of adjunctive antioxidants in overcoming oxidative stress-induced sequelae in periodontal and systemic diseases have been reviewed recently.<sup>121,116,117</sup>

A recent meta-analysis of longitudinal and cross-sectional studies has demonstrated that patients with chronic periodontitis are at risk of developing cardiovascular disease.<sup>122</sup> Periodontal pathogens play an important role in immune/inflammatory mechanisms that contribute to this phenomenon.<sup>123,39,124</sup> Periodontal pathogens and their products have been shown to instigate atherosclerotic changes in human and animal studies.<sup>125,126</sup> Evidence of chronic inflammatory processes and their markers as risk factors linking periodontal disease to cardiovascular events is well documented.<sup>127</sup> Buhlin et al<sup>128</sup> investigated the effect of mechanical and surgical intervention in periodontitis patients, on conventional atherosclerotic risk factors and the levels of cytokines, antibodies against heat shock proteins and markers of systemic inflammation. Fifty-four patients with severe periodontal disease underwent treatment consisting of root surface debridement for periodontal pockets. There was a successful periodontal outcome with significant reduction in pathological pockets. Markers of plasma glucose, systemic inflammation and lipids were not significantly changed after 3 months.

One year after initial phase periodontal treatment HDL-cholesterol concentrations increased significantly while LDL-cholesterol levels decreased; haptoglobin concentrations were also lower. Levels of IL-18 and interferon- $\gamma$  decreased after 12 months. Initial phase periodontal treatment was successful in reducing systemic biochemical risk markers for atherosclerosis in this study consisting of patients with severe periodontal disease. This investigation demonstrated that periodontal treatment ameliorates circulating levels of risk markers for cardiovascular disease such as the ratio of LDL:HDL although changes induced in response to periodontal treatment were modest. Decreased levels of HDL-cholesterol were seen in response to acute and chronic infections; these changes could occur as a result of an increase in apolipoprotein A-1 catabolism and changes in HDL-cholesterol subclass distribution.<sup>129,130</sup> LDL-cholesterol receptor expression levels, alterations in lipase and lipid transfer protein activities could account for decreased levels of LDL following periodontal treatment. Results need to be interpreted with caution in view of natural fluctuations that exist; and the lack of untreated controls during the period of the study due to ethical



implications of withholding an important clinical intervention under the circumstances.

Gene expression of peripheral blood monocytes was investigated in blood samples of 15 periodontal patients at 4 time points comprising 1 week before periodontal treatment, at initiation of treatment, 6 and 10 weeks later.<sup>131</sup> Periodontal status was recorded and subgingival plaque samples obtained at initiation of treatment and at 10 weeks. Periodontal therapy comprising surgery and extractions was completed within 6 weeks without adjunctive antibiotics. Serum levels of biomarkers were determined at the 4 time points. Peripheral blood monocytes were expression profiled and differential expression of selected genes confirmed by real time reverse transcriptase PCR in a subset of patients. Treatment resulted in substantial reduction in periodontal pathogen loading and improved periodontal parameters. About 33% of patients showed significant changes in gene expression relevant to innate immunity, apoptosis and cell signalling. It was concluded that periodontal therapy could alter monocytic gene expression compatible with a systemic anti-inflammatory effect.

The inflammatory pathway from cholesterol to ageing is a relevant one. IL-6-mediated inflammation is implicated in a range of systemic diseases including atherosclerosis, peripheral vascular disease, osteoporosis, type 2 DM, arthritis and cancer.

It is relevant that there is an increased prevalence of metabolic syndrome in patients with systemic lupus erythematosus (SLE) and a higher incidence of insulin resistance.<sup>132</sup> The association of SLE with cardiometabolic risk factors has implications on lifestyle interventions and therapeutic considerations.

Actions of statins and biphosphonates in inhibiting IL-6-mediated inflammation may be accounted for by indirect regulation of cholesterol synthesis and isoprenoid depletion. Polyphenolic compounds isolated from fruits and vegetables inhibit signal transduction pathways which contribute to IL-6-mediated inflammation.<sup>38</sup> Attenuation of this pathway could contribute to therapeutic targets. Available documentation on reversal of systemic risk factors pertaining to cardiometabolic disorders following control of periodontal disease progression provides pointers of a common process amenable to treatment.

## Summary and Conclusions

The inflammatory burden generated by periodontitis could contribute to a systemic trigger for inflammatory and immune-mediated responses caused by bacteraemia and endotoxaemia generated by periodontal pathogens.<sup>133</sup> Atherogenic events are influenced by specific virulence factors of periodontal pathogens<sup>3,134</sup> which have also been isolated from atherogenous plaque. Alteration in lipid metabolism as a result of chronic inflammatory diseases such as periodontitis and the unregulated generation of cytokines and enzymes are potential inducing factors for dyslipidaemic atherogenesis and insulin resistance. Resulting oxidation of lipids and formation of free fatty acids, triglycerides and LDL-cholesterol characterize a series of events which maintain cyclical release of cytokines and immune dysregulation. This series of events refuels oxidative stress, relevant to atherogenic events and insulin resistance with impaired wound healing and progression of periodontitis.<sup>135</sup>

Cholesterol rich diets in animal feed contributes to the progression of periodontitis. It is relevant that treatment of periodontitis results in reversal of risk markers for hyperlipidaemia with implications on improved disease status of both periodontitis and cardiometabolic co-morbidities. A significant increase in the HDL/LDL ratio and decreased serum levels of amyloid and CRP have been reported following periodontal therapy in systemically healthy subjects with periodontitis. The antiatherogenic effects of HDL have also been reported to be attenuated in untreated periodontitis,<sup>130</sup> increasing risk of coronary events. Statin therapy reduces high sensitivity-CRP largely independent of LDL.<sup>136</sup> Targeted anti-inflammatory therapies based on the biology of inflammation have potential for new treatment approaches. Evidence of common pathogenesis in periodontitis and cardiometabolic co-morbidities opens avenues for a better understanding of disease processes and innovative intervention for disease control.

## Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author



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