Epidemiological data demonstrate a clear link between periodontal disease and diabetes, and individuals with diabetes, particularly if poorly controlled, are at risk for advanced periodontitis. Diabetes is increasingly viewed as an inflammatory condition and dysregulated immune-inflammatory responses in diabetes may increase susceptibility to periodontal disease by disrupting local cytokine networks in the periodontium. Inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are important in the pathogenesis of both diseases, and together with other pro-inflammatory cytokines and adipokines, may provide a mechanistic link between the two diseases. Altered neutrophil function and deposition of advanced glycation end-products (AGEs) are also likely to be important in the increased susceptibility to periodontal disease seen in people with diabetes. Emerging data suggest that treating periodontal disease may have a beneficial effect on glycaemic control, and highlight the need to incorporate a full periodontal examination into management strategies for patients with diabetes. It is clear that the dental team must become increasingly involved in the management of patients with diabetes, and it is recommended that periodontal screening of all patients diagnosed with diabetes is undertaken as a matter of routine.

**Key words:** Periodontal diseases, type 1 diabetes mellitus, type 2 diabetes mellitus, risk factors, diabetes complications

It has long been recognised by the dental community that patients with diabetes have a greatly increased risk for periodontal disease. Patients with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) often present with advanced periodontal disease, particularly if they have poor glycaemic control. T1DM accounts for approximately 5% of all cases of diabetes, and is mainly due to auto-immune destruction of the β-cells in the pancreas. The precise aetiology is not fully understood, but may be triggered by viral infection. Destruction of β-cells leads to reduced levels of insulin and resultant hyperglycaemia, and typically requires treatment with exogenous insulin. T2DM develops as a result of both insulin resistance (i.e. an inability of the body to respond normally to insulin) and deficient β-cell function (resulting in failure to produce sufficient insulin). Onset of T2DM was previously typically in middle age, but as a result of high calorie food intake, obesity and sedentary lifestyles, younger individuals are now being diagnosed with T2DM. Early symptoms can be vague, however, and therefore many patients remain undiagnosed whereas others are diagnosed by chance during investigations for other conditions. T2DM is a heterogeneous condition and arises from interactions between environmental stressors (e.g. obesity, sedentary lifestyle) and genetic susceptibility that result in insulin resistance and the clinical manifestations of disease.

In 2000, approximately 150 million people worldwide were affected by T2DM, which is now regarded as a rapidly developing global epidemic predicted to affect approximately 300 million people by 2025. Prevention and management of diabetes, particularly T2DM, and associated complications have become major healthcare challenges throughout the world. The emergence of diabetes as a global epidemic is a recent phenomenon driven by the trends of poor diet and a collapse in physical activity. These environmental stressors unmask a genetic susceptibility, sometimes referred to as the ‘thrifty genotype’, to the disease. The thrifty gene hypothesis holds that certain genes have evolved to maximise metabolic efficiency, lipid storage and food searching behaviour to ensure survival during the periods of starvation that would have regularly confronted our ancestors. During such periods of food shortage, those individuals who could store energy in the form of lipid most efficiently would have had a survival advantage. However, in times of abundance, these same genes predispose their carriers to diabetes as a result of excessive nutritional intake and obesity. With the advent of relative inactivity and high fat, high carbohydrate and low fibre diets, this genotype is no longer advantageous because it is too efficient. This has led to obesity and related health problems throughout the world and is a clear example of how our evolutionary
development has become mismatched from our present day environment.

The complications of diabetes stem from chronic hyperglycaemia, which has wide ranging molecular and cellular effects resulting in oxidative stress, upregulation of pro-inflammatory responses and vascular changes. Collectively, these predispose individuals to the classic diabetes complications: retinopathy, nephropathy, neuropathy, macrovascular disease (including atherosclerosis) and altered wound healing.

**Diabetes and periodontal disease**

Oral manifestations of diabetes have been reported to include xerostomia, burning mouth syndrome, candidal infection, altered taste sensation, periodontal disease, dental caries and delayed wound healing. As early as 1993, periodontal disease was described as the 6th complication of diabetes. However, it has taken many years for this to become more widely accepted. Indeed, only in 2003 did the American Diabetes Association's Report of the Expert Committee on Diabetes Diagnosis and Classification state that "Hypertension, abnormalities of lipoprotein metabolism and periodontal disease are often found in people with diabetes".

The epidemiological links between T2DM and periodontal disease are compelling and have been extensively reviewed. Some of the earliest studies focussed on the Pima Indians, a population in the USA with a particularly high prevalence of T2DM. Thus, in a study of 2,273 Pima Indians between 1983 and 1989, tooth loss and interproximal bone loss were used to define periodontal disease (the diagnosis of periodontal disease was assigned if <24 teeth were present, or there were ≥ 6 teeth with ≥ 25% bone loss, or there were any teeth at all with ≥ 50% bone loss). The authors reported the prevalence of periodontal disease to be 60% in the 720 subjects with T2DM compared to 36% in 1,553 controls. These investigators also monitored those subjects with minimal or no periodontal disease at the initial screening (n=701) and identified the incidence (i.e. the onset of new cases of periodontal disease) to be 60 new cases per 1,000 person-years in the T2DM population and 17 new cases per 1,000 person-years in the control population. While we may criticise aspects of the methodology in these early studies (e.g. the criterion for ‘no periodontal disease’ permitted subjects to have up to 5 teeth with 25-50% bone loss and the rest of the dentition to demonstrate up to 25% bone loss), they were among the first to establish the epidemiological link between periodontal disease and T2DM.

In a further study of 359 Pima Indians, alveolar bone loss (up to 25% of the root length) was identified in 67% of 21 T2DM patients compared to 44% of 338 non-diabetic controls. These individuals were monitored for a mean duration of 2.3 years (range 1.2-6.9 years) and it was noted that there was a significantly greater risk for ongoing bone loss (odds ratio 11.4; 95% CI: 2.5, 53.3; p<0.001) if the diabetes was poorly controlled, but no significant risk for progressive bone loss (odds ratio 2.2; 95% CI: 0.7, 6.5; not significant) if diabetes was well controlled, compared to non-diabetic individuals. The threshold for defining good glycaemic control was glycated haemoglobin (HbA1c) < 9%. Interestingly, this study also provided evidence to support a possible negative effect of periodontitis on glycaemic control, as subjects with moderate or well controlled T2DM at baseline who also had severe periodontitis were approximately six times more likely to have poor glycaemic control at 2 years post-baseline than the subjects who did not have severe periodontitis at baseline.

In a study of 1,342 Pima Indians, the percentage of subjects with at least one periodontal site with attachment loss ≥ 5mm was recorded. For all age cohorts, the percentage of individuals demonstrating this level of periodontal disease was greater for those with T2DM compared to those without. These authors reported that individuals with T2DM had an increased risk for periodontal disease, with an odds ratio of 2.81 (95% CI 1.91, 4.13) when attachment loss ≥ 5mm at one or more site was used to define the presence of disease and an odds ratio of 3.43 (95% CI 2.28, 5.16) when bone loss ≥ 25% at one or more site was used.

Subsequent studies applied increasingly stringent classification criteria to define the presence or absence of periodontal disease in an attempt to better confirm the association with diabetes. In a study of 102 T2DM patients and 102 age- and sex-matched controls in Sweden, bone loss ≥ 33% of the root length was reported in 45% of the T2DM patients compared to 28% of the controls (p=0.006). Furthermore, T2DM patients suffered more from xerostomia than controls (54% vs. 28%, p=0.0003), and showed a greater need for periodontal treatment (p=0.05), caries prevention (p=0.002) and prosthetic treatment (p=0.004). In a further study of 191 patients with T2DM in Sweden, 20% had periodontal disease, defined as bone loss ≥ 33% of the root length in ≥ 30% of periodontal sites. Those with a diagnosis of periodontal disease had higher HbA1c than controls (7.1% vs. 6.5%, p=0.033) and higher prevalence of cardiovascular complications (25% vs. 4%, p=0.012).

When considering type 1 diabetes, a trend towards more alveolar bone destruction was seen in 35 adults aged 24-36 years with increasing severity of diabetes (determined from HbA1c values and the presence of diabetes complications such as retinopathy). In a large study of 350 children aged 6-18 years old (of whom 325 had T1DM) and 250 non-diabetic controls, subjects with diabetes had increased gingival inflammation and attachment loss compared to the controls. In this study, 21% of sites in the patients with diabetes had attachment loss > 2mm compared to 8% in the controls (p<0.001). Thus, it is clear that even at an early age,
diabetes increases the risk for periodontal destruction. These authors recommended that strategies to address periodontal treatment need should be implemented and become standard of care even in young children with diabetes.

It is clear from a large number of studies that diabetes (both T1DM and T2DM) is a significant risk factor for periodontal disease, and the risk is greater if glycemic control is poor. The next challenge is to understand why diabetes, especially if poorly controlled, has such an impact on periodontal health.

**Mechanisms linking diabetes and periodontal disease**

Periodontitis and diabetes share common pathogenic processes and both can be thought of as upregulated and/or maladapted responses of the immune system to environmental stressors acting on the host. In the case of periodontitis, susceptible individuals mount an aggressive, upregulated inflammatory response to the presence of plaque, with environmental stressors (e.g. smoking) adversely affecting the disease process. Environmental stressors in T2DM include excessive food intake, lack of exercise and obesity, and these combine with a genetic susceptibility to result in the signs and symptoms of diabetes.

The inflammatory response in the periodontal tissues is characterised by the local production of a variety of inflammatory mediators and enzymes, such as cytokines (e.g. interleukins), prostanoids, and matrix metalloproteinases (MMPs). Inappropriate cytokine secretion, whether quantitative (i.e. excessive cytokine release) and/or qualitative (e.g. an imbalance between the proportions of pro- and anti-inflammatory cytokines) is a manifestation of dysregulated immune responses and results in periodontal tissue destruction. As the inflammatory front induced by the subgingival biofilm extends laterally and apically, infiltrating cells such as polymorphonuclear leukocytes (PMNL), monocytes/macrophages and lymphocytes are recruited to the area, occupying a considerable volume of the soft tissues. As the inflammatory infiltrate extends towards the alveolar bone, osteoclastic bone resorption is enhanced so the bone retreats from the expanding area of inflammation. Key cytokines that drive these processes include interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), and local over-production of these cytokines is a major contributor to periodontal breakdown. Local networks of a range of both pro- and anti-inflammatory cytokines are critical in determining the extent of tissue destruction, and it is reasonable to assume that substantial changes in immunologically active molecules as a result of systemic disease (e.g. diabetes) might disturb finely balanced cytokine networks in the periodontium. This could alter local inflammatory responses and increase the susceptibility to periodontal disease in people with diabetes. The hypothesis that diabetes alters local inflammatory networks in the periodontium, and that this may explain the increased susceptibility to periodontal disease, is strengthened by the concept of diabetes as an inflammatory condition.

**T2DM is an inflammatory condition**

T2DM is increasingly viewed as an inflammatory condition. Thus, the development of T2DM is preceded by a low grade systemic inflammation. Plasma concentrations of IL-6 and TNF-α are increased in obesity and T2DM. Hyperglycaemia results in cellular oxidative stress and resultant inflammatory changes. The source of TNF-α in the serum of T2DM patients is partly from adipose tissue, and also from stimulation of leukocytes by advanced glycation end-products (AGEs – see below). Increased circulating IL-6 is also associated with insulin resistance and may predict future T2DM.

Although adipose tissue has previously been considered a passive store of lipid, it is now regarded as an active endocrine organ that secretes a wide range of immunologically active molecules involved in regulating food consumption and energy balance. These molecules are collectively known as adipokines, and include leptin, adiponectin, resistin and visfatin. Leptin activates inflammatory responses by acting as an acute-phase reactant and a stimulator of neutrophil function, and it can also stimulate cytokine secretion by monocytes. Leptin levels directly correlate with adipose tissue mass, and act to decrease food intake and increase energy consumption. Obese individuals have increased circulating levels of leptin and increased resistance to its actions in the control of food intake. High leptin levels have been associated with increased risk of developing T2DM. Leptin has also been identified in the gingiva in concentrations that inversely correlate with probing depths. Further details on the potential roles of leptin and other adipokines in periodontal pathogenesis have been reviewed elsewhere.

TNF-α and C-reactive protein (CRP) are also produced by adipose tissue and thus can be considered adipokines. There are clear associations between elevated serum TNF-α levels and obesity. CRP is synthesised in the liver and also by adipocytes. CRP production is regulated primarily by circulating IL-6 levels, and therefore is influenced by adipocytes which themselves secrete significant quantities of IL-6. CRP levels are elevated in obesity and T2DM, and elevated CRP levels have been associated with periodontitis. The association of elevated systemic CRP levels with periodontal disease and subsequent decreases following periodontal therapy are taken to indicate that the inflammatory response to periodontitis contributes to the overall inflammatory challenge throughout the body. However, the precise role of CRP in linking periodontal disease and diabetes remains unclear.
We can conclude that relationships between cytokine networks in the periodontium and T2DM are likely to be complex. Emerging research supports a contributory role for circulating inflammatory cytokines in insulin resistance and for upregulated inflammatory responses in the periodontium in the presence of hyperglycaemia. Thus, a trend for increasing GCF IL-1β concentrations has been identified as diabetes control decreases\(^{29}\). Furthermore, poorly controlled T2DM patients (HbA1c > 8.0%) with untreated periodontitis have significantly higher GCF IL-1β levels compared to T2DM patients with moderate or good glycaemic control\(^{29}\). More recently, in a study of 10 T2DM patients and 10 controls, GCF IL-1β levels were nearly twice as high in those with diabetes compared to the controls (though this did not reach statistical significance)\(^{30}\). Thus, individuals with diabetes, particularly those with poor glycaemic control, can be considered to mount upregulated immune-inflammatory responses against the subgingival biofilm, resulting in increased tissue damage and the clinical signs of disease. Dysregulation of cytokine networks may underpin a wide range of systemic disorders and may provide the basis for cross-susceptibility between diabetes and periodontal disease\(^{31,32}\). Furthermore, research supports a contributory role for circulating cytokines (which may, in part, be derived from the inflamed periodontium) in insulin resistance. For example, binding of TNF-α and IL-6 to receptors in muscle cells or hepatocytes can directly interfere with insulin signalling and consequently dampen the cellular response to insulin\(^{31,32}\).

**Impaired PMNL function**

Impaired function of PMNL may be a further mechanistic link between periodontal disease and diabetes. T2DM has been shown to result in impaired PMNL chemotaxis\(^{33}\), adherence\(^{33}\) and phagocytosis\(^{33}\). Furthermore, diabetic patients with severe periodontitis have been shown to have depressed PMNL chemotaxis compared to non-diabetics with periodontitis or diabetics with mild periodontitis\(^{34,37}\). Diabetes may also result in increased susceptibility to periodontal disease via impaired PMNL apoptosis (programmed cell death)\(^{38}\). Patients with diabetes have been reported to have defective PMNL apoptosis\(^{39}\), which may in turn lead to increased retention of PMNLs in the periodontium resulting in increased tissue destruction by continued release of MMPs and reactive oxygen species.

**Advanced glycation end-products**

In the hyperglycaemic state, proteins and matrix molecules undergo non-enzymatic glycosylation resulting in the formation of AGEs. This occurs in people who do not have diabetes too, but in the hyperglycaemic state formation of AGEs is excessive. Collagen becomes cross-linked by AGE formation, making it less soluble and less amenable to appropriate remodelling. Cellular migration through these tissues is impeded and tissue integrity is impaired. There is evidence that AGEs play a role in periodontal pathogenesis via their interaction with the cellular AGE receptor (RAGE) present on monocytes and macrophages\(^{40}\). Binding of AGE to RAGE results in upregulation of inflammatory cytokines such as IL-1β, IL-6 and TNF-α\(^{41}\) and monocytes from patients with diabetes produce greater quantities of cytokines in vitro compared to non-diabetic controls\(^{42}\).

AGE formation also results in the production of reactive oxygen species (ROS) and enhances oxidant stress. The subsequent endothelial cell changes that occur contribute to the vascular injury that is implicated in many diabetes complications\(^{43}\). AGEs also enhance the respiratory burst in neutrophils\(^{44}\) which may significantly increase local tissue damage in the periodontium.

Thus, there are several mechanisms that are likely to play a role in the increased susceptibility to periodontal disease observed in people with diabetes. Susceptible individuals are considered to mount excessive, dysregulated inflammatory responses to the presence of plaque bacteria, and this is exacerbated in diabetes. Figure 1 presents a model for the increased periodontal destruction observed in diabetes.

**Impact of periodontal treatment on diabetes**

A small number of studies have investigated whether effective periodontal treatment can improve diabetes control. Most have been somewhat under-powered and of varying designs, particularly with respect to the periodontal treatment provided. It is therefore difficult to draw clear conclusions as to the impact of periodontal therapy on glycaemic control. In a meta-analysis of 10 intervention studies to quantify the effects of periodontal therapy on HbA1c, a weighted mean absolute decrease in HbA1c of 0.66% was observed in T2DM patients following periodontal treatment, though this did not achieve statistical significance\(^{45}\). However, this suggests that there is a possibility that periodontal therapy may have an impact on diabetes control, but this remains to be confirmed in larger studies.

**Future recommendations**

In the latter part of the 20th century, the reported prevalence of advanced periodontitis in Western populations reduced from approximately 70%/\(^{46}\) to approximately 8-15%/\(^{47,48}\). Partly these decreases are artificial, resulting from the changes in methodology (e.g. diagnostic techniques and thresholds for defining periodontal disease) that have occurred over time. However, there is no doubt that these decreases have also arisen because of better awareness of the importance of oral hygiene...
and improved diagnostics and management. Taking all these factors into consideration, it has been estimated that the incidence of advanced periodontitis truly decreased by 31% from 1955 to 2000. One of the most significant contributors to this is likely to have been the decrease in smoking that occurred over the same time period. Indeed, Hujoel and colleagues suggested that “a periodontitis epidemic fuelled by smoking remained hidden for much of the 20th century. Because this epidemic was hidden, it distorted our understanding of the treatment and etiology of periodontitis.”

This decrease in the incidence in periodontal disease is to be welcomed. However, it is possible that we may now be at another turning point in the epidemiology of periodontitis, and this is because of the predicted increases in the prevalence of diabetes that will occur over the next 25 years. As has become very clear, diabetes is a major risk factor for periodontal disease, and it is possible that, following a period of decreasing prevalence of periodontitis in recent decades (associated with less smoking and better oral health behaviours), we may now be about to commence a period of increasing prevalence of periodontitis (associated with obesity and diabetes).

As dentists, we must remain alert to this possibility, and several recommendations for the future can be made.

- Careful oral and periodontal examination must be performed in all patients with diabetes, even in children
- We must be aware of the changing demographics of diabetes (and thus the increased risk for periodontal disease). Diabetes is increasingly common in emerging economies, and also in deprived segments of more affluent countries.
• We must liaise with our medical colleagues to become an integral part of the healthcare team managing patients with diabetes
• Early diagnosis and prevention of periodontal disease are of fundamental importance in people with diabetes
• The entire dental team, together with our medical colleagues, have a role in educating patients to maintain periodontal health
• Periodontal screening of all patients diagnosed with diabetes must become routine.

References


44. Wong RK, Pettit AI, Quinn PA, et al. Advanced glycation end products stimulate an enhanced neutrophil respiratory burst mediated through the activation of cytosolic phospholipase A2 and generation of arachidonic acid. *Circulation* 2003 **108**: 1858-1864.


Correspondence to: Dr. P.M. Preshaw, School of Dental Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4BW, UK. Email: p.m.preshaw@newcastle.ac.uk