Periodontitis and diabetes: a bi-directional relationship?

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Diabetes is emerging as one of the most significant diseases to threaten human health in modern times. Type 2 diabetes mellitus is predicted to affect more than 300 million people by 2025, and currently, 1 in 10 children worldwide are obese or grossly overweight. The huge increase in the numbers of individuals affected by type 2 diabetes is associated with poor diet, high calorie food intake and a collapse in physical activity in many populations throughout the world. The concept of the ‘thrifty gene’ hypothesis has emerged to explain this phenomenon.\(^1\) Simply stated, humans have evolved to be able to cope with the alternating periods of starvation and plenty that regularly confronted our ancestors. We therefore have evolved to rapidly and efficiently store energy in the form of lipid in adipose tissue to enable us to survive periods of famine. Clearly, until modern times, this conferred an evolutionary advantage. However, in the modern era of widely available and abundant food, this genetic make up is no longer advantageous, but instead results in obesity and predisposes us to diseases such as type 2 diabetes. The term ‘malnourished’ used to refer exclusively to people who had inadequate food intake, but now can equally well be applied to individuals who have excessive and inappropriate food intake.

Dentists have long been aware of the importance of a diagnosis of diabetes in their patients. Various oral conditions are associated with diabetes, including dry mouth, candidal infections, delayed wound healing and periodontal disease. Periodontitis was described as the 6\(^{th}\) complication of diabetes in 1993, along with retinopathy, nephropathy, neuropathy, macrovascular disease and altered wound healing.\(^2\) However, the links between periodontal disease and diabetes were not so well recognised by the medical community until rather more recently. Thus, in 2003, the American Diabetes Association stated that ‘hypertension, abnormalities of lipid metabolism, and periodontal disease are often found in people with diabetes’.\(^3\)

Much of the prevalence data linking periodontal disease and diabetes was gathered in studies of the Pima Indians. This population of native Americans in Arizona has an unusually high prevalence of diabetes. The reason for this may be linked to the thrifty gene hypothesis.\(^1\) The rivers that this population
depended upon for crop irrigation were diverted by European settlers to the region, leading to crop failure and widespread starvation among the Pima Indians. Those who survived would be more likely to possess the thrifty genotype, leading to the enrichment of this genotype in the modern day Pima population. In present times of plenty, this has resulted in a hugely increased prevalence of type 2 diabetes in this population with more than half the individuals affected.

Early studies of diabetes and periodontal disease in the Pima Indian population identified a greatly increased prevalence and incidence of periodontal disease in those individuals who also had type 2 diabetes compared to those who did not. This was evident in all age groups, and it was concluded that those individuals with type 2 diabetes were approximately 3 times more likely to also have periodontal disease. Similar findings of increased prevalence of periodontal disease have also been reported in European populations with type 2 diabetes. In the NHANES III survey in the USA, it was reported that adults with poorly controlled diabetes had an almost threefold increased risk of having periodontitis compared with adults without periodontitis. Furthermore, adults with diabetes under good glycaemic control had no significant increase in risk for periodontal disease.

Looking at the problem from the other perspective, it has also been reported that diabetics with severe periodontal disease are six times more likely to have poor glycemic control. Further, patients with severe periodontal disease have a significantly increased risk for microalbuminaemia and end stage renal disease compared to those who do not. It has also been reported that Pima Indians with severe periodontal disease have an increased risk of death from diabetic nephropathy or ischaemic heart disease.

Patients with type 1 diabetes, including children, have also been reported to have increased prevalence of periodontal disease. Thus, in a study of 350 children with diabetes aged 6-18 years old compared to 350 controls without diabetes, it was observed that >20% of periodontal sites in the children with
diabetes demonstrated attachment loss >2 mm compared to 8% of sites in the non-diabetic controls.\textsuperscript{12}

Taken collectively, the epidemiological studies confirm that diabetes is a significant risk factor for periodontal disease, and also that the risk for diabetes is greater if diabetes control is poor. People with well controlled diabetes do not appear to be at any significantly greater risk for periodontal disease than non-diabetics.

The mechanisms that link these two diseases have yet to be fully understood. The importance of the host response in periodontal pathogenesis has now become firmly established.\textsuperscript{13} Thus, the challenge presented by the subgingival microflora results in a chronic immune-inflammatory response in the periodontal tissues. This is characterised by the local production of inflammatory mediators including cytokines (such as interleukins), prostanoids (such as prostaglandins) and destructive enzymes (such as matrix metalloproteinases, including collagenase). The excessive or dysregulated production of these mediators leads to the clinical signs of disease, characterised by attachment loss, alveolar bone destruction and pocket formation. The concept of the ‘periodontal hyper-responder’ is now established which holds that some individuals mount an aggressive or excessive inflammatory response to a given plaque challenge, leading to more rapid periodontal tissue breakdown and the signs of periodontal disease. This hypothesis may explain why some patients are more susceptible to periodontal disease, including aggressive forms of periodontitis.

The inflammatory response in the periodontal tissues in response to the plaque challenge is complex and involves networks of cytokines functioning in synergy. It is likely that alterations in immunologically active molecules as a result of diabetes may alter cytokine networks in the periodontium, and this is the scientific basis for the increased susceptibility to periodontal disease seen in people with diabetes. That is, diabetes modifies inflammatory processes resulting in further dysregulation of immune-inflammatory responses, resulting in increased periodontal destruction. This hypothesis is supported by
emerging concepts of diabetes itself as an inflammatory condition. Thus, a low grade systemic inflammation precedes a diagnosis of type 2 diabetes.\textsuperscript{14} Further, plasma interleukin-6 (IL-6) and tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) levels are elevated in the plasma of obese patients and those with type 2 diabetes.\textsuperscript{15} Hyperglycaemia also results in increased levels of IL-6, IL-12 and TNF-\(\alpha\).

One important source of cytokines in diabetes is the adipose tissue. Previously, adipose tissue was considered to be a rather passive repository for the storage of lipid. However, it is now recognised that it is an active endocrine organ that secretes hormones that regulate appetite and metabolism. Adipose tissue also secretes cytokines such as TNF-\(\alpha\) and IL-6. These have direct pro-inflammatory effects on inflammatory cells, including those in the periodontal tissues. The adipose tissue also secretes adipokines, such as leptin and adiponectin. Leptin is an important stimulator of inflammatory responses. It stimulates neutrophil chemotaxis and stimulates cytokine release by monocytes.\textsuperscript{16} The levels of leptin correlate with the mass of adipose tissue, and are elevated in obese individuals.\textsuperscript{17} High leptin levels have also been associated with an increased risk of developing type 2 diabetes.\textsuperscript{18} It is therefore certainly plausible that elevated leptin levels in patients with diabetes may contribute to enhanced periodontal tissue destruction by activation of pro-inflammatory responses in the periodontium. A further adipokine that may be relevant in the context of periodontitis is adiponectin. Adiponectin is generally considered to have anti-inflammatory effects, and low levels of adiponectin have been associated with obesity, diabetes and cardiovascular disease.\textsuperscript{19}

Another mechanism that may link diabetes and periodontal disease is that of impaired neutrophil function. Impaired chemotaxis, adherence and neutrophil function have been reported in patients with diabetes. Furthermore, delayed apoptosis (programmed cell death) has been reported in patients with diabetes.\textsuperscript{20} Neutrophils are a key component of the defence mechanisms against periodontal plaque bacteria in periodontal disease. However, if apoptosis is delayed, this will lead to increased retention of neutrophils in the
periodontal tissues which in turn could lead to increased tissue damage by the release of destructive enzymes such as matrix metalloproteinases and reactive oxygen species by the neutrophils.

A further mechanism that links periodontal disease and diabetes is the formation of advanced glycation end-products (AGEs). In conditions of hyperglycaemia, glycosylation of structural proteins and matrix molecules occurs, resulting in the formation of AGEs. This process occurs in people without diabetes too, but the rate of formation of AGEs is greatly increased in people with diabetes. The formation of AGEs is irreversible, and increased cross-linking of collagen molecules by this process contributes to other complications of diabetes as a result of decreased elasticity of blood vessels. Monocytes possess a receptor for AGEs, known as RAGE (the receptor for AGE). Binding of RAGE on monocytes to AGEs results in the release of pro-inflammatory mediators by the monocytes, such as IL-1β, TNF-α and IL-6, which contribute to further periodontal tissue destruction. AGEs also enhance the respiratory burst in neutrophils, again resulting in increased tissue damage. AGE formation contributes to many of the classic complications of diabetes, particularly those associated with reduced elasticity of blood vessels, and also is very likely to contribute to enhanced tissue destruction in periodontitis.

Thus, there are many mechanisms that link periodontal disease and diabetes. Deposition of AGEs and subsequent activation of monocytes via RAGE and altered neutrophil function enhance inflammatory responses. Adipose tissue is responsible for the secretion of pro-inflammatory cytokines and adipokines which further enhance inflammatory responses. In inflamed periodontal tissues, the upregulation of inflammatory responses and dysregulation of cytokine networks is likely to result in enhanced tissue breakdown, leading to the signs of disease and the observed increased susceptibility to periodontitis that is seen in patients with diabetes. What is particularly exciting is to identify whether treating periodontal disease may have a beneficial impact on diabetes control. This issue was addressed in a meta-analysis of 10 intervention studies in which patients with diabetes and periodontal disease
received periodontal treatment\textsuperscript{23} Following treatment, there was a very small improvement in glycaemic control as measured by glycated haemoglobin levels (HbA1c), with an absolute reduction of HbA1c of 0.66% in patients with type 2 diabetes. The small number of studies to date and their varied design limits the ability to reach firm conclusions on this issue, but they give promise that periodontal therapy may have a positive impact on glycaemic control.

Taken together, we can firmly conclude that diabetes increases the risk for periodontal disease compared to non-diabetics. This increased susceptibility most likely results from pathological processes that are common to both diseases and/or upregulated in the context of diabetes. There is also evidence that periodontal treatment may improve glycaemic control, and this will become clearer as more research is conducted.

The implications for the dental team are quite clear. We need to be alert for a diagnosis of periodontal disease in people with diabetes, even in young children. Changing demographics and the huge increases in the numbers of people affected by diabetes may contribute to an increased prevalence of periodontal disease in the future. Individuals from emerging economies are particularly vulnerable to this when they adopt a more Western form of lifestyle characterised by excessive intake of high calorie foods and a reduction in physical exercise. As dentists, we need to liaise with our medical colleagues regarding the management of patients with diabetes and become more involved in their medical care. It is important to always ask patients with diabetes about their level of glycaemic control, including what their most recent HbA1c values are. If the patient does not know, this can provide good evidence of their likely level of control and/or compliance!

Prevention of periodontal diseases is fundamentally important in patients with diabetes because of the potential negative impact of untreated periodontitis on glycaemic control and diabetic complications. Improved awareness of the dental team and better joint working with our medical colleagues is important to improve the periodontal and medical management of people with diabetes.
Ideally, patients with diabetes would be routinely referred for periodontal screening as part of the long term management of their diabetes.
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