The innate immune system and diabetes mellitus: the relevance of periodontitis?

A hypothesis

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ABSTRACT

About a decade ago, a hypothesis was proposed suggesting that the innate immune system, including acute-phase reactants, contribute to the development of T2DM [Type 2 DM (diabetes mellitus)] and the metabolic syndrome. In this model, it was hypothesized that the innate immune system modulates the effects of many factors, including genes, fetal programming, nutrition and aging, upon the later development of metabolic problems associated with insulin resistance. In this present article, we expand this hypothesis by looking at the involvement of periodontitis in DM and its complications. Periodontitis is a common inflammatory process involving the innate immune system and is associated with DM. We will also illustrate how dental disease is important in patients with DM and could be implicated in various diabetic complications.

INTRODUCTION

The innate immune system contributes to the development of T2DM [Type 2 DM (diabetes mellitus)] [1,2]. In this model, it was suggested that the innate immune system modulates the effects of many factors, including genes, ethnicity, fetal programming, nutrition and aging, upon the later development of metabolic complications associated with insulin resistance. In this present article, we expand this hypothesis by looking at the involvement of periodontitis in DM. This is topical as the International Diabetes Federation has recently reported its recommendations for oral health in patients with DM [3].

Periodontitis is a disease affecting the supporting structures of the dentition, namely the gingiva, periodontal ligament and alveolar bone. It is an inflammatory disease caused by a host response to the subgingival microbial biofilm, which results in local tissue destruction resulting in attachment loss and an increase periodontal pocket depth; this can lead to the mobility and loss of teeth. The plaque biofilm, which consists of several hundred species of bacteria, initiates an immune response in the periodontal tissues. This is mainly an action of the innate immune system, but the adaptive immune system also plays a role [4]. Along with these local changes, it has been shown that systemic markers of inflammation, such as CRP (C-reactive protein) and IL (interleukin)-6, are increased in disease [5]. Global prevalence of periodontitis is difficult to estimate due to differing measurements used, but an extensive review [6] concluded that worldwide prevalence of severe periodontitis is less...
than 10–15 %, but that this varies depending on race and geographical region. Not all patients with gingival inflammation will progress to the tissue destruction characteristic of periodontal disease and there are several modifying factors in developing periodontal disease, including smoking [7] and DM [8]. There is also a genetic component to the development and propagation of periodontitis which the literature would suggest is caused by various gene polymorphisms affecting the expression of certain cytokines, most notably IL-1 [9].

For the purposes of the present article, we shall consider only the relationship of chronic periodontitis with diabetes and will not include aggressive periodontitis in our hypothesis. Aggressive periodontitis is characterized by having, among other features, a non-contributory medical history and familial aggregation of cases [10]. For these reasons, our hypothesis may not apply to aggressive periodontitis and that other factors may be more appropriate to consider when discussing this disease.

Treatment of periodontitis is usually via non-surgical debridement of affected sites, but can include surgical procedures and antimicrobial therapy, as well as the emerging use of host modulation therapies [11]. Thus local infection in the periodontal pockets initiates a systemic inflammatory response releasing inflammatory mediators and eliciting a strong immune response against periodontal pathogens. Elevated systemic antibody levels especially to Porphyromonas gingivalis are associated with this process [12]. In recent years, there has been speculation that viral infection, specifically with HIV or human herpes viruses, may play a role in the pathogenesis of periodontitis [13]. Diseases of the oral tissues and specifically the periodontium have long been recognized as being associated with HIV infection, although it is difficult to determine whether there is any effect of HIV on periodontal health beyond that caused by immunosuppression and confounding factors [14]. While there is some evidence that viruses may be implicated in periodontal disease, there remains doubt as to the validity of the findings [13].

The innate immune system, which is phylogenetically older than the so-called acquired or adaptive immunity, is a rapid and efficient first-line defensive mechanism based on non-lymphoid tissue components, including macrophages and neutrophils. The acute-phase response is part of this system and results in changes in the concentration of plasma proteins in response to a variety of stresses, including infection, tissue trauma or inflammation [1,2]. We propose that periodontitis evokes a chronic acute-phase response activating the innate immune system [15,16].

Acute-phase proteins, such as CRP, haptoglobin, fibrinogen and amyloid A, are synthesized in the liver and are stimulated by certain cytokines, e.g. IL-1, IL-6 and TNF-α (tumour necrosis factor-α), which are released from macrophages, monocytes and endothelium. In addition, adipose tissue can release cytokines, including adiponectin and, thus, low-grade chronic inflammation may in part be due to obesity.

In the short term, the acute-phase response has survival value and functions to restore homoeostasis after various environmental insults such as infection or trauma. The innate immune response is active in periodontitis, which we hypothesize may be an important mediator in the aetiology of insulin resistance and T2DM. Furthermore, an association between periodontal disease and low-birthweight babies has been postulated. This may link periodontitis with fetal in utero programming and the ‘thrifty’ phenotype model of the development of insulin resistance, although confounders need to be considered such as how periodontitis is defined and measured [17].

**PERIODONTITIS AND ITS RELATIONSHIP WITH DM**

We will expand further our hypothesis by discussing how the innate immune system contributes to the pathogenesis of T2DM and how a reciprocal relationship exists between chronic periodontitis and glycaemic control in DM.

It has long been accepted that there is a relationship between periodontitis and DM. It was initially understood that periodontitis is a complication of diabetes [8,18–20]. Glycaemic status is important for the well being of periodontal ligament cells, which are very susceptible to variation or rapid fluctuation of glucose levels. These observations by Nishimura and co-workers [21] suggest that hyperglycaemia could indirectly exacerbate inflammatory tissue destruction through the body’s scavenger system against AGEs (advanced glycation end products), and that both hyper- and hypo-glycaemia might directly perturb the biological functions of periodontal connective tissues via cell–matrix interactions. A study by Kaur et al. [20] confirmed an association between T2DM and periodontitis and tooth loss. However, as more research into this relationship emerges, there is an increasing body of opinion that suggests that there is a two-way relationship between periodontal disease and diabetes [22]. It may be that this apparent reciprocal relationship between diabetes and periodontitis may be due to a common genetic locus of control or, as yet unidentified, common risk factors separate from those traditional ones. However, a number of theories suggesting periodontitis as a causative/modulating factor in diabetes (as diabetes is in periodontitis) have been proposed [22], one being that the systemic inflammation caused by periodontitis has an effect on the development and control of diabetes. It is this hypothesis that we shall now explore further.
Some diabetes complications associated with periodontitis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor glycaemic control: hyperglycaemia, increased insulin requirements and raised HbA1c</td>
<td>[31]</td>
</tr>
<tr>
<td>Dyslipidaemia: abnormal LDL-cholesterol, low HDL-cholesterol and hypertriglycerolaemia</td>
<td>[39]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>[34]</td>
</tr>
<tr>
<td>Microalbuminuria and proteinuria</td>
<td>[31]</td>
</tr>
<tr>
<td>ESRD</td>
<td>[34]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>[41]</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>[37]</td>
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</tbody>
</table>

According to Bradford Hill [23], in trying to prove periodontitis as a causative risk factor for the development of diabetes it is necessary to demonstrate that a plausible temporal nature exists between the two, that is that periodontitis precedes the development of diabetes. As many of the studies into the link between the two diseases are cross-sectional in nature or focus on an already diseased population, this has been difficult to establish. However, a recent study by Demmer et al. [24] has suggested that a temporal causative relationship exists. Their cohort study showed that patients beginning as non-diabetic but with periodontitis had an increased risk of developing diabetes even after accounting for traditional risk factors. Thus it may be, as we have mentioned previously and Demmer et al. [24] concede, that there is an unidentified common genetic predisposition to either diseases or another unidentified risk factor, but it may also be, as we postulate, that the systemic effects of periodontitis predispose to the development of DM.

Acute focal dental inflammation can result in a sudden increase in insulin requirements and endodontic treatment of dental inflammation is associated with attenuation of insulin resistance and reduced insulin requirements [25] (Table 1). It has been shown that non-diabetic patients with periodontal disease demonstrate impaired glycaemic control as well as having higher BMIs (body mass indexes) and higher LDL (low-density lipoprotein)-cholesterol, triacylglycerol (triglyceride) and total cholesterol levels [26].

However, it is not fully established that periodontal therapy improves glycaemic control; meta-analysis of such studies [27] and the Consensus Report of the Sixth European Workshop on Periodontology [28] found that it is inconclusive that periodontal treatment results in improved metabolic control. More intense therapy, and longer follow-up times, may be necessary to see more pronounced therapeutic benefits. Furthermore, there are no studies, to our knowledge, that have investigated the effect of periodontal therapy on metabolic control in a non-diabetic population. Elimination of periodontal infection by using systemic antibiotics, e.g. doxycycline, or topical antiseptics, such as chlorhexidine or povidone-iodine, in conjunction with scaling and root planing improved metabolic control in patients with DM, as shown by a reduction in HbA1c (glycated haemoglobin) and a decrease in insulin requirements [29]. Local administration of minocycline microspheres into periodontal pockets as an adjunct to scaling and root planing resulted in improved HbA1c in diabetic patients [30].

Sustained systemic elevation of pro-inflammatory mediators via the innate immune system, evoked by chronic periodontitis may, if our hypothesis is correct, predispose individuals to the development of T2DM, and treatment of periodontitis would thus be expected to improve glycaemic control. Indeed, treatment of periodontitis by scaling and root planing, in combination with short-term administration of antimicrobials, can improve glycaemic control in patients with DM, particularly if the dental disease is advanced and there is poor glycaemic control before treatment.

A 6.7% improvement in glycaemic control in the T2DM control group was less compared with a 17.1% improvement in the group with periodontal treatment, although in that study the HbA1c in the control group may have differed from test group [31]. However, a large meta-analysis has concluded that a greater risk of periodontal disease progression was associated with T2DM, and the presence of T2DM correlated with the response to periodontal therapy [19]. Thus T2DM can be considered a risk factor for periodontitis.

PERIODONTITIS AND ITS ASSOCIATION WITH THE COMPLICATIONS OF DIABETES

It has long been established that there is an association between cardiovascular disease and diabetes [32,33]. Thorstensson et al. [34] conducted a small case-control study investigating the common complications of diabetes and found an association between periodontitis and cardiovascular disease and renal disease; however, they did not find any association between periodontitis and other common complications, although this may relate to their small population size. Saremi et al. [35] found that periodontitis was a predictor of mortality from diabetic complications in Pima Indians, with a 3.2 times increased risk of cardio-renal mortality when periodontal disease was present.

The incidence of macroalbuminuria was higher in individuals with moderate or severe periodontitis or those who were edentulous, compared with those with none/mild periodontitis. Furthermore, the incidence of ESRD (end-stage renal disease) in individuals with moderate or severe periodontitis or in those who were edentulous were higher than those with no or mild periodontitis.
Thus periodontitis predicts the development of overt nephropathy and ESRD in individuals with T2DM. The prevalence of proteinuria and cardiovascular complications, such as stroke, TIA (transient ischaemic attack), angina pectoris, myocardial infarction and intermittent claudication, were found to be higher in diabetic patients with severe periodontitis. An association between renal disease, cardiovascular complications and severe periodontitis appears to exist [36]. Similarly, diabetic retinopathy and nephropathy were more common in those DM patients with periodontitis than those without [37].

P. gingivalis may stimulate foam cell formation by its action on apolipoprotein-B100, the major apolipoprotein of LDL [38], which would suggest a potential mechanism by which periodontal bacteria may induce atheroma formation. Furthermore, periodontitis is associated with increased serum LDL-cholesterol and triacylglycerols, and this may relate to the severity of the periodontal disease [39]. A case-control study found that patients with periodontitis had higher LDL-cholesterol and lower HDL (high density lipoprotein)-cholesterol levels, higher total cholesterol/HDL-cholesterol ratios and higher adjusted triacylglycerol levels [40]. An epidemiological study found a link between the metabolic syndrome and periodontitis, with patients with periodontitis being 1.5 times as likely to have the metabolic syndrome compared with those that did not [41]. That study also showed an individual association between periodontitis and some constituents of the metabolic syndrome, namely obesity, hypertension and glucose intolerance.

ANTI-DIABETIC THERAPY AND PERIODONTITIS: IS THERE A RELATIONSHIP?

Glycaemic status is important for the well being of periodontal ligament cells, which are very susceptible to variation or rapid fluctuation of glucose levels. These observations by Nishimura and co-workers [21] suggest that hyperglycaemia could indirectly exacerbate inflammatory tissue destruction through the body’s scavenger system against AGEs, and that both hyper- and hypo-glycaemia might directly perturb the biological functions of periodontal connective tissues via cell-matrix interactions. A subsequent study demonstrated that high glucose levels inhibit the proliferation and differentiation of periodontal ligament cells [42].

Furthermore, Ren et al. [43] demonstrated that AGEs suppressed the viability of HGFs (human gingival fibroblasts) and inhibited their expression of certain collagen mRNAs and proteins, as well as showing high glucose levels suppressing the viability of HGFs. Osteocalcin, a biomarker of bone formation, is lower in patients with periodontitis and in DM patients with and without periodontitis than in non-diabetics without periodontitis [44]. A study by Kaur et al. [20] confirmed an association between T2DM with periodontitis and tooth loss.

Increased physical activity improves insulin sensitivity and glucose metabolism in DM and reduces insulin resistance, and has also been shown to reduce the severity of periodontitis [45]. Smoking cessation programmes not only improve diabetic glycaemic control and reduce complications, but also improve the severity of periodontitis [46]. Poor metabolic control together with smoking enhances dental attachment loss and may exacerbate periodontitis. Furthermore, there is increased prevalence of P. gingivalis and Tannerella forsythensis in dental plaques of DM patients, which may help activate the innate immune system [47].

Taylor et al. [48] found poor glycaemic control in T2DM correlated with the severity of periodontitis at baseline and was associated with increased risk of poor glycaemic control, which related to patient age, smoking and diabetes duration and suggested that physicians treating patients with T2DM should be alert to the presence of severe periodontitis. There was a significant association of the loss of dental attachment level with periodontitis in patients with poorly controlled T2DM as compared with better-controlled patients. Patients with poor glycaemic control exhibited an increased percentage of salivary gland calculi and a greater risk of periodontitis [49].

In addition, sites with advanced periodontitis were more frequent in the diabetic group as were initial caries lesions. Rosiglitazone, the high-affinity synthetic agonist for PPAR-γ (peroxisome-proliferator-activated receptor-γ), has been found to inhibit and prevent inflammatory periodontal bone loss by blocking osteoclastogenesis [50]. Thus rosiglitazone, by reducing acute and chronic inflammation, also attenuates periodontal inflammation.

Abnormal lipids are well described in DM and lipid-lowering drug therapy extensively used in such patients. Various studies have suggested improved periodontal disease in patients on statin therapy. There are experimental cell findings showing that statins are anti-inflammatory and reduce alveolar bone loss and periodontitis. In a large cohort study, the presence of periodontal infective pockets was positively associated with total cholesterol and LDL-cholesterol [51]. Simvastatin has been reported to reduce periapical dental lesions [52]. This has been supported by a retrospective study where fewer periodontal lesions were found in individuals on statins [53]. However, it is possible that other confounders could be contributing, such as smoking, and further studies are warranted to explore this further.

In summary, we have shown how periodontitis is associated with the complications of T2DM such as macrovascular and microvascular disease, including retinopathy and nephropathy. Treatment of periodontitis...
may be associated with improvements in glycaemic control, although further large and carefully controlled studies are needed to confirm this. Importantly the presence of T2DM can worsen the progression of periodontitis and thus a vicious cycle can be established (Figure 1).

Periodontitis is associated with the activation of the innate immune system and which may be a ‘driver’ for insulin resistance and the development of T2DM. Periodontitis we suggest is one of many inflammatory ‘insults’ which can provoke susceptible individuals to develop insulin resistance and maybe T2DM. In patients with existing T2DM, periodontitis can worsen glycaemic control which, in turn, may worsen the severity of periodontitis. We believe our hypothesis fulfils many of the Bradford Hill criteria [23] (Table 2) and we also suggest future translational research studies to try and test our hypothesis further (Table 3).

Table 2 Is periodontitis a causative factor in T2DM? A consideration of Bradford Hill’s criteria [23]

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Strength</td>
<td>Periodontal disease has been shown to cause a significant increase in systemic markers of inflammation [6]. There is a significant association between periodontitis and diabetes [10].</td>
</tr>
<tr>
<td>Consistency</td>
<td>Meta analysis shows a risk of progression of periodontitis associated with T2DM [19].</td>
</tr>
<tr>
<td>Specificity</td>
<td>The authors do not believe current evidence demonstrates periodontitis is a single causative factor for diabetes or cardiovascular disease. The hypothesis proposed would not support such a claim, but rather suggests that, alongside other risk factors, periodontitis may have a role to play in the progression, development and control of T2DM.</td>
</tr>
<tr>
<td>Temporality</td>
<td>One study, to our knowledge, has demonstrated that the presence of periodontitis preceding the development of diabetes is a risk factor for the development of diabetes separate to traditional risk factors [24].</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Periodontitis has been shown to decrease glycaemic control [27].</td>
</tr>
<tr>
<td>Plausibility</td>
<td>Periodontitis is a chronic inflammatory condition, which is known to activate the innate immune system. The suggestion that such a condition could have a role to developing T2DM is a logical extension of the ‘Pickup-Crook’ hypothesis [1].</td>
</tr>
<tr>
<td>Coherence</td>
<td>Experimental trials demonstrating improved glycaemic control following periodontal treatment [31] would appear to be coherent with epidemiological findings showing an increase in developing diabetes and its complications in patients with periodontitis [24].</td>
</tr>
<tr>
<td>Experiment</td>
<td>An improvement in periodontal health leads to an improvement in glycaemic control [31].</td>
</tr>
<tr>
<td>Analogy</td>
<td>A similar relationship between T2DM and rheumatoid arthritis and psoriasis (both chronic inflammatory conditions) has been suggested [54].</td>
</tr>
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</table>

Table 3 Suggestions for possible future translational research to test the hypothesis that periodontitis may be involved in the causation of T2DM

<table>
<thead>
<tr>
<th>Suggestion</th>
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<tbody>
<tr>
<td>Studies looking at relationship between severity of periodontitis in a carefully defined population and expression of certain cytokines, and also NF-κB, adiponectin and leptin (controlled for confounding variables such as smoking).</td>
</tr>
<tr>
<td>Carefully controlled trials looking at the treatment of periodontitis and whether expression of certain cytokines and also NF-κB are reduced as well as markers of insulin resistance, such as HOMA score.</td>
</tr>
<tr>
<td>Epidemiological studies looking at prevalence and incidence of periodontitis in populations more at risk of T2DM such as South Asians and Pacific Islands peoples.</td>
</tr>
<tr>
<td>Studies designed to test whether there is a reciprocal relationship between glycaemic control and severity of periodontitis.</td>
</tr>
<tr>
<td>Further studies to explore relationship between periodontitis and diabetes complications, such as microvascular and macrovascular disease, and whether these can be improved by treating periodontitis.</td>
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REFERENCES


© The Authors Journal compilation © 2010 Biochemical Society
Diabetes mellitus, inflammation and periodontitis


Received 10 February 2010/26 April 2010; accepted 1 June 2010
Published on the Internet 5 August 2010. doi:10.1042/CS20100098

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