DIABETES AND PERIODONTAL DISEASES: THE BIDIRECTIONAL ASSOCIATION AND ITS IMPLICATIONS.

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ABSTRACT

DIABETES MELLITUS (DM) and periodontitis are common, complex, chronic diseases with an established bidirectional relationship. Poorly controlled DM is associated with an increased prevalence and severity of periodontitis, being acknowledged as a true risk factor for periodontitis onset and progression. On the other hand, there is growing evidence that chronic infectious diseases, such as periodontitis, could increase the risk for DM development and compromise glycaemic control in people with DM. In addition, non-surgical periodontal treatment can improve glycaemic control in patients with DM. Therefore, this bidirectional association may have relevant implications for health professionals, for DM and periodontitis patients, as well as for the general population. Due to these implications, dental professionals may play an important role in the management of DM patients, not only by rendering periodontal care in people with DM, but also helping identify patients with undiagnosed DM or at high risk of developing it, by the use of appropriate screening tools. The aim of this narrative review was (1) to address the mechanistic links that have been proposed as basis of the periodontitis-DM relationship; (2) to report the epidemiological evidence from cross-sectional and longitudinal studies; and (3) to describe the impact of periodontal care on DM control. Recommendations for medical and dental professionals, as well as recommendations for patients/public are proposed.
INTRODUCTION

What is diabetes mellitus?
Diabetes mellitus (DM) represents a group of metabolic diseases characterized by hyperglycaemia, associated with defects in insulin secretion, insulin action or both. Chronic hyperglycaemia is associated with damage, dysfunction and/or failure in different organs, including eyes, nerves, kidney, heart or blood vessels.

A diagnosis of DM is normally established if Fasting Plasma Glucose (FPG) is ≥ 126 mg/dl or if glycated haemoglobin (HbA1c) is ≥ 6.5% (American Diabetes Association 2003, American Diabetes Association 2013).

A classification of conditions and risk categories within DM is presented here:

- **DM type 1** normally presents in thin young persons, with acute symptoms, together with ketosis and loss of weight. In 90% of the cases, organ-specific autoimmune markers are present [e.g. anti-GAD (antibodies against enzyme glutamic acid decarboxylase) or ICA (antibodies against islet cells of the pancreas)]. An idiopathic form, with no immune biomarkers is found in African and Asian ethnic groups.

- **DM type 2** has a silent onset and no ketosis or family aggregation. It is associated to overweight or obesity, and characterized by deficit in insulin secretion and resistance to its action. No genetic markers are evident.

- **Gestational DM** and **DM in pregnancy** are defined as an alteration of glucose metabolism, detected during pregnancy, in previously healthy women (United Nations 2013)

- **Other types of diabetes** include those associated with genetic defects (either in beta cells function or in insulin action), endocrine diseases (drug- or infection induced), exocrine pancreas diseases, or genetically or immune-driven conditions, including LADA (latent autoimmune diabetes of adult) or MODY (maturity onset diabetes of the young).

How important is diabetes mellitus?

**Worldwide prevalence**
According to IDF Diabetes Atlas (International Diabetes Federation 2015), the global prevalence of diabetes in adults (20-79 years) is 8.8% (7.2-11.4%), and it is estimated to increase to 10.4% (8.5-13.5%) by 2040. This represents 415 million adults with diabetes in 2015 and an expected figure of 642 million in 2040. Hyperglycaemia in pregnancy (20-49 years) affects 16.2% of live births and impaired glucose tolerance (20-79 years) has a global prevalence of 6.7%. Type 1 diabetes (0-14 years) affects 542,000 with a yearly increase of 86,000.

The information from Spain, thanks to the excellent study di@bet.es (Soriguer et al. 2012), calculated a total prevalence of DM type 2 of 13.79%, with diagnosed DM representing 7.78% and unknown DM 6.01%.
Human cost: complications
The IDF Diabetes Atlas has estimated the number of deaths caused by diabetes in 2015 at 5.0 million (International Diabetes Federation 2015). But, in terms of human cost, the relevance of DM is based on the importance of the associated complications.

DM is associated with frequent complications, which have been classically summarized as retinopathies, nephropathies, peripheral and autonomic neuropathies, and cardiovascular diseases (including hypertension and lipid metabolism alterations). These complications are briefly described here:

- **DM, due to hyperglycaemia, may affect small blood vessels (arterioles, venules and capillaries), which is known as diabetic microangiopathy (MAD), and it is responsible for retinopathies, diabetic nephropathy and even diabetic neuropathy. Among microvascular complications, diabetic nephropathy has the highest clinical relevance, as it is the main cause of chronic renal disease.**

- **Diabetic neuropathy may affect both peripheral and autonomic nervous systems, being a condition directly related to hyperglycaemia. Diabetic autonomic neuropathy has relevant clinical implications, since it may affect multiple organs (eyes, sweat glands, urinary bladder, sexual organs, oesophagus, gastrointestinal system, cardiovascular system, etc.).**

- **Cardiovascular diseases represent one of the most relevant complications of DM, normally associated with coronary atherosclerosis. Myocardial infarction is 3-5 times more frequent in persons with diabetes. The synergistic effect with other risk factors is very relevant, including obesity, dyslipidemia and hypertension, leading to the metabolic syndrome concept.**

- **Peripheral vascular disease may have a very early onset in people with diabetes, being one of the main risk factors for diabetic foot. Dermal complications include diabetic dermopathy or necrobiosis lipoidica diabeticorum.**

- **In recent years, periodontal diseases have also been considered a relevant complication of diabetes (Loe 1993), and this will be discussed in the present paper.**

Financial cost
According to the IDF Diabetes (International Diabetes Federation 2015), the health expenditure due to diabetes in adults is USD 673 billion in 2015, representing 12% of the global health expenditure.

In Spain, the overall direct cost per year has been estimated at €5.1 billion, with an additional €1.5 billion for the indirect costs derived from the management of its complications (Lopez-Bastida et al. 2013).
MECHANISTIC LINKS BETWEEN PERIODONTAL DISEASES AND DIABETES

Mechanisms underlying the effect of DM on periodontitis

**Periodontal microbiota**

Although early studies suggested the existence of distinct subgingival microbial profiles (Zambon et al. 1988), it does not appear that the microbial microbiota of people with diabetes differs from that of healthy individuals (Yuan et al. 2001, Lalla et al. 2006b, Ebersole et al. 2008). However, this conclusion came from studies mainly based on conventional methods, such as checkerboard DNA-DNA hybridization and polymerase chain reaction (PCR), instead of looking at the entire bacterial community. Recent studies using high-throughput 16S rDNA pyrosequencing have detected that subjects, with and without DM, harboured bacteria at several taxonomic levels with significantly different prevalence or abundance; certain genus being more prevalent in patients with healthy gums and diabetes (genus of Neisseria), or in subjects with both periodontitis and diabetes (Tannerella forsythia) than in their non-diabetic counterparts (Casarin et al. 2013, Zhou et al. 2013).

**Cytokines and matrix metalloproteinases (MMP)**

Inflammation is a central feature of both diabetes and periodontal diseases, and inflammatory processes are up-regulated in the periodontal tissues of patients with diabetes. Both type 1 and type 2 DM are associated with elevated gingival crevicular fluid (GCF) levels of inflammatory mediators, such as interleukin (IL)-1β and prostaglandin E2 (PGE2), when compared to non-diabetic controls matched with regard to periodontitis severity (Salvi et al. 1997, Engebretson et al. 2004, Mohamed et al. 2015).

Animal studies in diabetic mice corroborate these findings and highlight the role of tumour necrosis factor-α (TNF-α) in the enhanced immune response to periodontal bacteria (Graves et al. 2004, Liu et al. 2006). Recently, the concentration of a broad panel of cytokines in GCF from healthy and diseased sites of subjects with uncontrolled type 2 DM and of non-diabetic subjects has been studied (Duarte et al. 2014). Higher concentrations of TNF-α, granulocyte macrophage colony-stimulating factor-α, IL-6 and IL-12 were found in healthy and diseased sites of patients with diabetes, suggesting that the increased levels of proinflammatory mediators could partially explain the greater susceptibility of DM subjects to periodontal breakdown.

It has been hypothesized that DM-related alterations in GCF levels of MMPs, and/or their inhibitors, may be part of the mechanism by which diabetes affects periodontal health. However, no differences for MMP-8, MMP-13 and tissue inhibitor of MMP-1 were detected between systemically healthy and type 2 DM subjects with periodontitis, gingivitis or periodontal health (Kardesler et al. 2010). Data from gingival/periodontal tissue biopsies present conflicting results (Kumar et al. 2006, Hardy et al. 2012).

**Alveolar bone homeostasis**

The receptor activator of nuclear factor-kappa B ligand (RANKL) is responsible for stimulation osteoclast differentiation and bone resorption. RANKL can be blocked by osteoprotegerin (OPG), preventing its potential deleterious effects. In periodontitis subjects, RANKL is up-regulated while OPG is down-regulated, resulting in an increased RANKL/OPG ratio (Belibasakis & Bostanci 2012). Several studies have demonstrated that the RANKL/OPG ratio is higher in poorly controlled diabetic patients with periodontitis compared to well-controlled or non-diabetic subjects with similar periodontal status (Santos et al. 2010, Ribeiro et al. 2011).
Advanced glycation end-products (AGEs)
AGEs are resulting products after non-enzymatic glycation and oxidation of proteins and lipids that accumulate in plasma and tissues. Increased blood-glucose levels lead to excessive accumulation of AGEs in serum, cells and tissues, including the gingiva and the periodontium (Schmidt et al. 1996). Binding of AGEs to their cell surface receptors, RAGEs, activates host cells such as monocytes and endothelial cells to release pro-inflammatory cytokines (Lalla et al. 2001), and it is recognized as a major cause of diabetic complications (Sorci et al. 2013). Blockade of RAGEs significantly suppressed alveolar bone loss in diabetic mice infected with periodontal pathogens (Lalla et al. 2000), indicating that AGE-RAGE interaction may lead to the exacerbated inflammatory response contributing to the destruction of the periodontal tissues. Besides diabetes, periodontal inflammation alone leads to accumulation of AGEs in periodontal tissues, demonstrating an interaction between diabetes and periodontitis (Chang et al. 2013, Zizzi et al. 2013).

Reactive oxygen species (ROS)
ROS include free radicals (e.g. superoxide O2− and hydroxyl radicals OH−), non-radical oxygen species [e.g. hydrogen peroxide (H2O2)], and reactive lipids that are generated by physiological cellular functions such as neutrophil phagocytosis. In diabetes patients, leukocytes release elevated amounts of ROS compared with systemically healthy individuals, which are thought to be the major player in microvascular complications (Devaraj & Jialal 2000, Gorudko et al. 2012). The increase in vascular permeability caused by hyperglycemia and leukocyte-induced microvascular damage, may contribute to periodontal tissue destruction in diabetes (Sima et al. 2010, Gyurko et al. 2006).

Mechanisms underlying the effect of periodontitis on DM
Periodontal microbiota
Whether the subgingival microbial profile has any impact on diabetes, or glycaemic control, has not been investigated in depth. Just one study in Japan, in which patients with chronic periodontitis and type 2 DM received non-surgical periodontal therapy, addressed the issue (Makiura et al. 2008). After therapy, it was observed that Porphyromonas gingivalis, particularly the strain with type II fimbriae, was detected more frequently in those subjects who had increased HbA1c values when compared to those with decreased values relative to baseline examination. This finding suggests that glycaemic control in patients with periodontitis and DM could be influenced by the presence of P. gingivalis.

Inflammatory factors and oxidative stress
Periodontitis is associated with elevated levels of pro-inflammatory and pro-thrombotic mediators in serum, such as C-reactive protein (CRP), TNF-α and IL-6 (Paraskevas et al. 2008, Kebeschull et al. 2010), and dysregulation of the peripheral cytokine pool is now considered a central pathogenic factor in diabetes (Kolb & Mandrup-Poulsen 2010). Thus, it is possible that the systemic inflammation associated with the local inflammatory response triggered by periodontal microbiota leads to insulin resistance. For example, TNF-α, which is elevated in plasma of patients with periodontitis (Engbretson et al. 2007), is known to promote insulin resistance by interfering with insulin signalling (Abbatecola et al. 2004, Gupta et al. 2005). Also, periodontitis has proven to aggravate pancreatic β-cell failure in diabetic mice (Liu & Zhang 2016).
Oxidative stress and mitochondrial dysfunction have been also presented as shared factors in the pathogenesis of periodontitis and DM, as biochemical markers of systemic oxidative stress are elevated in both diseases (Bullen et al. 2009, Bullon et al. 2014). In addition, these markers have been positively correlated with CRP in periodontitis patients (D’Aiuto et al. 2010). However, although there are longitudinal data from epidemiological studies, there is little evidence for the exact mechanisms to explain how periodontitis could impact on the disease processes of DM. The various pathways proposed to link diabetes and periodontitis are illustrated in Figure 1.

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**Figure 1.**
Schematic representation of the two-way relationship between diabetes and periodontitis. Partially adapted from Preshaw et al. (2012).
Table 1. Selected studies evaluating diabetes mellitus as exposure for periodontitis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>DM Type</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hugoson et al. 1989)</td>
<td>Cases &amp; Controls</td>
<td>Type 1</td>
<td>154 diabetic and 77 non-diabetic subjects</td>
<td>Long-duration DM subjects presented increased severity of periodontitis both as ABL and AL</td>
</tr>
<tr>
<td>(Shlossman et al. 1990)</td>
<td>Cross-Sectional</td>
<td>Type 2</td>
<td>3219 Pima Indians</td>
<td>Mean AL and ABL was higher in DM for all age groups</td>
</tr>
<tr>
<td>(Nelson et al. 1990)</td>
<td>Prospective study</td>
<td>Type 2</td>
<td>701 Pima Indians were evaluated longitudinally</td>
<td>DM predicted a greater incidence of periodontitis (RR=2.6)</td>
</tr>
<tr>
<td>(Emrich et al. 1991)</td>
<td>Cross-sectional</td>
<td>Type 2</td>
<td>1342 Pima Indians</td>
<td>DM, age and calculus were identified as risk indicators (OR=2.8 for suffering periodontitis)</td>
</tr>
<tr>
<td>(Oliver &amp; Tervonen 1993)</td>
<td>Cases &amp; Controls</td>
<td>Types 1 and 2</td>
<td>114 diabetic patients</td>
<td>AL and tooth loss was comparable between groups. Prevalence of sites with PPD≥4 mm was higher for DM</td>
</tr>
<tr>
<td>(Thorstensson &amp; Hugoson 1993)</td>
<td>Cases &amp; Controls</td>
<td>Type 1</td>
<td>83 DM subjects and 99 controls</td>
<td>DM patients had more PPD≥6 mm and more extensive ABL</td>
</tr>
<tr>
<td>(Bridges et al. 1996)</td>
<td>Cases &amp; Controls</td>
<td>Non-specified</td>
<td>233 men (118 diabetic and 115 non-diabetic)</td>
<td>PPD and AL were significantly higher in DM</td>
</tr>
<tr>
<td>(Lalla et al. 2007b)</td>
<td>Cases &amp; Controls</td>
<td>Types 1 and 2</td>
<td>350 DM children and adolescents, 350 controls</td>
<td>Children with DM had significantly more gingival inflammation and a higher number of teeth with AL</td>
</tr>
<tr>
<td>(Hodge et al. 2012)</td>
<td>Cases &amp; Controls</td>
<td>Type 1</td>
<td>34 well controlled DM subjects, 169 poorly controlled DM subjects and 112 non-diabetic controls</td>
<td>Prevalence of periodontitis was higher in all DM subjects. ORs for the well controlled and poorly controlled groups were 1.35 and 1.58 respectively for suffering periodontitis</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; ABL, alveolar bone loss; AL, attachment loss; OR, odds ratio; RR, relative risk; PPD, probing pocket depth.

**EPIDEMIOLOGICAL EVIDENCE**

**Evidence for DM as a risk factor for periodontitis**

The role of DM as a risk factor for periodontitis has been debated for decades. Numerous studies (Table 1) have identified a higher prevalence and severity of periodontitis in patients with type 1 DM, particularly in subjects with a long duration of DM and poor metabolic control (Hugoson et al. 1989, Oliver & Tervonen 1993, Thorstensson & Hugoson 1993, Lalla et al. 2007a, Hodge et al. 2012). For type 2 DM, the evidence is even stronger, especially in certain subgroups, such as African Americans or the Pima Indians, who have an extremely high prevalence of type 2 DM (Fernandes et al. 2009, Bandyopadhyay et al. 2010, Shlossman et al. 1990, Nelson et al. 1990, Emrich et al. 1991, Bridges et al. 1996). Of particular relevance, longitudinal studies have clearly showed that DM precedes periodontitis, a finding supporting causality (Nelson et al. 1990, Bandyopadhyay et al. 2010), and that poorer glycaemic control leads to an increased risk for alveolar bone loss and periodontitis progression (Taylor et al. 1998). However, it should be stressed that the association between DM and periodontitis is just limited to those cases with poorly controlled DM, as neither well-controlled DM nor pre-diabetes have been related to a greater prevalence or severity of periodontitis (Kowall et al. 2015, Garcia et al. 2015).
The clinical and radiographic assessment of a type 2 DM patient (Clinical case 1) with poor metabolic control and periodontitis is presented in Figures. 2, 3 and 4.

Figure 3.
Clinical case 1: periodontal chart. Note the attachment loss and presence of deep pockets, as well as suppuration on certain sites.

Figure 2.
Clinical case 1: general view of a 40-year-old man with poorly controlled diabetes mellitus type 2 and generalized moderate, localized severe, chronic periodontitis.

Figure 4.
Clinical case 1: periapical radiographs. Note the presence of several intrabony defects.
Studies performed in children and adolescents with either type 1 or 2 DM documented more pronounced gingival inflammation and clinical attachment level (CAL) loss than their matched controls (Lalla et al. 2006a), establishing the age of onset of DM manifestations in the periodontium from 6 years old (Lalla et al. 2007a). A case (Clinical case 2) is presented showing the periodontal status of a teenager suffering from type 1 DM with poor metabolic control (Figures. 5, 6 and 7).

Meta-analysis of cross-sectional and longitudinal studies indicated a significantly higher mean CAL loss of 1 mm [95% confidence interval (CI): 0.15-1.84] and a greater mean probing pocket depth (PPD) of 0.46 mm (0.01-0.091) of type 2 DM patients compared with control subjects (Chavarry et al. 2009).
Evidence for the effects of periodontitis on DM

Periodontitis may also impact upon DM. The most extensively explored effects are related to glycaemic control, development of complications and onset of DM (Borgnakke et al. 2013).

Longitudinal studies performed in the Pima Indian population demonstrated that severe periodontitis (expressed either by CAL or radiographic bone loss) was associated with 4.2-13.6 times higher risk for poor glycaemic control (Taylor et al. 1996). Large population studies in Japan and Germany have associated deterioration in the periodontal status with a significant increase in HbA1c throughout 5-10 years, to the point that each additional mm in mean PPD corresponded with an 0.13% increase in HbA1c (Saito et al. 2004, Demmer et al. 2010).

Among patients without known DM, poorer periodontal health has also been associated with an increased risk for incident type 2 DM (Saito et al. 2004, Demmer et al. 2008, Morita et al. 2012). In USA population, people with gingivitis had 40% increased odds of developing DM, while those with periodontitis had 50% elevated risk (Demmer et al. 2008). In a Japanese population, those presenting sites with PPD≥6 mm had 3.45 times higher risk of developing DM (Morita et al. 2012).

People with DM are particularly susceptible to micro- and macro-vascular complications, which are primarily responsible for the increased morbidity and mortality associated with this condition. It has been proposed that periodontitis could be related to the development of complications in patients with DM, particularly nephropathy, ischemic heart disease and ictus (Saremi et al. 2005, Shultis et al. 2007, Thorstensson et al. 1996). Cross-sectional studies have associated other DM complications such as retinopathy or neuropathic foot ulceration with periodontitis, but longitudinal data is missing (Noma et al. 2004, Abrao et al. 2010).

Periodontitis has also been evaluated for a potential role in the development of gestational diabetes mellitus (GDM). In a case-control study with 53 pregnant women with GDM and 106 without GDM, and after adjusting for confounding variables, the odds ratio (OR) for periodontitis and GDM was calculated to be 2.6 (95% CI, 1.1-6.1), with higher adjusted ORs for the highest quartiles according to periodontitis severity (Xiong et al. 2009). A recent systematic review with meta-analysis of observational studies showed that periodontitis is associated with an increased risk of GDM by 66% (OR=1.66); with an even more robust association when considering only high-quality case-control studies that adjusted for potential confounders (OR=2.08). Although the authors indicated that the diagnostic criteria for periodontitis and GDM varied widely among studies, the results suggested an association between the two diseases (Abariga & Whitcomb 2016).

Proposed benefits of periodontal treatment for DM

Periodontal treatment and glycaemic control

Periodontal treatment resolves inflammation and reduces circulating cytokines among individuals with diabetes (Artese et al. 2015) and may thus reduce hyperglycemia in these subjects. Several randomized clinical trials (RCTs) have evaluated the effect of periodontal therapy on people with DM, with HbA1c being the most commonly used clinical endpoint. These trials have reported reductions in HbA1c ranging from 1.11% (Kiran et al. 2005) to 0.05% (Katagiri et al. 2009).

More than 10 systematic reviews with meta-analysis (Table 2) on the effectiveness of periodontal treatment to improve glycaemic control have been published, estimating an average reduction of 0.46% in HbA1c in patients with DM (Faggion et al. 2016). The consensus report of the Joint European Federation of Periodontology (EFP)/American Academy of Periodontology (AAP) Workshop on Periodontitis and Systemic Diseases recommended that these results should be interpreted with caution, as most of the studies were small unpowered trials, highlighting the need for larger clinical investigations (Engebretson & Kocher 2013, Chapple & Genco 2013).
In particular, a multicentre RCT including 514 patients was published just a few months after the Joint Workshop, reporting that non-surgical periodontal therapy did not improve glycaemic control in patients with type 2 DM and moderate to advanced chronic periodontitis (Engebretson et al. 2013). However, this study has relevant methodological problems that render the conclusions doubtful and led to a wave of letters to the editor and critical reviews (Merchant et al. 2014, Chapple et al. 2014, Vergnes et al. 2014, Borgnakke et al. 2014). It is important to highlight that, in the referred study, the periodontal therapy provided failed to clinically manage the periodontal infection and associated inflammatory burden, as the residual plaque levels (72%) and bleeding scores (42%) are far away from the accepted standard of care. In addition, most of the subjects included presented a control of diabetes that was predominantly good at baseline (mean HbA1c level 7.8%), with less than 60% of patients having HbA1c levels greater than 8.0%. With the mean HbA1c value close to the therapeutic target, a substantial improvement in HbA1c levels is difficult to expect. A third significant problem was the mean body mass index (BMI) of the participants, which was approximately 34 kg/m2, so most of them were obese (≥30 kg/m2). A recent systematic review concluded that there were significant differences in the metabolic response after periodontal therapy between obese and normal-weight patients (Papageorgiou et al. 2015), which would have masked the anti-inflammatory effect of periodontal treatment. Thus, it is possible that in this study most of the subjects were resistant to the elimination of the periodontitis-related systemic inflammation due to the overwhelming influence of obesity.

Table 2. Selected systematic reviews evaluating the effect of periodontal therapy on HbA1c levels.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Designs</th>
<th>Number of patients (range)</th>
<th>Follow-up (range; weeks)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Janket et al. 2005)</td>
<td>CCTs, RCTs</td>
<td>10-113</td>
<td>2-96</td>
<td>Periodontal therapy decrease HbA1c levels by non-significant 0.38% for both type 1 and type 2 DM. A reduction of 0.71% was observed among just type 2 DM</td>
</tr>
<tr>
<td>(Darre et al. 2008)</td>
<td>CCTs, RCTs</td>
<td>20-72</td>
<td>2-104</td>
<td>MA of 9 studies showed significant improvement of HbA1c with periodontal treatment</td>
</tr>
<tr>
<td>(Teeuw et al. 2010)</td>
<td>CCTs, RCTs</td>
<td>44-165</td>
<td>12-36</td>
<td>MA of 5 studies showed a weighted mean difference in HbA1c of -0.40% in type 2 DM for at least 3 months</td>
</tr>
<tr>
<td>(Simpson et al. 2010)</td>
<td>RCTs</td>
<td>30-113</td>
<td>12-24</td>
<td>MA of 3 RCTs showed SS reduction in HbA1c following periodontal treatment (-0.40%)</td>
</tr>
<tr>
<td>(Sgolastra et al. 2013)</td>
<td>RCTs</td>
<td>40-126</td>
<td>12-24</td>
<td>MA of 5 RCTs showed that SRP was effective in reducing HbA1c and FPG</td>
</tr>
<tr>
<td>(Corbella et al. 2013)</td>
<td>RCTs</td>
<td>NR</td>
<td>12-24</td>
<td>MA of 15 studies showed periodontal treatment reduced HbA1c by -0.38% after 3-4 months and of -0.31% after 6 months</td>
</tr>
<tr>
<td>(Liew et al. 2013)</td>
<td>RCTs</td>
<td>40-154</td>
<td>12-24</td>
<td>MA of 6 studies showed SS reduction in HbA1c (-0.41%)</td>
</tr>
<tr>
<td>(Engebretson &amp; Kocher 2013)</td>
<td>RCTs</td>
<td>40-165</td>
<td>12-36</td>
<td>MA of 9 studies demonstrated a treatment effect of -0.36%</td>
</tr>
<tr>
<td>(Sun et al. 2014)</td>
<td>RCTs</td>
<td>40-157</td>
<td>12-36</td>
<td>MA of 6 studies demonstrated a mean periodontal treatment effect of 1.03% in HbA1c</td>
</tr>
</tbody>
</table>

CCT, controlled clinical trial; RCT, randomized clinical trial; DM, diabetes mellitus; HbA1c, glycated haemoglobin; MA, meta-analysis; SS, statistically significant; SRP, scaling and root planing; FPG, fasting plasma glucose.
A recent prospective cohort study including more than 120,000 subjects with DM and periodontitis treated in the VA's (Veteran Administration) medical centers in the USA, reported that periodontal treatment reduced HbA1c by 0.02% to 0.074% after initial treatment and an average of 1.7 years of supportive periodontal therapy respectively (Merchant et al. 2016). Beneficial effects were greater among never-smokers and individuals with higher baseline HbA1c levels. Long-term periodontal care increased the likelihood of individuals achieving proper diabetes control by 5% and 3% at the HbA1c <7% and <9% thresholds, respectively. These findings compelled the authors to conclude that periodontal treatment improved long-term glycaemic control among individuals with type 2 DM and periodontitis.

At this moment, when all the available evidence is combined, the effects of periodontal treatment on HbA1c still points to an improvement in glycaemic control in diabetic patients, although attention should remain on the evolution of these data as several trials are still ongoing.

Clinical relevance of the reduction in HbA1c
The benefits derived from the control of hyperglycaemia are clear in terms of preventing its complications. Each percentage point of decrease in HbA1c results in a reduction in risk of micro-vascular complications of about 35% (Stratton et al. 2000). Furthermore, an average reduction in HbA1c of 0.20% is associated with a reduction in all-cause mortality of approximately 10% (Khaw et al. 2004).

Therefore, it is reasonable to expect that a reduction in HbA1c of approximately 0.4%, found to be associated with non-surgical periodontal treatment in patients with diabetes, would have clinically significant effects on systemic health, especially in patients with poorly controlled diabetes. Of course, trials evaluating the effect of periodontal therapy on diabetic complications are needed.

SUMMARY

CONVINCING EVIDENCE EXISTS to support the fact that DM (types 1 and 2, particularly if poorly controlled) is a risk factor for periodontitis, increasing the risk of onset and progression of periodontitis. Evidence also suggests that advanced periodontitis compromises glycaemic control. It appears that this is a bidirectional relationship, and that patients with severe periodontitis and DM suffer from more cardio-renal mortality and microalbuminuria than patients with DM and no periodontitis. Periodontal treatment has been associated with improvements in glycaemic control in the short term (with HbA1c reductions of approximately 0.4%, reported in systematic reviews with meta-analysis). However, further studies are needed to determine the optimal periodontal care to achieve and sustain better glycaemic control as well as to determine if prevention or treatment of periodontitis will result in the reduction of diabetes complications, such as cardiovascular and renal diseases.
CONCLUSIONS

PERIODONTAL HEALTH IS A CRUCIAL COMPONENT of general health, particularly in subjects with diabetes. For that reason, periodontal assessment and management are crucial in this population. People with DM should be aware of their increased risk for periodontitis as well as the negative impact of this condition upon their glycemic control. Dental professionals have an important role not just in the periodontal treatment of people with DM but also helping to identify patients at high risk of developing this disorder.

IMPLICATIONS FOR ACTION

FOR DENTISTS
Patients with DM have several direct implications for the dental professional, as (1) they are at a higher risk of suffering periodontitis, particularly if poorly controlled; (2) they may improve their glycaemic control after successful periodontal therapy; (3) they are at risk of hypoglaecemic episodes while attending the dental surgery; and (4) people with undiagnosed DM attending the dental surgery could have an opportunity for being screened and identified as having a high risk of suffering diabetes, leading to an earlier diagnosis.

FOR MEDICAL DOCTORS
Physicians and other medical health professionals should be aware that periodontitis risk is increased by DM, and that patients with both DM and periodontitis could have a greater difficulty in achieving glycemic control and are at higher risk for diabetic complications, such as cardiovascular and kidney disease. For these reasons, patients with type 1, 2 or gestational diabetes should receive a thorough oral examination, including comprehensive periodontal examination. Patients with DM should be placed on a preventive care regime and monitored regularly (at least annually) for periodontal changes; for children and adolescents annual oral screening should ideally start at 6 years.

FOR THE GENERAL POPULATION
People with DM should receive oral-health education and understand their increased risk for periodontitis and the importance of keeping healthy gums in order to control DM. Like DM, periodontitis is a chronic condition that requires life-long maintenance and regular dental check-ups. Even if no symptom is present, patients with DM should follow a regular recall programme in order to identify early signs of gum disease. For those who do not suffer from DM but present some risk factors, including periodontitis, it is important to get a medical check-up to identify potential undiagnosed hyperglycaemia.
REFERENCES


