

# 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.

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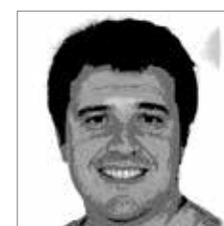
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## INTRODUCTION

### 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  $\geq 126$  mg/dl or if glycated haemoglobin (HbA1c) is  $\geq 6.5\%$  (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 diabetorum.
- 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)-1 $\beta$  and prostaglandin E2 (PGE2), when compared to non-diabetic controls matched with regard to periodontitis severity (Salvi et al. 1997, Engbretson et al. 2004, Mohamed et al. 2015).

Animal studies in diabetic mice corroborate these findings and highlight the role of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) 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- $\alpha$ , granulocyte macrophage colony-stimulating factor- $\alpha$ , 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 O<sub>2</sub><sup>-</sup> and hydroxyl radicals OH<sup>-</sup>), non-radical oxygen species [e.g. hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)], 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 HbA<sub>1c</sub> 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- $\alpha$  and IL-6 (Paraskevas et al. 2008, Kebschull 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- $\alpha$ , which is elevated in plasma of patients with periodontitis (Engebretson 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  $\beta$ -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 (Bullon 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.

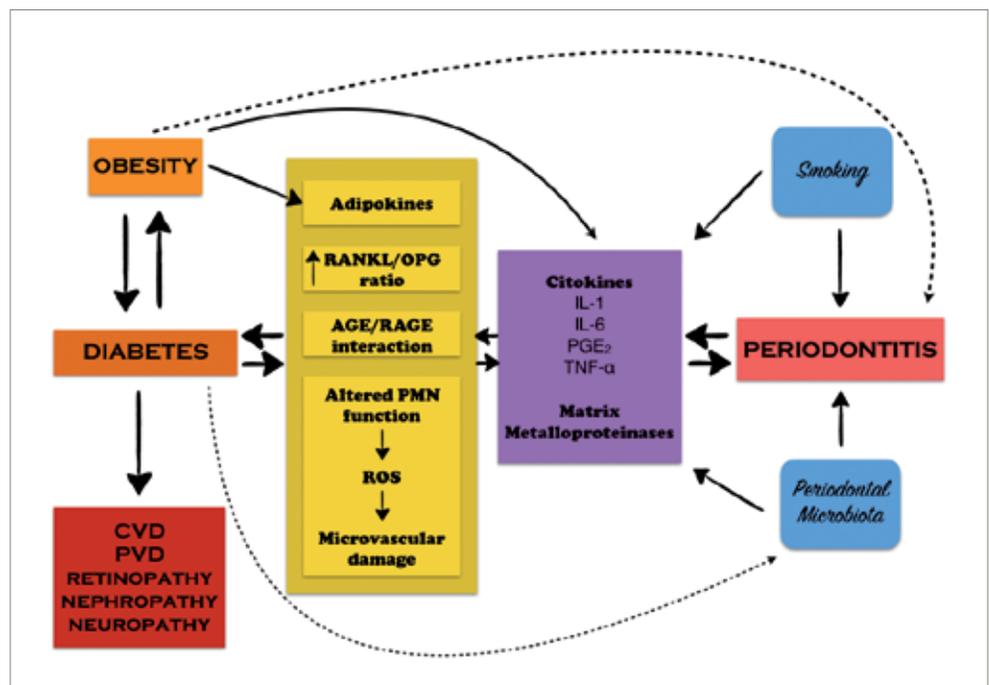


Figure 1. Schematic representation of the two-way relationship between diabetes and periodontitis. Partially adapted from Preshaw et al. (2012).

**Table 1.** Selected studies evaluating diabetes mellitus as exposure for periodontitis.

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

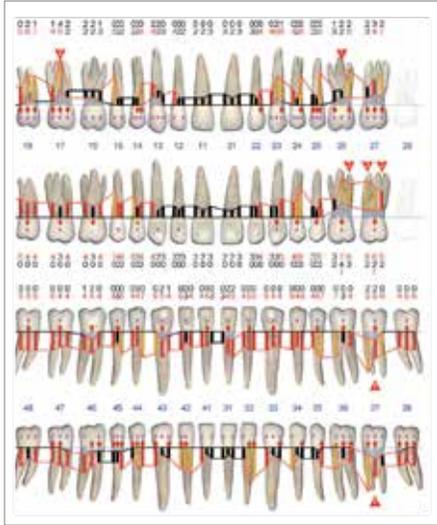
DM, diabetes mellitus; ABL, alveolar bone loss; AL, attachment loss; OR, odds ratio; RR, relative risk; PPD, probing pocket depth.

## 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).

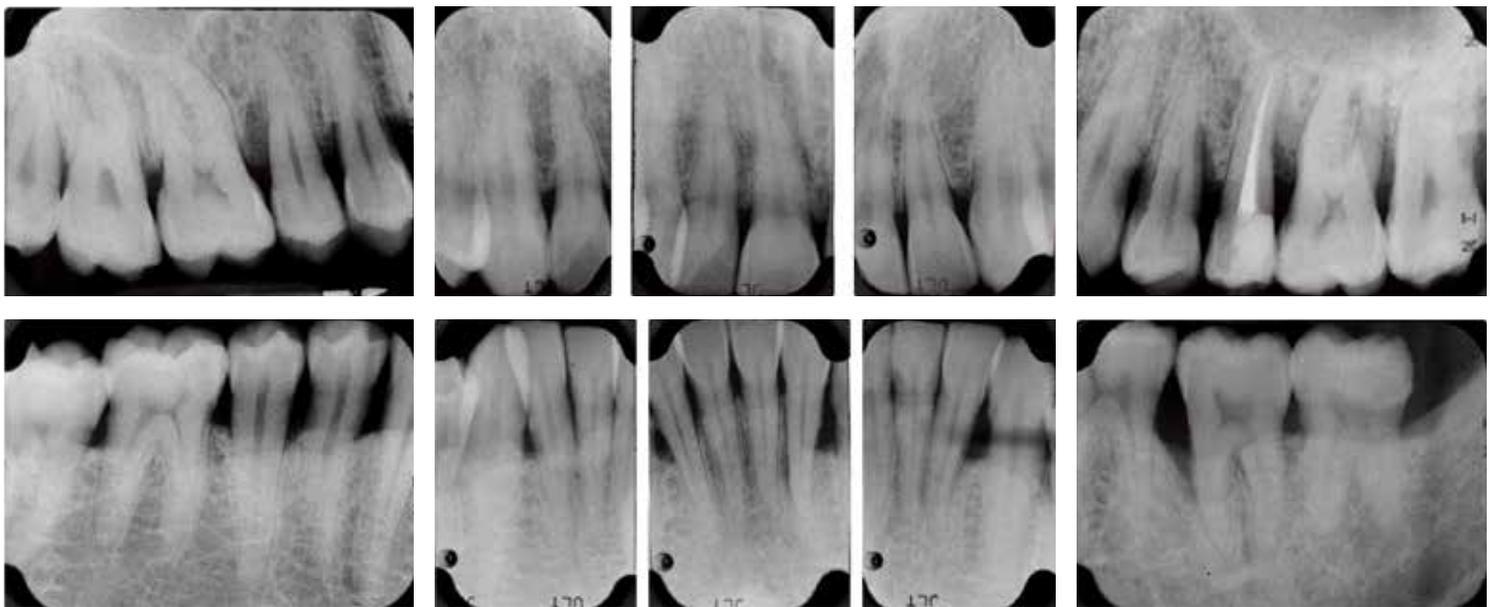
The clinical and radiographic assessment of a type 2 DM patient (Clinical case 1) with poor metabolic control and periodontitis is presented in Figures. 2, 3 and 4.



**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).

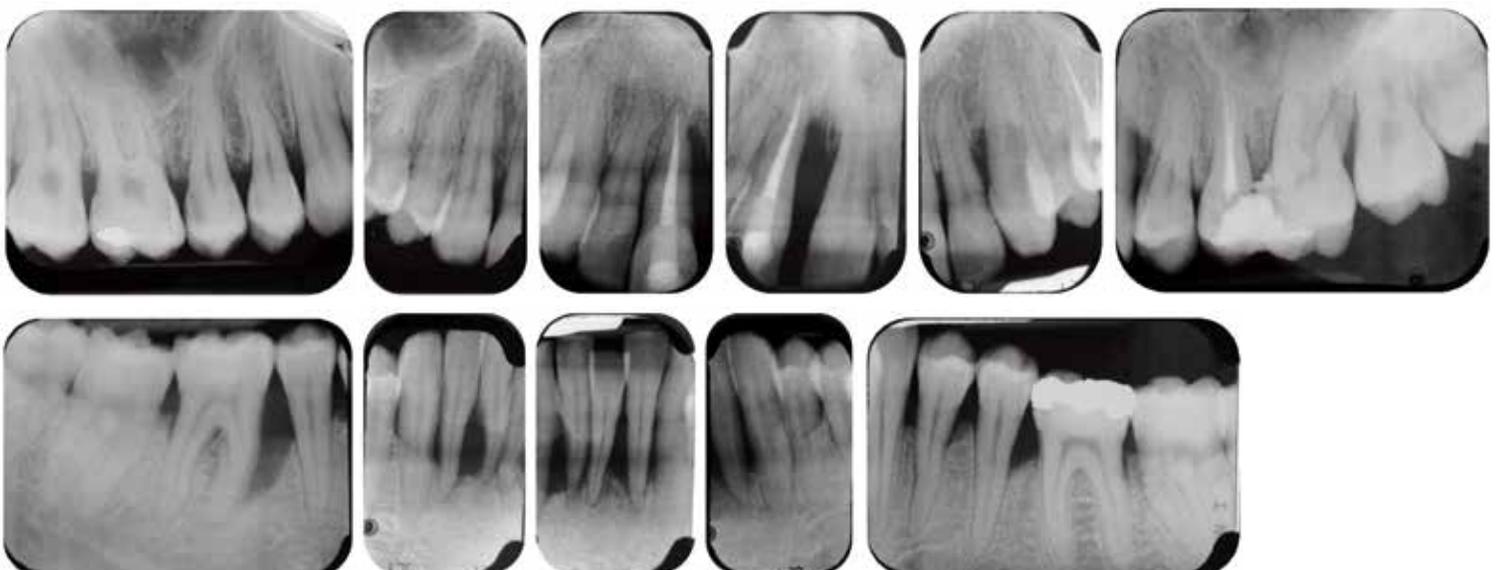
Meta-analysis of cross-sectional and longitudinal studies indicated a significantly higher mean CAL loss of 1 mm [95% confidence interval (CI): 0.15-1.84] and a greater mean probing pocket depth (PPD) of 0.46 mm (0.01-0.091) of type 2 DM patients compared with control subjects (Chavarry et al. 2009).



**Figure 5.** Clinical case 2: overview of a 18 year old female with diabetes mellitus type 1 and severe aggressive periodontitis. Courtesy of Dr. Estefanía Laguna.



**Figure 6.** Clinical case 2: periodontal chart of patient.



**Figure 7.** Clinical case 2: periapical radiographs of patient.

### **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 $\geq$ 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 (Engbretson & Kocher 2013, Chapple & Genco 2013).

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

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

**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.

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/m<sup>2</sup>, so most of them were obese ( $\geq 30$  kg/m<sup>2</sup>). 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.

A recent prospective cohort study including more than 120,000 subjects with DM and periodontitis treated in the VAs (Veteran Administration) medical centres 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 on going.

### **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

- Abariga SA & Whitcomb BW. (2016) Periodontitis and gestational diabetes mellitus: a systematic review and meta-analysis of observational studies. *BMC Pregnancy Childbirth* **16**, 344.
- Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L & Ferrucci L. (2004) Insulin resistance and executive dysfunction in older persons. *Journal of the American Geriatric Society* **52**, 1713-1718.
- Abrao L, Chagas JK & Schmid H. (2010) Periodontal disease and risk for neuropathic foot ulceration in type 2 diabetes. *Diabetes Research and Clinical Practice* **90**, 34-39.
- American Diabetes Association (2003) Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* **26 Suppl 1**, S5-20.
- American Diabetes Association (2013) Diagnosis and classification of diabetes mellitus. *Diabetes Care* **36 Suppl 1**, S67-74.
- Artese HP, Foz AM, Rabelo Mde S, Gomes GH, Orlandi M, Suvan J, D'Aiuto & Romito GA. (2015) Periodontal therapy and systemic inflammation in type 2 diabetes mellitus: a meta-analysis. *PLoS One* **10**, e0128344.
- Bandyopadhyay D, Marlow NM, Fernandes JK & Leite RS. (2010) Periodontal disease progression and glycaemic control among Gullah African Americans with type-2 diabetes. *Journal of Clinical Periodontology* **37**, 501-509.
- Belibasakis GN & Bostanci N. (2012) The RANKL-OPG system in clinical periodontology. *Journal of Clinical Periodontology* **39**, 239-248.
- Borgnakke WS, Ylostalo PV, Taylor GW & Genco RJ. (2013) Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *Journal of Clinical Periodontology* **40 Suppl 14**, S135-152.
- Bridges RB, Anderson JW, Saxe SR, Gregory K & Bridges SR. (1996) Periodontal status of diabetic and non-diabetic men: effects of smoking, glycaemic control, and socioeconomic factors. *Journal of Periodontology* **67**, 1185-1192.
- Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN & Battino M. (2009) Metabolic syndrome and periodontitis: is oxidative stress a common link? *Journal of Dental Research* **88**, 503-518.
- Bullon P, Newman HN & Battino M. (2014) Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction? *Periodontology* **2000** **64**, 139-153.
- Casarin RC, Barbagallo A, Meulman T, Santos VR, Sallum EA, Nociti FH, Duarte PM, Casati MZ & Goncalves RB. (2013) Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. *Journal of Periodontal Research* **48**, 30-36.
- Chang PC, Chien LY, Yeo JF, Wang YP, Chung MC, Chong LY, Kuo MY, Chen CH, Chiang HC, Ng BN, Lee QQ, Phay YK, Ng JR & Erk KY. (2013) Progression of periodontal destruction and the roles of advanced glycation end products in experimental diabetes. *Journal of Periodontology* **84**, 379-388.
- Chapple IL & Genco R. (2013) Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Clinical Periodontology* **40 Suppl 14**, S106-112.
- Chavarry NG, Vettore MV, Sansone C & Sheiham A. (2009) The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral Health & Preventive Dentistry* **7**, 107-127.
- Corbella S, Francetti L, Taschieri S, De Siena F & Fabbro MD. (2013) Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. *Journal of Diabetes Investigation* **4**, 502-509.
- D'Aiuto F, Nibali L, Parkar M, Patel K, Suvan J & Donos N. (2010) Oxidative stress, systemic inflammation, and severe periodontitis. *Journal of Dental Research* **89**, 1241-1246.
- Darre L, Vergnes JN, Gourdy P & Sixou M. (2008) Efficacy of periodontal treatment on glycaemic control in diabetic patients: A meta-analysis of interventional studies. *Diabetes Metabolism* **34**, 497-506.
- Demmer RT, Desvarieux M, Holtfreter B, Jacobs DR, Jr Wallaschofski H, Nauck M, Volzke H & Kocher T. (2010) Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). *Diabetes Care* **33**, 1037-1043.
- Demmer RT, Jacobs DR, Jr & Desvarieux M. (2008) Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care* **31**, 1373-1379.
- Devaraj S & Jialal I. (2000) Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effect of alpha-tocopherol supplementation. *Circulation* **102**, 191-196.
- Duarte PM, Bezerra JP, Miranda, TS, Feres M, Chambrone L & Shaddox LM. (2014) Local levels of inflammatory mediators in uncontrolled type 2 diabetic subjects with chronic periodontitis. *Journal of Clinical Periodontology* **41**, 11-18.
- Ebersole JL, Holt SC, Hansard R & Novak MJ. (2008) Microbiologic and immunologic characteristics of periodontal disease in Hispanic americans with type 2 diabetes. *Journal of Periodontology* **79**, 637-646.
- Emrich LJ, Shlossman M & Genco RJ. (1991) Periodontal disease in non-insulin-dependent diabetes mellitus. *Journal of Periodontology* **62**, 123-131.
- Engelbreton S, Chertog R, Nichols A, Hey-Hadavi J, Celenti R & Grbic J. (2007) Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes. *Journal of Clinical Periodontology* **34**, 18-24.
- Engelbreton S & Kocher, T. (2013) Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. *Journal of Clinical Periodontology* **40 Suppl 14**, S153-163.
- Engelbreton SP, Hey-Hadavi J, Ehrhardt FJ, Hsu D, Celenti RS, Grbic JT & Lamster IB. (2004) Gingival crevicular fluid levels of interleukin-1beta and glycemic control in patients with chronic periodontitis and type 2 diabetes. *Journal of Periodontology* **75**, 1203-1208.
- Engelbreton SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, Seaquist ER, Reddy MS, Lewis CE, Oates TW, Tripathy D, Katancik JA, Orlander PR, Paquette DW, Hanson NQ & Tsai MY. (2013) The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. *Journal of the American Medical Association* **310**, 2523-2532.
- Faggion CM, Jr Cullinan MP & Atieh M. (2016) An overview of systematic reviews on the effectiveness of periodontal treatment to improve glycaemic control. *Journal of Periodontal Research* **51**, 716-725.
- Fernandes JK, Wiegand RE, Salinas CF, Grossi SG, Sanders JJ, Lopes-Virella MF & Slate EH. (2009) Periodontal disease status in Gullah African Americans with type 2 diabetes living in South Carolina. *Journal of Periodontology* **80**, 1062-1068.
- Garcia D, Tarima S & Okunseri C. (2015) Periodontitis and glycemic control in diabetes: NHANES 2009 to 2012. *Journal of Periodontology* **86**, 499-506.
- Gorudko IV, Kostevich VA, Sokolov AV, Shamova EV, Buko IV, Konstantinova EE, Vasiliev VB, Cherenkevich SN & Panasenko OM. (2012) Functional activity of neutrophils in diabetes mellitus and coronary heart disease: role of myeloperoxidase in the development of oxidative stress. *Bulletin of Experimental Biology and Medicine* **154**, 23-26.
- Graves DT, Al-Mashat H & Liu R. (2004) Evidence that diabetes mellitus aggravates periodontal diseases and modifies the response to an oral pathogen in animal models. *Compendium of Continuing Education in Dentistry* **25**, 38-45.
- Gupta A, Ten S & Anhalt H. (2005) Serum levels of soluble tumor necrosis factor-alpha receptor 2 are linked to insulin resistance and glucose intolerance in children. *Journal of Pediatric Endocrinology and Metabolism* **18**, 75-82.
- Gyurko R, Siqueira CC, Caldon N, Gao L, Kantarci A & Van Dyke TE. (2006) Chronic hyperglycemia predisposes to exaggerated inflammatory response and leukocyte dysfunction in Akita mice. *Journal of Immunology* **177**, 7250-7256.
- Hardy DC, Ross JH, Schuyler CA, Leite RS, Slate EH & Huang Y. (2012) Matrix metalloproteinase-8 expression in periodontal tissues surgically removed from diabetic and non-diabetic patients with periodontal disease. *Journal of Clinical Periodontology* **39**, 249-255.
- Hodge PJ, Robertson D, Paterson K, Smith GL, Creanor S & Sherriff A. (2012) Periodontitis in non-smoking type 1 diabetic adults: a cross-sectional study. *Journal of Clinical Periodontology* **39**, 20-29.
- Hugoson A, Thorstensson H, Falk H & Kuylensstierna J. (1989) Periodontal conditions in insulin-dependent diabetics. *Journal of Clinical Periodontology* **16**, 215-223.
- International Diabetes Federation (2015) *IDF Diabetes Atlas*. Brussels, Belgium.
- Janket SJ, Wightman A, Baird AE, Van Dyke TE & Jones JA. (2005) Does periodontal treatment improve glycaemic control in diabetic patients? A meta-analysis of intervention studies. *Journal of Dental Research* **84**, 1154-1159.
- Kardesler L, Biyikoglu B, Cetinkalp S, Pitkala M, Sorsa T & Buduneli N. (2010) Crevicular fluid matrix metalloproteinase-8, -13, and TIMP-1 levels in type 2 diabetics. *Oral Diseases* **16**, 476-481.
- Katagiri S, Nitta H, Nagasawa T, Uchimura I, Izumiya H, Inagaki K, Kikuchi T, Noguchi T, Kanazawa M, Matsuo A, Chiba H, Nakamura N, Kanamura N, Inoue S, Ishikawa I & Izumi Y. (2009) Multi-center intervention study on glycohemoglobin (HbA1c) and serum, high-sensitivity CRP (hs-CRP) after local anti-infectious periodontal treatment in type 2 diabetic patients with periodontal disease. *Diabetes Research and Clinical Practice* **83**, 308-315.
- Kebschull M, Demmer RT & Papapanou PN. (2010) "Gum bug, leave my heart alone!" epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. *Journal of Dental Research* **89**, 879-902.
- Khaw KT, Wareham N, Bingham S, Luben R, Welch A & Day N. (2004) Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Annals of Internal Medicine* **141**, 413-420.
- Kiran M, Arpak N, Unsal E & Erdogan MF. (2005) The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *Journal of Clinical Periodontology* **32**, 266-272.
- Kolb H & Mandrup-Poulsen T. (2010) The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* **53**, 10-20.
- Kowall B, Holtfreter B, Volzke H, Schipf S, Mundt T, Rathmann W & Kocher T. (2015) Pre-diabetes and well-controlled diabetes are not associated with periodontal disease: the SHIP Trend Study. *Journal of Clinical Periodontology* **42**, 422-430.
- Kumar MS, Vamsi G, Sriprya R & Sehgal PK. (2006) Expression of matrix metalloproteinases (MMP-8 and -9) in chronic periodontitis patients with and without diabetes mellitus. *Journal of Periodontology* **77**, 1803-1808.

- Lalla E, Cheng B, Lal S, Kaplan S, Softness B, Greenberg E, Goland RS & Lamster IB. (2007a) Diabetes mellitus promotes periodontal destruction in children. *Journal of Clinical Periodontology* **34**, 294-298.
- Lalla E, Cheng B, Lal S, Kaplan S, Softness B, Greenberg E, Goland RS & Lamster IB. (2007b) Diabetes-related parameters and periodontal conditions in children. *Journal of Periodontal Research* **42**, 345-349.
- Lalla E, Cheng B, Lal S, Tucker S, Greenberg E, Goland R & Lamster IB. (2006a) Periodontal changes in children and adolescents with diabetes: a case-control study. *Diabetes Care* **29**, 295-299.
- Lalla E, Kaplan S, Chang SM, Roth GA, Celenti R, Hinckley K, Greenberg E & Papapanou PN. (2006b) Periodontal infection profiles in type 1 diabetes. *Journal of Clinical Periodontology* **33**, 855-862.
- Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, Kislenger T, Lu Y, Stern DM & Schmidt AM. (2000) Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. *Journal of Clinical Investigation* **105**, 1117-1124.
- Lalla E, Lamster IB, Stern DM & Schmidt AM. (2001) Receptor for advanced glycation end products, inflammation, and accelerated periodontal disease in diabetes: mechanisms and insights into therapeutic modalities. *Annals of Periodontology* **6**, 113-118.
- Liew AK, Punnathinont N, Lee YC & Yang J. (2013) Effect of non-surgical periodontal treatment on HbA1c: a meta-analysis of randomized controlled trials. *Australian Dental Journal* **58**, 350-357.
- Liu R, Bal HS, Desta T, Krothapalli N, Alyassi M, Luan Q & Graves DT. (2006) Diabetes enhances periodontal bone loss through enhanced resorption and diminished bone formation. *Journal of Dental Research* **85**, 510-514.
- Liu Y & Zhang Q. (2016) Periodontitis aggravated pancreatic beta-cell dysfunction in diabetic mice through interleukin-12 regulation on Klotho. *Journal of Diabetes Investigation* **7**, 303-311.
- Loe H. (1993) Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* **16**, 329-334.
- Lopez-Bastida J, Boronat M, Moreno JO & Schurer W. (2013) Costs, outcomes and challenges for diabetes care in Spain. *Global Health* **9**, 17.
- Makiura N, Ojima M, Kou Y, Furuta N, Okahashi N, Shizukuishi S & Amano A. (2008) Relationship of *Porphyromonas gingivalis* with glycemic level in patients with type 2 diabetes following periodontal treatment. *Oral Microbiology and Immunology* **23**, 348-351.
- Merchant AT, Georgantopoulos P, Howe CJ, Virani SS, Morales DA & Haddock KS. (2016) Effect of Long-Term Periodontal Care on Hemoglobin A1c in Type 2 Diabetes. *Journal of Dental Research* **95**, 408-415.
- Mohamed HG, Idris SB, Ahmed MF, Astrom AN, Mustafa K, Ibrahim SO & Mustafa M. (2015) Influence of type 2 diabetes on local production of inflammatory molecules in adults with and without chronic periodontitis: a cross-sectional study. *BMC Oral Health* **15**, 86.
- Morita I, Inagaki K, Nakamura F, Noguchi T, Matsubara T, Yoshii S, Nakagaki H, Mizuno K, Sheiham A & Sabbah W. (2012) Relationship between periodontal status and levels of glycated hemoglobin. *Journal of Dental Research* **91**, 161-166.
- Nelson RG, Shlossman M, Budding LM, Pettitt DJ, Saad MF, Genco RJ & Knowler WC. (1990) Periodontal disease and NIDDM in Pima Indians. *Diabetes Care* **13**, 836-840.
- Noma H, Sakamoto I, Mochizuki H, Tsukamoto H, Minamoto A, Funatsu H, Yamashita H, Nakamura S, Kiriya K, Kurihara H & Mishima HK. (2004) Relationship between periodontal disease and diabetic retinopathy. *Diabetes Care* **27**, 615.
- Oliver RC & Tervonen T. (1993) Periodontitis and tooth loss: comparing diabetics with the general population. *Journal of the American Dental Association* **124**, 71-76.
- Papageorgiou SN, Reichert C, Jager A & Deschner J. (2015) Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis. *Journal of Clinical Periodontology* **42**, 247-261.
- Paraskevas S, Huizinga JD & Loos BG. (2008) A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *Journal of Clinical Periodontology* **35**, 277-290.
- Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K & Taylor R. (2012) Periodontitis and diabetes: a two-way relationship. *Diabetologia* **55**, 21-31.
- Ribeiro FV, de Mendonca AC, Santos VR, Bastos MF, Figueiredo LC & Duarte PM. (2011) Cytokines and bone-related factors in systemically healthy patients with chronic periodontitis and patients with type 2 diabetes and chronic periodontitis. *Journal of Periodontology* **82**, 1187-1196.
- Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M & Koga T. (2004) The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. *Journal of Dental Research* **83**, 485-490.
- Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP & Offenbacher S. (1997) Monocytic TNF alpha secretion patterns in IDDM patients with periodontal diseases. *Journal of Clinical Periodontology* **24**, 8-16.
- Santos VR, Lima JA, Goncalves TE, Bastos MF, Figueiredo LC, Shibli JA & Duarte PM. (2010) Receptor activator of nuclear factor-kappa B ligand/osteoprotegerin ratio in sites of chronic periodontitis of subjects with poorly and well-controlled type 2 diabetes. *Journal of Periodontology* **81**, 1455-1465.
- Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, Shlossman M, Bennett PH, Genco R & Knowler WC. (2005) Periodontal disease and mortality in type 2 diabetes. *Diabetes Care* **28**, 27-32.
- Schmidt AM, Weidman E, Lalla E, Yan SD, Hori O, Cao R, Brett JG & Lamster IB. (1996) Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes. *Journal of Periodontal Research* **31**, 508-515.
- Sgolastra F, Severino M, Pietropaoli D, Gatto R & Monaco A. (2013) Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. *Journal of Periodontology* **84**, 958-973.
- Shlossman M, Knowler WC, Pettitt DJ & Genco RJ. (1990) Type 2 diabetes mellitus and periodontal disease. *Journal of the American Dental Association* **121**, 532-536.
- Shultz WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, Knowler WC & Nelson RG. (2007) Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. *Diabetes Care* **30**, 306-311.
- Sima C, Rhourida K, Van Dyke TE & Gyurko R. (2010) Type 1 diabetes predisposes to enhanced gingival leukocyte margination and macromolecule extravasation in vivo. *Journal of Periodontal Research* **45**, 748-756.
- Simpson TC, Needleman I, Wild SH, Moles DR & Mills EJ. (2010) Treatment of periodontal disease for glycaemic control in people with diabetes. *Cochrane Database of Systematic Reviews*, CD004714.
- Sorci G, Riuizi F, Giambanco I & Donato R. (2013) RAGE in tissue homeostasis, repair and regeneration. *Biochimica et Biophysica Acta* **1833**, 101-109.
- Soriguer F, Goday A, Bosch-Comas A, Bordiu E, Calle-Pascual A, Carmena R, Casamitjana R, Castano L, Castell C, Catala M, Delgado E, Franch J, Gaztambide S, Girbes J, Gomis R, Gutierrez G, Lopez-Alba A, Martinez-Larrad MT, Menendez E, Mora-Peces I, Ortega E, Pascual-Manich G, Rojo-Martinez G, Serrano-Rios M, Valdes S, Vazquez JA & Vendrell J. (2012) Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. *Diabetologia* **55**, 88-93.
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC & Holman RR. (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal* **321**, 405-412.
- Sun QY, Feng M, Zhang MZ, Zhang YQ, Cao MF, Bian LX, Guan QB & Song KL. (2014) Effects of periodontal treatment on glycemic control in type 2 diabetic patients: a meta-analysis of randomized controlled trials. *Chinese Journal of Physiology* **57**, 305-314.
- Taylor GW, Burt BA, Becker MP, Genco RJ & Shlossman M. (1998) Glycemic control and alveolar bone loss progression in type 2 diabetes. *Annals of Periodontology* **3**, 30-39.
- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC & Pettitt DJ. (1996) Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *Journal of Periodontology* **67**, 1085-1093.
- Teeuw WJ, Gerdes VE & Loos BG. (2010) Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. *Diabetes Care* **33**, 421-427.
- Thorstenson H & Hugoson A. (1993) Periodontal disease experience in adult long-duration insulin-dependent diabetics. *Journal of Clinical Periodontology* **20**, 352-358.
- Thorstenson H, Kuylenstierna J & Hugoson A. (1996) Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *Journal of Clinical Periodontology* **23**, 194-202.
- United Nations (2013) *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Geneva, Switzerland.
- Xiong X, Elkind-Hirsch KE, Vastardis S, Delarosa RL, Pridjian G & Buekens P. (2009) Periodontal disease is associated with gestational diabetes mellitus: a case-control study. *Journal of Periodontology* **80**, 1742-1749.
- Yuan K, Chang CJ, Hsu PC, Sun HS, Tseng CC & Wang JR. (2001) Detection of putative periodontal pathogens in non-insulin-dependent diabetes mellitus and non-diabetes mellitus by polymerase chain reaction. *Journal of Periodontal Research* **36**, 18-24.
- Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R & Genco RJ. (1988) Microbiological and immunological studies of adult periodontitis in patients with noninsulin-dependent diabetes mellitus. *Journal of Periodontology* **59**, 23-31.
- Zhou M, Rong R, Munro D, Zhu C, Gao X, Zhang Q & Dong Q. (2013) Investigation of the effect of type 2 diabetes mellitus on subgingival plaque microbiota by high-throughput 16S rDNA pyrosequencing. *PLoS One* **8**, e61516.
- Zizzi A, Tirabassi G, Aspriello SD, Piemontese M, Rubini C & Lucarini G. (2013) Gingival advanced glycation end-products in diabetes mellitus-associated chronic periodontitis: an immunohistochemical study. *Journal of Periodontal Research* **48**, 293-301.