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Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks

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Abstract

Objectives: To review the evidence for the association between diabetes and periodontal and peri-implant conditions and the impact of periodontal therapy in subjects with diabetes.

Material and Methods: A search of MEDLINE-PubMed was performed up to and including December 2007. The search was limited to clinical studies published in English. Publications on animal studies were excluded. The selection criteria included all levels of available evidence.

Results: Evidence on the association between diabetes and periodontitis supports the concept of increased severity but not extent of periodontitis in subjects with poorly controlled diabetes. Subjects with controlled diabetes do not show an increase in extent and severity of periodontitis. Periodontitis is associated with poor glycaemic control and diabetes-related complications. It is inconclusive that periodontal therapy with or without the use of antibiotics results in improvements of glycaemic control and of markers of systemic inflammation. Evidence is lacking to indicate that implant therapy in subjects with diabetes yields long-term outcomes comparable with those of non-diabetic subjects.

Conclusions: Poorly controlled diabetes may be considered a risk factor for increased severity of periodontitis. The effects of periodontal therapy on glycaemic control and systemic inflammation is not proven beyond doubt and need to be confirmed in large-scale randomized-controlled clinical trials.

Key words: diabetes; glycaemic control; host response; inflammation; oral implants; periodontal disease; periodontal therapy; periodontitis

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Periodontal diseases represent chronic inflammatory responses to a bacterial challenge. Although bacterial biofilms have been shown to be necessary in the initiation of gingival inflammation and subsequent destruction of periodontal tissues (Socransky & Haffajee 2005), its presence alone explains a relatively small proportion (i.e. 20–30%) of the variance in disease expression (Grossi et al. 1994). Based on an established model of pathogenesis (Offenbacher 1996), the bacterial biofilm alone is insufficient to explain disease initiation and progression. Evidence suggests that periodontal tissues destruction is mainly due to the host's inflammatory response to the bacterial challenge (Offenbacher 1996). In addition to other factors, diabetes mellitus has been shown to modify the host response to the bacterial challenge and in time may increase the risk for periodontal disease (for a review, see Mealey & Oates 2006, Southerland et al. 2006, Graves et al. 2007, Preshaw et al. 2007).

Diabetes mellitus represents a heterogeneous group of metabolic disorders characterized by elevated blood glucose levels. Destructive autoimmune processes of the pancreatic β cells leading to insufficient insulin secretion are

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the main features of type 1 diabetes, whereas resistance of tissues to circulating insulin is the main feature of type 2 diabetes (American Diabetes Association 2005). Type 2 diabetes may be preceded by the ''metabolic syndrome'' consisting of six parameters including obesity, dyslipidemia, insulin resistance, high blood pressure and a pro-inflammatory and pro-thrombotic status (Festa et al. 2000, Fernandez-Real & Ricart 2003, Grundy et al. 2004). Major systemic complications of diabetes such as retinopathy, nephropathy, neuropathy and vascular disorders represent the result of a prolonged hyperglycaemic state (Taylor et al. 1996, Thorstensson et al. 1996, Saremi et al. 2005, Shultis et al. 2007). In subjects with diabetes, chronically elevated blood glucose levels lead to the accelerated formation of advanced glycation end products (AGEs). Endothelial cells and monocytes possess specific receptors for AGEs (i.e. RAGEs) located on their cell surfaces (Hudson & Schmidt 2004). There is strong indication that the interaction of AGEs with their receptors plays an important role in the development of diabetic complications (for a review: Hudson et al. 2003). The interaction of macrophages with AGEs has been shown to stimulate increased secretions of pro-inflammatory mediators such as tumour necrosis factor α (TNF-α) and interleukin-1 (IL-1) (Vlassara et al. 1988). In subjects with type 2 diabetes, deterioration of periodontal status was associated with elevated serum levels of AGEs (Takeda et al. 2006).

Approximately 85–90% of all subjects with diabetes are diagnosed with type 2, whereas the remaining 5–10% represent type 1 diabetic subjects (Zimmet et al. 2001, Green et al. 2003, Stumvoll et al. 2005). Outcomes from analyses of NHANES III databases showed that a self-reported medical history combined with clinical evidence of periodontal disease provided an efficient tool for the estimation of the probability of an undiagnosed diabetic status (Borrell et al. 2007). While type 1 diabetes is one of the most common chronic diseases of young individuals (Gale 2002), type 2 diabetes is most prevalent in middle-aged individuals characterized by the presence of obesity [i.e. Body Mass Index (BMI) $\geqslant$ 30 kg/m^2], sedentary lifestyle and high-fat diet (for a review: Preshaw et al. 2007). The association between type 2 diabetes and periodontal conditions was recently investigated in the first National Periodontal and Systemic Examination Survey (NPASES) in France (Mattout et al. 2006). The outcomes of that survey (Mattout et al. 2006) confirmed previous reports yielding significantly worse periodontal conditions (i.e. gingival inflammation and clinical attachment loss) in type 2 diabetic subjects compared with those of non-diabetic controls.

The hypothesis of more severe periodontal disease in women with a history of gestational diabetes mellitus (GDB) compared with that of pregnant women without a history of diabetes during pregnancy was tested in several studies (Mittas et al. 2006, Novak et al. 2006, Xiong et al. 2006). Collectively, an association of more severe periodontitis or increased gingival inflammation was found when pregnant women with GDB were compared with pregnant women without GDB.

Hence, the aim of the present review was to update the evidence associating diabetes mellitus with periodontal and peri-implant conditions as well as to discuss the impact of periodontal therapy on periodontal status, on systemic markers of inflammation and on the level of glycaemic control.

Material and Methods

Literature search

A search in the electronic MEDLINE-PubMed database up to and including December 2007 was performed. Standard search guidelines for the identification of relevant publications on the topics of periodontal disease(s), periodontitis, diabetes, diabetes mellitus and glycaemic control were followed. Only peer-reviewed clinical studies in English were considered. The selection criteria included the following levels of evidence: systematic reviews, meta-analyses, randomized-controlled clinical trials, controlled clinical trials, prospective and retrospective cohort studies and cross-sectional studies. In addition, the reference lists of publications selected for inclusion in this review were systematically screened.

Findings from animal studies on the relationship between diabetes and periodontal disease (Pontes Andersen et al. 2007) and between diabetes and outcomes of implant therapy (Kotsovilis et al. 2006) were recently summarized and were excluded from this review.

Effects of diabetes on periodontal status

Although several studies investigated the relationship between diabetes mellitus and periodontal disease, outcomes were often controversial. Several factors complicate our understanding of the role of diabetes as a risk factor for the severity of periodontitis. For example, diagnostic parameters and methodologies are not universally defined making comparisons of the available evidence difficult. Furthermore, in subjects with diabetes the onset and duration of the disease, the level of glycaemic control, duration and type of treatment and the presence of systemic complications vary. This additional heterogeneity may in part explain the variability of the outcomes and the fact that not all subjects with diabetes suffer equally from periodontitis as a complication of their diabetic status.

Effects of glycaemic control

Chronic hyperglycaemia is one of the key features of diabetes mellitus. Glycaemic levels assessed using fasting plasma glucose concentrations or a 2-h oral glucose tolerance test are widely used and reflect glycaemic control at a given time point. However, these parameters may vary within a few hours due to diet, physical activity and use of medications. The assessment of fructosamine and glycosylated haemoglobin (HbA_{1C}) levels is widely used to monitor glycaemic control over a period of 4–6 and 4–12 weeks, respectively (for a review: Mealey & Ocampo 2007). The necessity to determine an arbitrary cut-off point to assess the level of glycaemic control (e.g. HbA_{1C}) and the absence of a generally accepted definition of periodontal disease severity makes the comparison of different studies difficult. Furthermore, large variations in study designs and study populations contribute to the inconsistencies of the findings related to the effect of glycaemic control. While some studies found no relationship between the level of glycaemic control and periodontal status (Hove & Stallard 1970, Barnett et al. 1984, Bacic et al. 1988, Hayden & Buckley 1989, Sastrowijoto et al. 1989, 1990, Pinson et al. 1995), other studies indicated that the degree of glycaemic control may influence the severity of periodontal disease (Gislén et al. 1980, Ervasti et al. 1985, Unal et al. 1993, Firatli et al. 1994, Bridges et al. 1996,

Taylor et al. 1996, 1998, Tsai et al. 2002, Campus et al. 2005). Despite similar plaque scores, poorly controlled subjects with diabetes displayed more gingival bleeding sites compared with those of subjects with diabetes with good or moderate control (Ervasti et al. 1985). Children with poor glycaemic control displayed higher Gingival Index scores than non-diabetic children but no such difference was found between subjects with diabetes with good glycaemic control and subjects without diabetes displaying similar plaque levels (Gislén et al. 1980). Fructosamine levels were correlated to the percentage of gingival bleeding in subjects with type 2 diabetes (Unal et al. 1993) and to the Gingival Index system in subjects with type 1 diabetes (Firatli et al. 1994). In the presence of similar plaque levels, poorly controlled subjects with type 1 diabetes of long duration (e.g. mean of 16.5 years) displayed more severe attachment and alveolar bone loss (Safkan-Seppälä & Ainamo 1992) as well as increased tooth loss (Seppälä et al. 1993, 1994) compared with well-controlled subjects with diabetes. This is in agreement with other reports that well-controlled subjects with type 1 and type 2 diabetes had on average three more teeth compared with subjects with poorly controlled diabetes of similar age (Tervonen & Oliver 1993). Well-controlled subjects with diabetes were reported to have similar or even better periodontal conditions compared with subjects without diabetes (Ervasti et al. 1985, Tervonen & Knuuttila 1986, Katz et al. 1991).

Although the level of glycaemic control plays a central role with respect to periodontal status, the combination of diabetes with other risk modifiers for periodontal disease such as cigarette smoking or genetic polymorphisms may confer cumulative risks not yet elucidated. Recently, findings from an underpowered study in subjects with type 2 diabetes with periodontal disease suggested that the prevalence of severe periodontal disease increased with decreasing glycaemic control (Guzman et al. 2003). However, the small sample size and the stratification of *IL-1* genotypes with respect to ethnicity made the interpretation of the results difficult (Guzman et al. 2003).

Findings from a cross-sectional study of insulin-dependent subjects with diabetes aged $\geqslant 30$ years showed that the combined effect of poor glycaemic control (e.g. $HbA_{1C} > 8.5\%$) and cigarette smoking significantly increased the risk for clinical attachment loss (Syrjälä et al. 2003).

Effects of diabetes onset and duration

Controversial results were reported on the effect of diabetes duration on periodontal conditions. While outcomes from some studies did not yield any correlation between diabetes duration and periodontal status (Hove & Stallard 1970, Nichols et al. 1978, Barnett et al. 1984, Bacic et al. 1988, Rosenthal et al. 1988), other outcomes showed that diabetes duration was of critical importance (Glavind et al. 1968, Cianciola et al. 1982, Hugoson et al. 1989, Löe 1993, Firatli et al. 1996, 1997). In the presence of similar plaque scores, young subjects with type 1 diabetes of long duration suffered from more severe gingival inflammation and periodontal tissue destruction compared with subjects with diabetes of short duration (Cianciola et al. 1982) or non-diabetic subjects (Firatli et al. 1996, 1997).

Unfortunately, diabetes duration was not always assessed independently from the age of onset. In determining periodontal disease severity, outcomes from some studies showed that age of onset was as critical as diabetes duration (Thorstensson & Hugoson 1993, Cerda et al. 1994, Moore et al. 1999). In a cross-sectional study comparing subjects with type 1 diabetes of long duration with subjects without diabetes of three different age groups, subjects with diabetes aged 40–49 years were not only found to have a higher percentage of pocket probing depths $\geqslant 6$ mm and more advanced bone loss compared with age-matched subjects without diabetes, but also alveolar bone loss comparable with that of 60–69-year-old subjects without diabetes (Thorstensson & Hugoson 1993). On the other hand, poorly controlled subjects with type 1 diabetes with late onset (i.e. mean age 11.9 years) displayed a higher extent of periodontal disease compared with that of age-matched subjects with diabetes with early onset (i.e. mean age 4.8 years) (Moore et al. 1999).

Effects of non-oral diabetes-related complications

Outcomes from a cross-sectional investigation showed that non-oral diabetes-related complications occurred in 45% of type 1 and in 71% of subjects with type 2 diabetes with periodontal disease, respectively (Mattheos et al. 2008). While in subjects with type 1 diabetes the most frequent complications were retinopathy (18.5%), micro-albuminuria (18.5%) and neuropathy (11.1%), the corresponding frequencies for subjects with type 2 diabetes were 18%, 21.4% and 42%, respectively (Mattheos et al. 2008).

According to the outcomes of several studies, the presence and severity of non-oral diabetes-related complications were correlated to the severity of periodontal conditions (Rylander et al. 1987, Bacic et al. 1988, Rosenthal et al. 1988, Karjalainen et al. 1994, Thorstensson et al. 1996, Moore et al. 1998, 1999).

Subjects with type 1 diabetes with retinopathy displayed more attachment loss compared with subjects with diabetes without retinal changes (Glavind et al. 1968). Moreover, subjects with type 1 and type 2 diabetes with advanced retinopathy displayed more sextants with deep pocket probing depths (PPD) compared with subjects with diabetes with incipient or no retinal complications (Bacic et al. 1988). Pima Indians with type 2 diabetes and retinopathy were five times more likely to develop periodontal disease compared with those without retinopathy (Löe 1993). When comparing poorly controlled subjects with type 1 diabetes with or without advanced retinopathy, higher percentages of sites bleeding on probing, of pocket probing depths (PPD) $\geqslant 4$ mm and clinical attachment loss were observed in diabetic subjects with advanced retinopathy (Karjalainen et al. 1994). Subjects with type 1 diabetes with $\geqslant 1$ systemic complication and poor glycaemic control displayed greater marginal bone loss compared with subjects with good/moderate control (Tervonen et al. 2000). On the other hand, subjects with type 1 diabetes with a good glycaemic control and without diabetes-related complications were not more susceptible to marginal bone loss compared with age-matched subjects without diabetes (Tervonen et al. 2000).

Effects on local markers of inflammation

A series of cross-sectional investigations indicated that subjects with type 1 diabetes displayed an elevated secretion of inflammatory mediators (e.g. PGE_2 and IL-1β) in the gingival crevicular fluid (GCF) compared with that of subjects without diabetes (Salvi et al. 1997b,

1998). These findings were corroborated by the fact that subjects with type 1 diabetes with gingivitis or mild periodontal disease displayed significantly elevated GCF levels of PGE_2 and IL-1β compared with those of subjects without diabetes. This indicated that an up-regulated inflammatory response existed in diabetic subjects independently of the presence of severe periodontal disease.

Levels of inflammatory mediators in the GCF were analysed in a cross-sectional study (Engebretson et al. 2004) as well as in a case–control study (Engebretson et al. 2006) involving subjects with type 2 diabetes with periodontal disease. Subjects with poor glycaemic control (e.g. $HbA_{1C} \geqslant 8\%$) and untreated periodontal disease had significantly higher mean GCF IL-1β levels compared with well-controlled diabetic subjects (e.g. $HbA_{1C} < 8\%$) (Engebretson et al. 2004). These findings (Engebretson et al. 2004) confirmed those of previous reports (Cutler et al. 1999, Kurtis et al. 1999, Bulut et al. 2001).

In 45 subjects with type 2 diabetes and periodontal disease GCF levels of interleukin-8 (IL-8) and β-glucuronidase (BG) were assessed and compared with those of 32 subjects without diabetes with comparable periodontal disease severity (Engebretson et al. 2006). The main outcome of that study showed that GCF levels of polymorphonuclear neutrophil (PMN) markers (e.g. IL-8 and BG) were significantly lower in subjects with type 2 diabetes compared with those of subjects without diabetes. These findings suggested that PMN activity at the local sites was impaired in subjects with type 2 diabetes. However, this seems to be in contrast with the elevated levels of other GCF inflammatory mediators reported above.

In a case–control study, gingival biopsy levels of IL-1β and IL-6 from subjects with type 2 diabetes with periodontal disease were assessed and compared with those of subjects without diabetes with and without periodontal disease (Duarte et al. 2007). Significantly higher levels of both IL-1β and IL-6 were detected in gingival biopsies of subjects with type 2 diabetes with periodontal disease compared with those of subjects without diabetes with comparable periodontal conditions.

Effects on ex vivo inflammatory cells

Elevated monocytic levels of PGE_2, IL-1β and TNF-α in response to *Porphyromonas gingivalis* lipopolysaccharide challenge were observed in subjects with type 1 diabetes compared with those of subjects without diabetes (Salvi et al. 1997a, 1998). Moreover, monocytes from subjects with type 1 diabetes with gingivitis or mild periodontal disease released significantly elevated levels of PGE_2, IL-1β and TNF-α compared with those of subjects without diabetes upon bacterial challenge.

Collectively, these findings indicated that both type 1 and type 2 diabetes were associated with a dysregulated response of GCF and gingival biopsy markers of inflammation suggesting a biological mechanism to account for the association between glycaemic control and periodontal conditions.

Effects on the development of experimental gingivitis

Based on the above-mentioned findings, the hypothesis of an altered inflammatory response in subjects with diabetes compared with that in non-diabetic subjects was tested. The development of gingival inflammation upon experimental plaque accumulation was investigated in subjects with diabetes and compared with that of subjects without diabetes (Salvi et al. 2005). Subjects with type 1 diabetes and controls without diabetes underwent a 3-week period of experimental plaque accumulation followed by 2 weeks of optimal self-performed plaque control. The mean duration of diabetes was 9.0 ± 5.3 years (SD) and the mean HbA_{1C} level at baseline was $8.1 \pm 0.7\%$ (SD). Between baseline, Day 21 and Day 35, no significant differences in mean Plaque and Gingival Index scores were observed between subjects with and without diabetes. At Day 21, however, subjects with diabetes were 16 times more likely to display extensive gingival bleeding (e.g. $\geqslant 35\%$ of sites) compared with subjects without diabetes. No significant differences in total counts and proportions of red and orange complex species (Socransky et al. 1998) were observed between subjects with and without diabetes (Salvi et al. 2005). These findings showed that young subjects with type 1 diabetes developed an earlier and stronger gingival inflammatory response compared with that of subjects without diabetes indicating a dysfunctional host response.

Effects of type of diabetes

Recent evidence for the association between type 1 diabetes and periodontal status emerged from studies in children and adolescents (Lalla et al. 2006, 2007a, b, Lal et al. 2007). In a cross-sectional study, the comparison of 182 children and adolescents aged 6–18 years with type 1 diabetes with 160 controls without diabetes showed that subjects with diabetes exhibited significantly increased clinical attachment loss (Lalla et al. 2006). These findings (Lalla et al. 2006) were expanded and confirmed in a case–control study involving 700 individuals aged 6–18 years (Lalla et al. 2007a). Young subjects with type 1 diabetes exhibited increased gingival inflammation and clinical attachment loss compared with subjects without diabetes. Regression analysis yielded worsened periodontal conditions for subjects with type 1 diabetes compared with adolescents without diabetes using three different criteria for periodontal disease with odds ratios (ORs) ranging from 1.84 to 3.72. Separate analysis of 6–11 and 12–18-year-old subgroups showed that the effect of diabetes on periodontal status remained significant.

The diabetic status may already influence gingival conditions around primary teeth. Findings from a case–control study showed that the risk of gingival bleeding in children with type 1 diabetes aged 6–13 years was significantly elevated compared with that of children without diabetes (Lal et al. 2007).

The relationship between type 2 diabetes and periodontal disease is complicated by the fact that diabetes onset generally occurs after the age of 40 years, coinciding with the time point when periodontal disease becomes more prevalent. Data analysis from the NHANES III on 4343 subjects aged 45–90 years provided insight on the association between glycaemic control of type 2 diabetes and severe periodontal disease (Tsai et al. 2002). Severe periodontal disease was defined as $\geqslant 2$ sites with $\geqslant 6$ mm clinical attachment loss and $\geqslant 1$ site with probing pocket depth (PPD) $\geqslant 5$ mm. Subjects with poorly controlled diabetes had levels of $HbA_{1C} > 9\%$ whereas better-controlled diabetic subjects had levels of $HbA_{1C} \leqslant 9\%$. The outcomes showed that poorly controlled subjects with type 2 diabetes displayed a significantly higher prevalence of severe periodontal disease compared with subjects without

diabetes [OR: 2.90; 95% confidence interval (CI): 1.40, 6.03]. Further evidence of type 2 diabetes as a risk factor for more severe periodontal disease has been reported (Sandberg et al. 2000, Campus et al. 2005, Jansson et al. 2006) and comprehensively been reviewed (Mealey & Oates 2006).

The relationship between markers of glycaemic control and the severity of periodontal disease was reported in a study of 181 subjects aged 21–65 years with types 1 or 2 diabetes (Lim et al. 2007). Diabetic subjects with HbA_{1C} levels $<8\%$ (i.e. good to moderate glycaemic control) displayed significantly lower percentages of sites with bleeding on probing and with pocket probing depth $\geqslant 5$ mm compared with diabetic subjects with HbA_{1C} levels $\geqslant 8\%$ (i.e. poor glycaemic control). Again, this confirmed that poor glycaemic control of both type 1 and type 2 diabetes emerged as a significant risk factor for periodontitis.

Summary

Comprehensive evidence on the association between both type 1 and type 2 diabetes and periodontal disease was recently presented (Mealey & Oates 2006, Mealey & Ocampo 2007, Preshaw et al. 2007) and summarized in a meta-analysis (Khader et al. 2006). This meta-analysis (Khader et al. 2006) included 23 publications encompassing the period 1970–2003 and comparing periodontal conditions of subjects with type 1 and type 2 diabetes with those of subjects without diabetes. Results were reported for 19,245 subjects aged from 5 to 78 years. The main outcome revealed increased severity but similar extent of periodontal disease when subjects with diabetes were compared with subjects without diabetes. Irrespective of the type of diabetes, loss of clinical attachment was significantly greater in subjects with diabetes compared with subjects without diabetes. The extent of gingival inflammation as assessed by the percentage of sites with Gingival Index score $\geqslant 2$ as well as the extent of sites bleeding on probing, did not differ significantly comparing subjects with and without diabetes. However, considerable heterogeneity of the included publications with respect to study populations, sample sizes, onset and duration of diabetes, level of glycaemic control and diagnosis of periodontal disease represented a limitation of this meta-analysis (Khader et al. 2006).

Risk assessment

The outcomes of a multivariate analysis of a subject sample with a high prevalence of type 2 diabetes (e.g. Pima Indians) showed that diabetic subjects were three times more likely to suffer from periodontal disease compared with subjects without diabetes (Emrich et al. 1991). Grossi et al. (1994) reported an OR of 2.32 for subjects with diabetes to experience clinical attachment loss compared with subjects without diabetes.

A meta-analysis of four publications including 3524 adult individuals yielded a significant association between diabetes and periodontal disease with an estimated twofold risk for periodontal disease in subjects with diabetes compared with subjects without diabetes (Papapanou 1996).

Evidence from longitudinal data investigating the role of diabetes as a risk factor for periodontal disease was reported in a 2-year follow-up study (Taylor et al. 1998). In that study (Taylor et al. 1998) type 2 diabetes conferred an OR of 4.2 for progressive alveolar bone loss when compared with a non-diabetic status. Subjects with poor glycaemic control (i.e. $HbA_{1C}\geqslant 9\%$) were 11 times more likely to loose alveolar bone when compared with subjects without diabetes, while better glycaemic control (i.e. $HbA_{1C}<9\%$) yielded an OR of 2.2 for alveolar bone loss when compared with subjects without diabetes (Taylor et al. 1998).

The findings of the previous report (Taylor et al. 1998) were confirmed in the analysis of the NHANES III database (Tsai et al. 2002). While poor glycaemic control (i.e. $HbA_{1C}>9\%$) of type 2 diabetes conferred an OR of 2.9 (95% CI: 1.40, 6.03) for severe periodontal disease compared with a non-diabetic status, there was only a slight tendency (OR: 1.56; 95% CI: 0.90, 2.68) for a higher prevalence of severe periodontal disease in subjects with diabetes with better glycaemic control (i.e. $HbA_{1C}\leqslant 9\%$).

Collectively, these findings provided evidence that poorly controlled diabetes was associated with periodontitis (Table 1).

Effects of periodontal status on diabetic control

If subjects with diabetes suffer from more severe periodontal disease compared with subjects without diabetes, one would also expect that subjects suffering from periodontal disease would yield a higher prevalence of diabetes compared with periodontally healthy subjects. In order to test this hypothesis, subsets of data from the NHANES III were analysed (Soskolne & Klinger 2001). Diabetes was a self-reported disease. Periodontal disease was defined as subjects with $\geqslant 1$ site

Table 1. Association of diabetes type 1 and type 2 with periodontal status

Publication	Study design	*N*	Diabetes type	Odds ratio (OR)	95% confidence interval (CI)
Emrich et al. (1991)	Cross-sectional	1324	1+2		
				2.81 (based on clinical parameters)	1.91–4.13
				3.43 (based on radiographic parameters)	2.28–5.16
Grossi et al. (1994)	Cross-sectional	1426	2	2.32	1.17–4.60
Taylor et al. (1998)	Longitudinal	14	2	2.2 ($HbA_{1C}<9\%$)	0.7–6.5
		7	2	5.4 ($HbA_{1C}\geqslant 9\%$)	0.8–53.3
Tsai et al. (2002)	Cross-sectional	4343			
			2	1.56 ($HbA_{1C}\leqslant 9\%$)	0.90–2.68
			2	2.90 ($HbA_{1C}>9\%$)	1.40–6.03
Lalla et al. (2007a)	Cross-sectional	350	1*	1.84–3.72	

*7% of cases were diagnosed as type 2.

N, number of subjects; HbA_{1C}, glycosylated haemoglobin.

with both a PPD $\geqslant$ 5 mm and clinical attachment loss $\geqslant$ 2 mm. The findings showed that the prevalence of diabetes in periodontally diseased subjects ($N = 1293$) was 12.5% while 6.3% of the periodontally healthy subjects ($N = 12{,}178$) had a self-reported diagnosis of diabetes. Based on this analysis, it was suggested that the prevalence of diabetes in periodontally compromised subjects was twofold higher compared with that in periodontally healthy subjects.

Unfortunately, knowledge on how periodontitis may influence glycaemic control is limited. Outcomes from longitudinal studies showed that severe periodontitis at baseline was associated with poor glycaemic control and diabetes-related complications at follow-up (e.g. overt nephropathy and end-stage renal disease, cardiovascular disease and associated mortality) (Taylor et al. 1996, Thorstensson et al. 1996, Saremi et al. 2005, Shultis et al. 2007). In a retrospective study, the level of HbA_{1C} deteriorated in subjects with non-insulin-dependent diabetes with severe periodontitis compared with that of subjects with diabetes without such periodontal conditions (Collin et al. 1998). Findings in non-diabetic Japanese women showed that the severity of periodontitis was associated with the development of glucose intolerance (Saito et al. 2004). In the same study population, it was found that when subjects exhibited signs of the metabolic syndrome, parameters of periodontal destruction were more prevalent (Shimazaki et al. 2007). Subjects with type 2 diabetes with severe periodontitis had significantly elevated HbA_{1C} levels and more cardiovascular complications compared with periodontally healthy subjects with diabetes (Jansson et al. 2006).

An association of serum TNF-α levels with insulin resistance and type 2 diabetes has been established (Festa et al. 2000, Mishima et al. 2001, Fernandez-Real et al. 2002). Circulating TNF-α levels were shown to be associated with periodontal disease in a cohort of geriatric patients after adjusting for diabetes status and BMI (Bretz et al. 2005). Outcomes from a cross-sectional study demonstrated that chronic periodontitis was positively associated with plasma levels of TNF-α in subjects with type 2 diabetes (Engebretson et al. 2007).

However, based on this evidence, important questions remain to be answered: what is the temporal sequence between the onset of periodontal disease and that of non-oral diabetes-related complications? And what are the effects of periodontal therapy on clinical parameters, systemic inflammatory markers and on glycaemic control?

Efficacy of periodontal therapy in subjects with diabetes

Effects on periodontal parameters

Findings from case–control and cohort studies in subjects with both type 1 and type 2 diabetes investigating the response to mechanical periodontal therapy with or without the adjunctive use of antibiotics, antiseptics or non-steroidal anti-inflammatory drugs yielded improvements in periodontal conditions (i.e. PPD reduction, reduction of bleeding sites and gain of clinical attachment level) (Sastrowijoto et al. 1989, Tervonen et al. 1991, Aldridge et al. 1995, Westfelt et al. 1996, Grossi et al. 1997, Christgau et al. 1998, Rocha et al. 2001, Sims et al. 2001, Al-Mubarak et al. 2002, Rodrigues et al. 2003, Martorelli de Lima et al. 2004, Skaleric et al. 2004, Kiran et al. 2005, Llambés et al. 2005, Promsudthi et al. 2005, Faria-Almeida et al. 2006, Lalla et al. 2007c, Navarro-Sanchez et al. 2007). Recently, findings from the first randomized, single blind, controlled clinical trial in poorly controlled type 2 diabetic subjects were reported (Jones et al. 2007). The main aim of that study was to determine the efficacy of non-surgical periodontal therapy on the improvement in glycaemic control. Although periodontal destruction at baseline was not severe, approximately 60% of the deep sites (e.g. PPD > 5 mm) remained unchanged after 4 months of healing.

Effects on systemic inflammatory markers

The effect of mechanical periodontal treatment with or without the adjunctive use of antibiotics on the level of systemic inflammatory markers was investigated in several studies (Iwamoto et al. 2001, Nishimura et al. 2003, Talbert et al. 2006, Lalla et al. 2007c). Outcomes from two studies (Iwamoto et al. 2001, Nishimura et al. 2003) showed that non-surgical periodontal therapy with adjunctive local delivery of minocycline reduced circulating levels of TNF-α. On the other hand, serum levels of TNF-α were not significantly affected 4 weeks (Lalla et al. 2007c) and 12 weeks (Talbert et al. 2006) following mechanical periodontal therapy. In a pilot study, systemic levels of mediators involved in the pathogenesis of vascular diseases such as high-sensitivity C-reactive protein (hs-CRP) and soluble E-selectin were significantly reduced following non-surgical periodontal debridement (Lalla et al. 2007c).

Nevertheless, current evidence on the impact of periodontal therapy on systemic markers of inflammation should be classified as preliminary, since one study (Iwamoto et al. 2001) reported short-term outcomes on 13 subjects with type 2 diabetes, one study (Nishimura et al. 2003) was a case report with a 2-year follow-up and two investigations (Talbert et al. 2006, Lalla et al. 2007c) were pilot studies.

Effects on glycaemic control

Outcomes of a meta-analysis including 456 subjects with diabetes of both types showed that following mechanical periodontal debridement HbA_{1C} levels decreased on average by 0.38% for all studies, by 0.66% when restricted to subjects with type 2 diabetes and by 0.71% if antibiotics where administered. However, the magnitude of such improvements was not statistically significant (Janket et al. 2005). The findings of this meta-analysis (Janket et al. 2005) were confirmed in a single blind, randomized, controlled clinical trial on the efficacy of non-surgical mechanical debridement with adjunctive systemic doxycycline for 14 days and chlorhexidine rinses twice daily for 4 months (Jones et al. 2007). Veterans with poorly controlled type 2 diabetes were included. Additional periodontal therapy to current diabetes medication failed to provide a statistically significant reduction in the levels of HbA_{1C} compared with those of untreated type 2 diabetic subjects. Although some trends were observed, subjects who received periodontal therapy were not more likely to yield statistically significant reductions in HbA_{1C} levels of 0.5% or 1% compared with untreated control subjects. Similarly, the observation that untreated subjects were twice as likely to increase insulin from baseline to 4 months and less likely to decrease insulin compared with periodontally treated subjects was not statistically significant.

Additional intervention studies on the effect of periodontal therapy on glycaemic control (i.e. HbA_{1C} levels) not included in the meta-analysis of Janket et al. (2005) are summarized in Table 2.

Effects of diabetes on outcomes of implant therapy

A limited number of studies on the effects of diabetes on the outcomes of implant therapy are available. A retrospective cohort study of 1140 patients treated by the same surgeon over a 21-year period reported implant survival rates in medically compromised patients including diabetic subjects (Moy et al. 2005). The outcomes showed that, despite moderate to good glycaemic control in most of the 48 diabetic subjects included in that study (Moy et al. 2005), implants yielded a statistically significantly lower survival rate compared with that of non-diabetic subjects. In diabetic subjects, implant loss was reported to occur a few months after placement and to continue for more than 10 years resulting in an implant survival rate of 68.75% with a relative risk ratio of 2.75 (95% CI: 1.46, 5.18; $p<0.05$) compared with healthy subjects (Moy et al. 2005). Recently, a comprehensive and critical review of dental implant placement in diabetic subjects was performed (Kotsovilis et al. 2006). In this review four prospective (Shernoff et al. 1994, Morris et al. 2000, Olson et al. 2000, Peled et al. 2003) and five retrospective (Balshi & Wolfinger 1999, Fiorellini et al. 2000, Abdulwassie & Dhanrajani 2002, Elsubeihi & Zarb 2002, Farzad et al. 2002) clinical studies were included. The majority of the findings indicated that diabetes did not represent an absolute contraindication for implant placement, provided that there was good glycaemic control. No statistically significant difference was observed for early implant failures comparing subjects with controlled type 2 diabetes with non-diabetic subjects (Alsaadi et al. 2007). Implants in diabetic subjects were significantly associated with an increased risk for peri-implantitis compared with implants placed in non-diabetic subjects (Ferreira et al. 2006). Currently, however, evidence is lacking to indicate that implant therapy in subjects with diabetes yields long-term outcomes comparable with those of non-diabetic subjects.

Conclusions: from scientific evidence to patient management

Diabetes mellitus and periodontitis represent common chronic diseases that may have reciprocal influence. Available evidence on the association between diabetes and periodontitis supports the concept of increased severity but not extent of periodontitis in subjects with poorly controlled diabetes. Subjects with controlled diabetes do not show an increase in extent and severity of periodontitis compared with non-diabetic subjects. Longitudinal

Table 2. Effects of non-surgical periodontal therapy with or without adjunctive drug delivery on glycaemic control (i.e. HbA_{1C} levels)

Publication	Study design	*N*	Diabetes type	Follow-up	Therapy	Change in HbA1C (%)
Rocha et al. (2001)	RCT	40	2	6 months	SRP+alendronate *versus* SRP+placebo	Test: -2.5 ± 2.5 Control: -2.3 ± 2.1 $p = 0.78$
Al-Mubarak et al. (2002)	RCT	52	1+2	3 months	SRP+water irrigation *versus* SRP alone	Test: 8.06 ± 0.29 to 7.7 ± 0.36 Control: 8.5 ± 0.31 to 8.3 ± 0.36 $p > 0.05$
Skaleric et al. (2004)	Pilot RCT	20	1	6 months	SRP+MINO	Baseline to 3 months Test: -0.63 ± 0.97 Control: -0.58 ± 1.12 $p = 0.92$ Baseline to 6 months Test: -0.61 ± 0.93 Control: -0.96 ± 1.27 $p = 0.49$
Kiran et al. (2005)	RCT	44	2	3 months	SRP *versus* no treatment	Test: -0.86 Control: -0.31 $p = 0.033$
Promsudthi et al. (2005)	Controlled clinical trial	52	2	3 months	SRP+DOXY *versus* no treatment	Test: -0.19 ± 0.74 Control: 0.12 ± 1.05 $p > 0.05$
Faria-Almeida et al. (2006)	Prospective	20	2	6 months	SRP	Baseline to 3 months: 7.6 ± 1.5 to 6.3 ± 1.1 $p < 0.05$ Baseline to 6 months 7.6 ± 1.5 to 5.8 ± 0.6 $p < 0.003$
Navarro-Sanchez et al. (2007)	Case–control	20	2	6 months	SRP	Cases: -1.3 ± 1.4 $p < 0.0016$
Jones et al. (2007)	RCT	165	2	4 months	SRP+DOXY+CHX *versus* no treatment	Test: -0.65 Control: -0.51 $p = 0.47$

N, Number of subjects; HbA_{1C}, glycosylated haemoglobin; RCT, randomized clinical trial; SRP, scaling and root planing; MINO, minocycline; DOXY, doxycycline; CHX, chlorhexidine.

studies have demonstrated that periodontitis is associated with poor glycaemic control and non-oral diabetes-related complications.

As with smoking-cessation programmes, the reviewed evidence emphasizes the need to promote oral health in subjects with diabetes as an integral component of comprehensive patient care in the dental office (Kunzel et al. 2005, 2006, 2007, Bakhshandeh et al. 2007). Based on the fact that $\approx 30\%$ of diabetic subjects may be undiagnosed (Centers for Disease Control and Prevention 2006, Cowie et al. 2006), opportunistic screening for diabetes in the dental office using self-reported data and clinical periodontal parameters was shown to be effective (Borrell et al. 2007).

Moreover, as reported in follow-up studies over a 30-year period (Axelsson et al. 2004), providing supportive therapy to prevent recurrence of periodontal disease and ultimately tooth mortality in subjects with diabetes should be considered an important phase in the comprehensive treatment sequence. When assessing residual periodontal risk at the end of active therapy in subjects with diabetes, glycaemic control, diabetes duration and presence of non-oral complications should be considered.

Studies are needed to evaluate oral and non-oral long-term outcomes of periodontal therapy in subjects with diabetes. Furthermore, large-scale studies are required to investigate the synergistic influence of glycaemic control, lipid control, inflammatory serum markers, cigarette smoking and ethnicity on periodontal conditions in subjects with diabetes.

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Clinical Relevance

Scientific rationale for the study: Diabetes mellitus and periodontal disease represent common chronic diseases that may have reciprocal influence. The main objective was to review the evidence for the association between diabetes and periodontal and peri-implant conditions and the impact of periodontal therapy in subjects with diabetes.

Principal findings: Poorly controlled subjects with diabetes show an increased severity but not extent of periodontitis. Subjects with controlled diabetes do not show an increase in extent and severity of periodontitis compared with non-diabetic subjects. Periodontitis is associated with poor glycaemic control and non-oral diabetes-related complications. It is inconclusive that periodontal therapy with or without the use of antibiotics results in improvements of glycaemic control and of markers of systemic inflammation. Evidence is lacking to indicate that implant therapy in subjects with diabetes yields long-term outcomes comparable with those of non-diabetic subjects.

Practical implications: The impact of periodontal therapy on diabetes should be evaluated in large-scale randomized clinical trials. Opportunistic screening for diabetes in the dental office may help reducing the percentage of undiagnosed diabetic subjects.