

SPECIAL REVIEW IN PERIODONTAL MEDICINE

Periodontal disease: associations with diabetes, glycemic control and complications

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OBJECTIVE: This report reviews the evidence for adverse effects of diabetes on periodontal health and periodontal disease on glycemic control and complications of diabetes.

DESIGN: MEDLINE search of the English language literature identified primary research reports published on (a) relationships between diabetes and periodontal diseases since 2000 and (b) effects of periodontal infection on glycemic control and diabetes complications since 1960.

RESULTS: Observational studies provided consistent evidence of greater prevalence, severity, extent, or progression of at least one manifestation of periodontal disease in 13/17 reports reviewed. Treatment and longitudinal observational studies provided evidence to support periodontal infection having an adverse effect on glycemic control, although not all investigations reported an improvement in glycemic control after periodontal treatment. Additionally, evidence from three observational studies supported periodontal disease increasing the risk for diabetes complications and no published reports refuted the findings.

CONCLUSION: The evidence reviewed supports diabetes having an adverse effect on periodontal health and periodontal infection having an adverse effect on glycemic control and incidence of diabetes complications. Further rigorous study is necessary to establish unequivocally that treating periodontal infections can contribute to glycemic control management and to the reduction of the burden of diabetes complications.

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Introduction

Diabetes mellitus and periodontal disease are two common chronic diseases that have long been considered to be biologically linked. Diabetes is an important chronic disease globally as reflected in the World Health Organization (WHO) declaring the rate of increase in diabetes prevalence is an epidemic. The WHO estimated there were 30 million people who had diabetes worldwide in 1985. This number increased to 135 million by 1995, and reached 217 million in 2005. By 2030 WHO predicts this number to increase to at least 366 million (Smyth and Heron, 2006). This growth in diabetes prevalence, driven principally by increasing prevalence of type 2 diabetes, is occurring in both developing and developed countries. The two countries with the largest predicted increases are India and China and the US ranked third (Smyth and Heron, 2006).

Susceptible individuals with diabetes and those with chronically poor metabolic control can experience microvascular and macrovascular complications leading to a significant burden for the individual and society. This burden includes direct costs of medical care and indirect costs, such as lost productivity, which result from diabetes-related morbidity and premature mortality (Harris, 1995; Hogan *et al*, 2003). Health care spending for people with diabetes is more than double what spending would be without diabetes, and direct and indirect expenditures attributable to diabetes in 2002 in the US were conservatively estimated at \$132 billion, with slightly more spent on chronic complications attributable to diabetes than on diabetes care itself (Hogan *et al*, 2003). The International Diabetes Federation estimated that diabetes accounts for 5–10% of the total healthcare budget in many countries (Smyth and Heron, 2006).

Gingivitis and periodontitis are the most common periodontal diseases. For example, in the US approximately 50% of the population in all age groups exhibit reversible gingival inflammation (Albandar and Kingman, 1999). Moderate or severe periodontitis, with destruction of periodontal attachment tissues is much

less common than gingivitis yet still a common chronic disease, affecting approximately 5–15% of any population (Albandar *et al*, 1999; Burt, 2005).

Current evidence regarding the biologic link between diabetes and periodontal disease supports diabetes and persisting hyperglycemia leading to an exaggerated immuno-inflammatory response to the periodontal pathogenic bacterial challenge (Southerland *et al*, 2006; Nishimura *et al*, 2007), resulting in more rapid and severe periodontal tissue destruction. In the metabolic dysregulation of diabetes, persisting hyperglycemia causes non-enzymatic glycation and oxidation of proteins and lipids, and the subsequent formation of advanced glycation endproducts (AGEs), which accumulate in the plasma and tissues (Brownlee, 1994; Schmidt *et al*, 1996b; Ramasamy *et al*, 2005). Hyperglycemia and resultant AGE formation are considered to be a major causal factor in the pathogenesis of diabetes complications (Brownlee, 1994; Vlassara, 1994). In subjects with diabetes who also have periodontitis, AGEs with accompanying markers for increased oxidant stress have been demonstrated in human gingiva (Schmidt *et al*, 1996a). Cell surface binding sites or receptors for AGE (RAGE) have been identified on the cell surfaces of several cell types exhibiting a heightened inflammatory response and involved with the pathogenesis of complications of diabetes. These cell types include mononuclear phagocytes, endothelial cells, fibroblasts, smooth muscle cells, lymphocytes, podocytes, and neurons (Brett *et al*, 1993; Ramasamy *et al*, 2005). The receptor for AGEs, RAGE, is the principal signal transducer for the AGE ligand (Schmidt *et al*, 2000).

The underlying postulate associated with these findings is that enhanced oxidant stress in the gingival tissues could contribute to more frequent and more severe periodontal tissue destruction in individuals with diabetes. For example, it has been hypothesized that the AGE-RAGE interaction induces an oxidant stress that may contribute to chronic monocytic upregulation, activation of NF- κ B, and subsequent expression of mRNA and secretion of proinflammatory cytokines (such as TNF- α , IL-1 β , and IL-6) by monocytic phagocytes involved in periodontal tissue inflammation and destruction (Baeuerle, 1991; Schreck *et al*, 1991; Moughal *et al*, 1992; Collins, 1993; Schmidt *et al*, 1994, 1996a; Takahashi *et al*, 1994; Yan *et al*, 1994). These mediators are recognized as effectors in periodontal tissue inflammation and destruction (Salvi *et al*, 1998). Blockade of RAGE has been shown to diminish *Porphyromonas gingivalis*-triggered alveolar bone loss in the periodontium and limit the enhanced inflammatory response in peripheral wounds, accelerating wound closure and facilitating angiogenesis (Lalla *et al*, 2000; Goova *et al*, 2001). Additionally, AGE interaction with endothelial cell RAGE has been shown to enhance endothelial cell vascular hyperpermeability and expression of vascular cell adhesion molecule-1, an adherence molecule capable of attracting mononuclear cells to the vascular wall (Schmidt *et al*, 1995; Wautier *et al*, 1996; Lalla *et al*, 1998b). Hence, AGE-RAGE interaction has

been proposed to result in perturbation of cellular properties, exaggerated and sustained inflammatory response, impaired wound healing, and more severe diabetes-associated periodontal disease (Lalla *et al*, 1998a).

The specific ways in which diabetes-enhanced inflammation and apoptosis may specifically impact on periodontal tissues of was recently thoroughly reviewed (Graves *et al*, 2006). In their review, Graves and colleagues describe that diabetes has been reported to adversely affect bone repair by decreasing expression of genes that induce osteoblast differentiation, and diminishing growth factor and extracellular matrix production (Bouillon, 1991; Kawaguchi *et al*, 1994; Lu *et al*, 2003). One proposed mechanism for these adverse effects is through the contribution of AGEs to decreased extracellular matrix production and inhibition of osteoblast differentiation (McCarthy *et al*, 2001; Cortizo *et al*, 2003; Santana *et al*, 2003). AGEs may also delay wound-healing by inducing apoptosis of extracellular-matrix-producing cells. This enhanced apoptosis would reduce the number of osteoblastic and fibroblastic cells available for the repair of resorbed alveolar bone (Graves *et al*, 2006). In addition to promoting apoptosis, AGEs could affect oral tissue healing by reducing expression of collagen and promoting inflammation. The mechanisms suggested for AGE-enhanced apoptosis include the direct activation of caspase activity, and indirect pathways that increase oxidative stress or the expression of pro-apoptotic genes that regulate apoptosis (Graves *et al*, 2006).

Diabetes mellitus and its effects on periodontal disease

Evidence establishing the link between diabetes mellitus and adverse effects on periodontal health have been extensively reviewed (Taylor, 2001; Mealey *et al*, 2006). In a narrative review of the English language literature published between 1960 and 2000 Taylor (2001) reported that 44 of 48 observational studies provided supportive evidence of diabetes adversely affecting periodontal health provided (37 of the 41 cross-sectional and seven of the seven cohort studies).

The review conducted for this current report extends that 2001 review to include reports published into 2007. The search used MEDLINE as well as reviewed reference lists of relevant papers obtained from the search to identify primary research reports on investigations of relationships between diabetes/diabetes control and periodontal diseases/periodontal treatment. While the literature review is extensive in conducting the MEDLINE search, it is not exhaustive in that no other databases were searched. This review does not provide a formal assessment of the quality of the reports. The reports identified are displayed in table-form and the corresponding description is organized according to the following groupings of studies: (1) The effects of having diabetes on periodontal diseases in studies that include a non-diabetes comparison group (Table 1) and (2) Effect of the degree of glycemic

control, usually measured by level of glycosylated hemoglobin, on periodontal status in studies that included assessment of degree of glycemic control while evaluating periodontal status in participants with diabetes (Table 2).

The reports included in Table 1 were restricted to studies which compared periodontal health in subjects with and without diabetes. This subject has attracted

increasing attention with greater numbers of publications in consecutive decades, ranging from six in the 1960s, eight in the 1970s, and 12 in the 1980s to 20 in the 1990s. This review identified 17 reports published in the current decade starting in the year 2000. Table 1 presents a summary of the evidence on the relationship between diabetes and periodontal disease. Studies were broadly classified and ordered by type of diabetes and

Table 1 Effects of diabetes on periodontal diseases in studies including a non-diabetes control group; ordered by diabetes type and subject age

Reference	Country	Study design	Diabetes type ^a	No. subjects a. Diabetes b. Control	Ages ^b a. Diabetes b. Control	Perio. Measure: diabetes effect ^c	Other diabetes-related variables considered
Tervonen <i>et al</i> (2000)	Finland	Cross-sectional	1	a. 35 b. 10	a. 29.7 (mean) b. 29.0 (mean)	XRBL: 1e	Glycemic control Duration of diabetes Diabetes severity based on presence of complications
Endean <i>et al</i> (2004)	Australia	Cross-sectional	2	a. 58 b. 231	All: 15–45+ a. Unknown b. Unknown	Ppd: 1p, 1s	None
Mattout <i>et al</i> (2006)	France	Cross-sectional	2	a. 71 b. 2073	All: 35–75 a. 54.5 (mean) b. 49.0 (mean)	Ging: 1p, 1s Ppd: 0p, 0s Lpa: 1p, 1s	Fasting blood glucose
Campus <i>et al</i> (2005)	Italy	Cross-sectional	2	a. 71 b. 141	a. 36–75 b. 35–75	Ging: 1e Ppd: 1e, 1s	Glycemic control
Orbak <i>et al</i> (2002)	Turkey	Cross-sectional	2	a. 40 b. 20	a1. 46 (mean) a2. 43 (mean) b. 41 (mean)	Ging: 1e, 1p, 1s	Glycemic control Diabetes complications
Tsai <i>et al</i> (2002)	USA	Cross-sectional	2	a. 502 b. 3841	a. 45+ b. 45+	Lpa & Ppd: 1p	Glycemic control
Lu and Yang (2004)	Taiwan	Cross-sectional	2	a. 72 b. 92	a. 54.3 (mean) b. 54.9 (mean)	Ging: 1p, 1e, 1s Lpa: 1p, 1e, 1s	Glycemic control Duration of diabetes
Chuang <i>et al</i> (2005)	Taiwan	Cross-sectional	2	a. 43 b. 85	All: 28–85 a. 60.2 (mean) b. 56.1 (mean)	Ppd: 0s	Glycemic control
Sandberg <i>et al</i> (2000)	Sweden	Cross-sectional	2	a. 102 b. 102	a. 64.8 (mean) b. 64.9 (mean)	Ging: 1e Ppd: 1e XRBL: 1p	Glycemic control Duration of diabetes
Zielinski <i>et al</i> (2002)	USA	Cross-sectional	2	a. 32 b. 40	All: 60+ a. 71 (mean) b. 74 (mean)	Ppd: 0e, 0p, 0s	Glycemic control Duration of diabetes
Borges-Yáñez <i>et al</i> (2006)	Mexico	Cross-sectional	2	a. 247 b. 78	All: 60+ a. 73.4 (mean) b. Unknown	Lpa: 0p	Fasting blood glucose
Lalla <i>et al</i> (2007)	USA	Cross-sectional	1, 2	a. 350 b. 350	a. 6–18 b. 6–18	Ging: 1e, 1p, 1s Ppd: 1e, 1p, 1s Lpa: 1e, 1p, 1s	Duration of diabetes Glycemic control
Arrieta-Blanco <i>et al</i> (2003)	Spain	Cross-sectional	1, 2	a. 70 b. 74	a. 11–81 b. 11–75	Ging: 1e Ppd: 0s, 0e Lpa: 1e, 1s XRBL: 0s, 0e	Glycemic control Duration of diabetes Diabetes complications
Ogunbodede <i>et al</i> (2005)	Nigeria	Cross-sectional	1, 2	a. 65 b. 54	a. 25–82 b. 25–82	Ppd: 0p	Duration of diabetes
Xiong <i>et al</i> (2006)	USA	Cross-sectional	1, 2, GDM	a. 81 b. 4339	All: 15–44 a. Unknown b. Unknown	Ppd or Lpa: 1p	None
Novak <i>et al</i> (2006)	USA	Cross-sectional	2, GDM	a. 113 b. 4131	All: 20–59 a. Unknown b. Unknown	Ging & ppd & lpa: 1p, 1s	Glycemic control Duration of diabetes
Mittas <i>et al</i> (2006)	Greece	Cross-sectional	GDM	a. 64 b. 88	a. 31.1 (mean) b. 26.5 (mean)	Ging: 1s	None

^aDM type = diabetes type: 1 = type 1 diabetes mellitus; 2 = type 2 diabetes mellitus; 1,2 = both subjects with type 1 and type 2 diabetes mellitus included; GDM = gestational diabetes mellitus; 9 = diabetes type not specified and not clearly ascertainable from other information in the report.

^bAges: subjects' ages presented as minimum – maximum reported for those with a. diabetes (DM) and b. controls (Control) unless otherwise specified.

^cMeasure of periodontal disease status: Measures used include Ging = gingivitis or gingival bleeding, Ppd = probing pocket depth, Lpa = loss of periodontal attachment, XRBL = radiographic bone loss, JPS = juvenile periodontal score, MGI = modified gingival index, PI = Russell's Periodontal Index, PDR = periodontal disease rate (proportion of teeth affected by periodontal disease). The number following the measure corresponds to greater disease in those with diabetes (1) or no difference between those with diabetes and controls (0). The letters following the number correspond to the parameter(s) assessed in the study: e = extent, i = incidence, p = prevalence, s = severity, r = progression.

Table 2 Effect of degree of glycemic control on periodontal status, ordered by level of evidence, diabetes type, and subject age

Reference	Country	Study design	Diabetes type ^b	Age group	Effect ^c	Non-DM comparison group ^d	Evidence level ^e
Karikoski and Murtomaa (2003)	Finland	Prospective	1, 2, other	Adults	0	No	II-2
Tervonen <i>et al</i> (2000)	Finland	Cross-sectional	1	Adults	1	Yes	III
Sandberg <i>et al</i> (2000)	Sweden	Cross-sectional	2	Adults	0	Yes	III
Tsai <i>et al</i> (2002)	USA	Cross-sectional	2	Adults	1	Yes	III
Lu and Yang (2004)	Taiwan	Cross-sectional	2	Adults	1	Yes	III
Campus <i>et al</i> (2005)	Italy	Cross-sectional	2	Adults	1	Yes	III
Chuang <i>et al</i> (2005)	Taiwan	Cross-sectional	2	Adults	0	No	III
Peck <i>et al</i> (2006)	South Africa	Cross-sectional	2	Adults	1	No	III
Jansson <i>et al</i> (2006)	Sweden	Cross-sectional	2	Adults	1	No	III
Arrieta-Blanco <i>et al</i> (2003)	Spain	Cross-sectional	1, 2	Mixed ages	0	Yes	III
Guzman <i>et al</i> (2003)	USA	Cross-sectional	1, 2*	Adults	1	No	III
Negishi <i>et al</i> (2004)	Japan	Cross-sectional	1, 2* ^d	Adults	1	No	III

^aHierarchy of evidence based on classification scheme used (U.S. Preventive Services Task Force, 1996) where: I = evidence obtained from at least one properly randomized controlled trial; II-1 = evidence obtained from well-designed controlled trial without randomization; II-2 = evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group; II-3 = evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence; III = opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

^bDiabetes type: 1 = type 1 diabetes mellitus; 2 = type 2 diabetes mellitus; 1,2 = both subjects with type 1 and type 2 diabetes mellitus included; GDM = gestational diabetes mellitus; 9 = diabetes type not specified and not clearly ascertainable from other information in the report; * = diabetes type not specified but ascertained by reviewers from other information in the report or from other sources, such as direct communication with the authors.

^cEffect: 1 = subjects with poorer glycemic control had poorer health than the comparison group(s); 0 = no difference in the periodontal health status between subjects with poorer glycemic control and comparison group(s).

^dDiabetes types are 1 and 2 for all but one subject who had drug-induced diabetes mellitus.

age of subjects (Table 1). In contrast to seven reports of prospective studies published prior to 2000, all of the studies identified for this review are cross-sectional and thus limited in their ability to provide evidence for causal inferences. There was one study of type 1 diabetes and it reported more extensive radiographic bone loss in participants with type 1 diabetes (Tervonen *et al*, 2000).

Regarding the relationship between type 2 diabetes and periodontitis the review identified 10 reports. One report comprised 15–45+ year olds (Endean *et al*, 2004), and nine (Sandberg *et al*, 2000; Orbak *et al*, 2002; Tsai *et al*, 2002; Zielinski *et al*, 2002; Lu and Yang, 2004; Campus *et al*, 2005; Chuang *et al*, 2005; Borges-Yáñez *et al*, 2006; Mattout *et al*, 2006) included only adults. Seven of these 10 studies reported significantly poorer periodontal health in subjects with type 2 diabetes, whereas no significant difference was discerned in a study of mostly older Taiwanese dialysis patients with and without ‘insulin-dependent (type II) diabetes’ (Chuang *et al*, 2005) as well as in a study of U. S. university clinic patients 60+ years of age with good medical and dental care comparing well-controlled (mean HbA1c = 7.3% with 70% having HbA1c > 7.5%) subjects with diabetes to subjects without diabetes (Zielinski *et al*, 2002); whereas in a study of Mexicans 60+ years of age there was a marginally significantly greater prevalence ($P = 0.09$) of periodontitis in the group with diabetes (61.5%) than in the group without diabetes (49.5%) (Borges-Yáñez *et al*, 2006).

Several reports consist of analyses in which subjects with type 1 and type 2 diabetes were not distinguished. All of the studies in this subset were cross-sectional. One

study included children only (Lalla *et al*, 2007), and all other studies included adult subjects, although one also included children or adolescents (Arrieta-Blanco *et al*, 2003). Two of these three studies reported greater prevalence, extent, or severity of periodontal disease for at least one measure or index of periodontal disease (Arrieta-Blanco *et al*, 2003; Lalla *et al*, 2007). One report did not find significant differences in periodontal disease between subjects with and without diabetes (Ogunbodede *et al*, 2005).

Two studies report on analyses on National Health and Nutrition Examination Survey III data from over 4000 women with a history of gestational diabetes (GDM) in the US. One report included ages 15–44 (Xiong *et al*, 2006) the other ages 20–59 (Novak *et al*, 2006). Both reports concluded there is a strong relationship between GDM and periodontal disease. Xiong *et al* (2006) found periodontitis in 45% of pregnant women with GDM vs 13% in the group without diabetes, with an adjusted odds ratio of 9.11. In non-pregnant women, 40% of women with type 1 or 2 diabetes, 25% of those with a history of GDM, and 14% of women without diabetes had periodontal disease. The odds ratio for those with type 1 and 2 diabetes was 2.76 (Xiong *et al*, 2006). Novak *et al* (2006) found the prevalence of periodontal disease to be higher in women with a history of GDM and concluded that women with a history of GDM may be at greater risk for developing more severe periodontal disease. A smaller Greek study of 34–36 weeks pregnant women also concluded gingival inflammation was more prevalent in the women with GDM (Mittas *et al*, 2006), but also found more plaque in that group.

As with other complications of diabetes, current evidence also supports poorer glycemic control contributing to poorer periodontal health. Primary research reports in the literature published since 2000 investigating relationships between glycemic control level and periodontal disease have included studies with subjects with type 1 diabetes exclusively (one study), type 2 diabetes exclusively (seven studies), or a combination of individuals with either type 1 or type 2 diabetes (three studies) (Table 2). Only seven of the 12 reports published regard the association between degree of glycemic control and periodontal disease specifically in type 2 diabetes (Sandberg *et al*, 2000; Tsai *et al*, 2002; Lu and Yang, 2004; Campus *et al*, 2005; Chuang *et al*, 2005; Jansson *et al*, 2006; Peck *et al*, 2006). Five of the latter found poorer glycemic control to be a significant factor associated with poorer periodontal health, the association was borderline significant in one study of dialysis patients (Chuang *et al*, 2005) and no difference was found in the remaining study (Sandberg *et al*, 2000). Among the studies providing information on differences in periodontal health classified by glycemic control status, most have been cross-sectional, with eight of 12 publications reporting more prevalent or more severe periodontal disease in those with poorer glycemic control (Tervonen *et al*, 2000; Tsai *et al*, 2002; Guzman *et al*, 2003; Lu and Yang, 2004; Negishi *et al*, 2004; Campus *et al*, 2005; Jansson *et al*, 2006; Peck *et al*, 2006) and four reporting no differences (Sandberg *et al*, 2000; Arrieta-Blanco *et al*, 2003; Karikoski and Murtomaa, 2003; Chuang *et al*, 2005). There was one follow-up study identified (evidence level II-2) that was published since 2000 (Karikoski and Murtomaa, 2003).

The preponderance of studies included in this review of reports published since 2000 on the adverse effects of diabetes on periodontal health are cross-sectional and describe findings of convenience samples, principally from outpatients in hospitals and clinics. While limitations on causal inference must be considered, these reports continue to support previous consistent evidence of greater prevalence, severity or extent of at least one manifestation of periodontal disease in the large majority of studies. The reports reviewed also provide additional evidence to support a 'dose-response' relationship, i.e., as glycemic control worsens, the adverse effects of diabetes on periodontal health become greater. Further, focused study of the relationship between gestational diabetes and periodontal health is emerging in body of literature.

Finally, the findings and conclusions from this review are consistent with two published meta-analyses that have provided quantitative summaries of the adverse effects of diabetes on periodontal health (Papapanou, 1996; Khader *et al*, 2006).

Periodontal disease: its effects on glycemic control and complications of diabetes mellitus

In addition to the substantial evidence demonstrating diabetes as a risk factor for poor periodontal health, there is a growing body of evidence supporting

periodontal infection adversely affecting glycemic control in diabetes and contributing to increased risk for the pathogenesis of diabetes complications. Because of the high vascularity of the inflamed periodontium, this inflamed tissue may serve as an endocrine-like source for TNF- α and other inflammatory mediators (Offenbacher *et al*, 1996; Grossi and Genco, 1998). Because of the predominance of Gram-negative anaerobic bacteria in periodontal infection, the ulcerated pocket epithelium is thought to constitute a chronic source of systemic challenge from bacteria, bacterial products and locally produced inflammatory mediators. TNF- α , IL6, and IL1, all mediators important in periodontal inflammation, have been shown to have important effects on glucose and lipid metabolism, particularly following an acute infectious challenge or trauma (Feingold *et al*, 1989; Ling *et al*, 1995; Grossi and Genco, 1998). TNF- α has been reported to interfere with lipid metabolism and to be an insulin antagonist (Grunfeld *et al*, 1990; Feingold and Grunfeld, 1992). IL6 and IL1 have also been reported to antagonize insulin action (Ling *et al*, 1995; Michie, 1996; Pickup *et al*, 1997).

More direct, empirical evidence regarding the effects of periodontal infection on glycemic control of diabetes comes from treatment studies using non-surgical periodontal therapy and observational studies (Table 3). The treatment studies are a heterogeneous set of reports that include randomized clinical trials (RCTs) and non-RCTs. The RCTs used control groups that were either non-treated controls (Aldridge *et al*, 1995; Kiran *et al*, 2005), positive controls (Grossi *et al*, 1997; Rodrigues *et al*, 2003; Skaleric *et al*, 2004), or controls advised to continue with their usual source of dental care (Jones *et al*, 2007). Of the seven RCTs, four reported a beneficial effect for periodontal therapy (Grossi *et al*, 1997; Rodrigues *et al*, 2003; Skaleric *et al*, 2004; Kiran *et al*, 2005).

An important source of variation in the RCTs is the use of adjunctive antibiotics with the non-surgical periodontal therapy. Among the RCTs, four included adjunctive antibiotics used systemically (Grossi *et al*, 1997; Rodrigues *et al*, 2003; Jones *et al*, 2007) or delivered locally (Skaleric *et al*, 2004). Three of these four RCTs using antibiotics showed beneficial effects on glycemic control (Grossi *et al*, 1997; Rodrigues *et al*, 2003; Skaleric *et al*, 2004). However, it is important to note the significant improvement for one study was in the positive control group that did not receive the systemic antibiotic (Rodrigues *et al*, 2003) and one of the four RCTs reporting a beneficial effect did not use antibiotics (Kiran *et al*, 2005). Hence, to date there is no clear-cut evidence to support a requirement for the use of antibiotics in combination with non-surgical periodontal treatment in order to observe an improvement in glycemic control associated with periodontal therapy.

Among the set of thirteen periodontal treatment studies that were not RCTs, eight reported a beneficial effect on glycemic control (Williams and Mahan, 1960; Wolf, 1977; Miller *et al*, 1992; Seppala *et al*, 1993; Seppala and Ainamo, 1994; Iwamoto *et al*, 2001; Faria-Almeida *et al*, 2006; Schara *et al*, 2006) and five

Table 3 Effects of periodontal disease and its treatment on glycemic control: clinical and epidemiological evidence, ordered by evidence level

Reference	Study design	Diabetes type ^{a,b,*}	No. subjects a. Treatment (Age) b. Control (Age)	Follow-up time	Periodontal treatment		Metabolic control outcome measure	Effects on metabolic control	Evidence level ^a
					a. Treatment group	b. Control group			
Aldridge <i>et al</i> (1995); Study 1	RCT	1	a. 16 (16–40) b. 15 (16–40)	2 months	a. Oral hygiene instruction, scaling, adjustment of restoration margins, and reinforcement after 1 month. b. No treatment		Glycated hemoglobin Fructosamine	Periodontal treatment had no effect on change in glycated hemoglobin	I
Aldridge <i>et al</i> (1995); Study 2	RCT	1	a. 12 (20–60) b. 10 (20–60)	2 months	a. Oral hygiene instruction, scaling and root planning, extractions, root canal therapy b. No treatment		Glycated hemoglobin	Periodontal treatment had no effect on change in glycated hemoglobin	I
Skalaric <i>et al</i> (2004)	RCT	1	All: 26–58 (41.8 = mean) a. 10 (42.0 = mean) b. 10 (41.6 = mean)	24 weeks	a. Sealing and root planning + minocycline microspheres (Arestin [®]) in pockets ≥ 5 mm at baseline and at 12 weeks b. Sealing and root planning		Glycated hemoglobin	Decreased glycated hemoglobin in test and control groups; Adjunct local Arestin [®] treatment is significantly more effective than sealing and root planning only	I
Grossi <i>et al</i> (1996, 1997)	RCT	2	a. 89 (25–65) b. 24 (25–65)	12 months	a. Either systemic doxycycline or placebo and ultrasonic bactericidal curettage with irrigation using either H ₂ O, chlorhexidine, or povidone-iodine b. Ultrasonic bacterial curettage with H ₂ O irrigation and placebo		Glycated hemoglobin	The three groups receiving doxycycline and ultrasonic bacterial curettage showed significant reductions ($P \leq 0.05$) in mean glycated hemoglobin at 3 months	I
Kiran <i>et al</i> (2005)	RCT	2	a. 22 (31–79) (56 = mean) b. 22 (31–79) (53 = mean)	3 months	a. Sealing and root planning Oral hygiene instruction b. No treatment		Glycated hemoglobin Fasting plasma glucose 2-h post-prandial glucose	Decreased glycated hemoglobin and 2-h post-prandial glucose levels in treatment group only	I
Rodrigues <i>et al</i> (2003)	RCT	2	a. 15 (unknown) b. 15 (unknown)	3 months	a. Initial full-mouth scaling and root planning Systemic amoxicillin/clavulanic acid 875 mg Oral hygiene instruction at baseline Control/re-instruction and prophylaxis every two weeks b. Same as a, except no medication		Glycated hemoglobin Fasting plasma glucose	Periodontal therapy was associated with improved glycemic control expressed as glycated hemoglobin and fasting plasma glucose, (but only significant improvement in glycated hemoglobin in b)	I

Table 3 Continued

Reference	Study design	Diabetes type ^{b,*}	No. subjects		Follow-up time	Periodontal treatment		Metabolic control outcome measure	Effects on metabolic control	Evidence level ^c
			a. Treatment (Age)	b. Control (Age)		a. Treatment group	b. Control group			
Jones <i>et al</i> (2007)	RCT	2 ^{**c}	a. 82 (59 = mean) b. 83 (60 = mean)		4 months	a. Early Tx: scaling/root planing; 100 mg doxycycline daily for 14 days; two daily 30 cc chlorhexidine rinses for 4 months. b. Usual care: usual dental and medical care		Glycated hemoglobin Insulin use	The results...suggest that the addition of periodontal therapy to current medical therapy may have promise in regard to improvement of glycemic control'. No significant differences between early treatment and usual care groups Periodontal treatment did not decrease HbA1c levels	I
Talbert <i>et al</i> (2006)	Treatment study, non-RCT	2	a. 25 (16-64) b. 0		3 months	a. Scaling and root planing b. No control group		Glycated hemoglobin Fasting insulin Fasting glucose		II-2
Smith <i>et al</i> (1996)	Treatment study, non-RCT	1	a. 18 (26-57) b. 0		2 months	a. Scaling and root planing with ultrasonic and curesettes; oral hygiene instruction b. No control group		Glycated hemoglobin	Found no statistically or clinically significant change in glycated hemoglobin	II-1
Westfelt <i>et al</i> (1996)	Treatment study, non-RCT	1, 2	a. 20 (45-65) b. 20 (45-65) ^e		5 years	a. Baseline oral hygiene instruction, scaling and root planing followed by periodic prophyls, OHI, localized subgingival plaque removal, and surgery at sites with bleeding on probing and PPD > 5 mm b. Same as group a		Glycated hemoglobin	The mean value of HbA1c between BL-24 months was not signif different from that between 24-60 months'	II-1
Christgau <i>et al</i> (1998)	Treatment study, non-RCT	1, 2	a. 20 (30-66) b. 20 (30-66) ^e		2 months	a. Scaling/root planing; subgingival irrigation with chlorhexidine; OHI; and extractions b. Same as group a		Glycated hemoglobin	No effect on glycated hemoglobin	II-1
Taylor <i>et al</i> (1996)	Historical prospective cohort	2	a. b. No tx or control subjects 49 (sev. periodis) 56 (less sev. periodis)		2-4 years	Not applicable		Glycated hemoglobin	Those with severe periodontitis were ~6 times more likely to have poor glycemic control at follow-up	II-2
Collin <i>et al</i> (1998)	Retrospective cohort	2	a. b. No subjects received treatment 25 with diabetes (ages 58-76) 40 without diabetes (ages 59-77)		2-3 years	Not applicable		Glycated hemoglobin	Among subjects with type 2 diabetes the HbA1c level significantly increased in those with advanced periodontitis, but not in those without advanced periodontitis	II-2

Table 3 Continued

Reference	Study design	Diabetes type ^{a,b}	No. subjects		Follow-up time	Periodontal treatment		Metabolic control outcome measure	Effects on metabolic control	Evidence level ^c
			a. Treatment (Age)	b. Control (Age)		a. Treatment group	b. Control group			
Schara <i>et al</i> (2006)	Treatment study, non-RCT	1	a. 10 (26-55) (38.6 = mean) b. 0		12 months	a. At baseline: Full-mouth disinfection; At 6 months: ultrasonic debridement; scaling & root planing; crown polishing; chlorhexidine gel, rinse, and irrigation followed by 14 days of chlorhexidine rinsing b. No control group		Glycated hemoglobin	Reduction in HbA1c 3 months after each treatment, but not at 6 months post-treatment. [Baseline mean HbA1c = 10.5% (range 8.4-16.4%)]	III
Seppala <i>et al</i> (1993, 1994)	Treatment study, non-RCT	1	a. 38-ly; 22-2y 26 PIDD-1y (48 ± 6) ^d 12 CIDD-1y (43 ± 5) 16 PIDD-2y 6 CIDD-2y b. 0		1-2 years	a. Scaling and root planing, periodontal surgery, and extractions b. No control group		Glycated hemoglobin blood glucose	Reported an improvement of the HbA1 levels of the PIDD and CIDD subjects ($P = 0.068$, t -test)	III
Miller <i>et al</i> (1992)	Treatment study, non-RCT	1	a. 10 (Unknown) b. 0		8 weeks	a. Scaling and root planing, systemic doxycycline b. No control group		Glycated hemoglobin Glycated albumin	Found decrease in glycated hemoglobin and glycated albumin in patients with improvement in gingival inflammation ($P < 0.01$); Patients with no improvement had either no change or increase in glycated hemoglobin post treatment	III
Wolf (1997)	Treatment study, non-RCT	1, 2	a. 117 (16-60) b. 0		8-12 months	a. Scaling and home care instr.; periodontal surgery; extractions; endodontic treatment; restorations; denture replacement or repair b. No control group		Blood glucose, 24-h urinary glucose Insulin dose	Compared 23 subjects with improved oral infect. with 23 who had no improvem aft tx for oral infec. and inflam. The subj. with improved oral inflam. and infect. tended to demonstrate diab. ctrl. improvement ($P < 0.1$). However, Wolf states in discussion, 'tx of periodontal inflam. and periapical lesions... does little to improve the control of diabetes'. Anti-infectious treatment is effective in improving metabolic control	III
Iwamoto <i>et al</i> (2001)	Treatment study, non-RCT	2	a. 13 (19-65) b. 0		1 month	a. Local minocycline in every perio-dontal pocket and mechanical debridement once a week for a month b. No control group		Glycated hemoglobin	Anti-infectious treatment is effective in improving metabolic control	III

Table 3 Continued

Reference	Study design	Diabetes type ^{b,*}	No. subjects		Follow-up time	Periodontal treatment		Metabolic control outcome measure	Effects on metabolic control	Evidence level [†]
			a. Treatment (Age)	b. Control (Age)		a. Treatment group	b. Control group			
Faria-Almeida <i>et al</i> (2006)	Treatment study, non-RCT	2	All: 35–70 a. 10 (Unknown) b. 10 (Unknown) [§]		6 months	a. Scaling and root planning b. Same as group a		Glycated hemoglobin	Significant reductions in HbA1c values from baseline to 3- and 6-months follow-up, respectively	III
Stewart <i>et al</i> (2001)	Treatment study, non-RCT	2	a. 36 (DM +) (62 = mean) b. 36 (DM +) (67 = mean)		18 months	a. Scaling, sub-gingival curettage, and root planing Oral hygiene instruction b. No intervention		Glycated hemoglobin Changes in medications/ dosages	Periodontal therapy was associated with improved glycemic control	III
Promsudthi <i>et al</i> (2005)	Treatment study, non-RCT	2	a. 27 (55–80) b. 25 (55–73)		3 months	a. Mechanical perio treatment and systemic doxycycline 100 mg daily for 15 days b. No intervention		Glycated hemoglobin Fasting plasma glucose	Test group: the reductions in the levels of fasting plasma glucose and HbA1c did not reach significance; *no association between periodontal treatment with adjunctive antimicrobial treatment and changes in HbA1c levels [†]	III
Williams and Mahan (1960)	Descriptive clinical study	9	a. 9 (20–32) b. 0		3–7 months	a. Extractions, scaling and curettage, gingivectomy, systemic antibiotics b. No control group		Insulin requirement Diabetes control (not operationally defined)	7/9 subjects had 'significant' reduction in insulin requirements	III

[†]Hierarchy of evidence based on classification scheme used (U.S. Preventive Services Task Force, 1996) where: I = evidence obtained from at least one properly randomized controlled trial; II-1 = evidence obtained from well-designed controlled trial without randomization; II-2 = evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence; III = opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

^bDM type = diabetes type: 1 = type 1 diabetes mellitus; 2 = type 2 diabetes mellitus; 1,2 = both subjects with type 1 and type 2 diabetes mellitus included; 9 = diabetes type not specified and not clearly ascertainable from other information in the report; *diabetes type not specified but ascertained by reviewers from other information in the report or from other sources, such as direct communication with the authors.

[§]Five subjects at most might have diabetes type 1, but the majority have type 2.

[¶]38 subjects were followed for 1 year and 22 for 2 years. PIDD: poorly controlled insulin dependent diabetes; CIDD: controlled insulin dependent diabetes.

^eControl group consists of healthy subjects without diabetes mellitus, not of subjects with diabetes.

did not (Smith *et al*, 1996; Westfelt *et al*, 1996; Christgau *et al*, 1998; Promsudthi *et al*, 2005; Talbert *et al*, 2006). Only two of these studies had control or comparison groups (Stewart *et al*, 2001; Promsudthi *et al*, 2005). Like the RCTs there was marked variation in the use of adjunctive antibiotics, with three of the five studies that used systemic antibiotics reporting a beneficial effect on glycemic control (Williams and Mahan, 1960; Miller *et al*, 1992; Iwamoto *et al*, 2001).

As shown in Table 3, there is marked heterogeneity in the studies' designs, conduct, length of follow-up, types of participants, and periodontal treatment protocols. The details of the variation in this body of literature have been extensively described in several detailed reviews (Grossi and Genco, 1998; Taylor, 1999; Janket *et al*, 2005).

Additional evidence to support the effect of severe periodontitis on increased risk for poorer glycemic control comes from two longitudinal observational studies. A longitudinal epidemiological study of the Pima Indians in Arizona, USA (Taylor *et al*, 1996) found subjects with type 2 diabetes in good to moderate control and with severe periodontitis at baseline were approximately six times more likely to have poor glycemic control at approximately 2-years follow-up than those without severe periodontitis at baseline. In another observational study of 25 adults with type 2 diabetes, aged 58–77 years, Collin *et al* (1998) also reported an association between advanced periodontal disease and impaired metabolic control.

It is well recognized that poor glycemic control is a major determinant for the development of the chronic complications of diabetes. Results from the landmark Diabetes Control and Complications Trial (type 1 diabetes) and the UK Prospective Diabetes Study (type 2 diabetes) demonstrated that attaining and maintaining good glycemic control could reduce the risk for and slow the progression of microvascular complications in patients with type 1 and type 2 diabetes (Anonymous, 1993, 1998a,b) (Diabetes Control and Complications Trial Research Group, 1993). Additionally, the UKPDS observed a 16% reduction ($P = 0.052$) in the risk of combined fatal or nonfatal myocardial infarction and sudden death. Further epidemiological analysis from the UKPDS showed a continuous association between the risk of cardiovascular complications and glycemia; every percentage point decrease in HbA1c (e.g., 9–8%), was associated with 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and 18% reduction in combined fatal and nonfatal myocardial infarction (Genuth *et al*, 2003).

There is emerging evidence from observational studies regarding the association between periodontal disease and the risk for diabetes complications. Thorstensson *et al* (1996) studied 39 case-control pairs of individuals with type 1 and type 2 diabetes for 6 years median follow-up time in Jönköping, Sweden. In each pair the cases had severe alveolar bone loss and controls had gingivitis or minor alveolar bone loss. They found that cases were significantly more

likely to have prevalent proteinuria, and cardiovascular complications including stroke, transient ischemic attacks, angina, myocardial infarction, and intermittent claudication than controls at their follow-up medical assessments.

Two recent reports from the on-going longitudinal study of diabetes and its complications in the Gila River Indian Community in Arizona, USA, conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, address nephropathy and cardiovascular disease. Saremi *et al* (2005) studied a cohort of 628 individuals for a median follow-up time of 11 years. Individuals with severe periodontal disease had 3.2 times greater risk for cardio-renal mortality (i.e., ischemic heart disease and diabetic nephropathy combined) than those with no, mild, or moderate periodontal disease. This estimate of significantly greater risk persisted while controlling for several major risk factors of cardio-renal mortality including: age, sex, diabetes duration, HbA1c, body mass index (BMI), hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macroalbuminuria, and smoking.

In the second report Shultis *et al* (2007) investigated the effect of periodontitis on risk for development overt nephropathy (macroalbuminuria) and end-stage renal disease (ESRD) in a group of 529 Gila River Indian Community adults with type 2 diabetes. Their proportional hazards models analyses, adjusted for age, sex, diabetes duration, body mass index, and smoking, indicated periodontitis and edentulism were significantly associated with the risk of overt nephropathy and ESRD. The incidence of macroalbuminuria was 2.0, 2.1, and 2.6 times greater in individuals with moderate or severe periodontitis or in those who were edentulous, respectively, than those with none/mild periodontitis. The incidence of ESRD was also 2.3, 3.5, and 4.9 times greater for individuals with moderate or severe periodontitis or for those who were edentulous, respectively, than those with none/mild periodontitis.

The clinical and epidemiological evidence reviewed provides support for the concept that periodontal infection contributes to poorer glycemic control and the risk for diabetes complications in people with diabetes mellitus. However, further rigorous, controlled trials in diverse populations are warranted to firmly establish that treating periodontal infections can be influential in contributing to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus.

Summary and conclusion

The evidence reviewed in this report supports previous conclusions that diabetes is associated with increased occurrence and progression of periodontitis and periodontal infection is associated with poorer glycemic control in people with diabetes. There is also evidence emerging that gestational diabetes may adversely affect periodontal health. Additionally, evidence is emerging to suggest that periodontal disease is associated with increased risk for diabetes complications. While treating

periodontal infection in people with diabetes is clearly an important component in maintaining oral health, it may also have an important role in establishing and maintaining glycemic control and possibly in delaying the onset or progression of diabetes complications. Further rigorous, systematic study in diverse populations is warranted to support existing evidence that treating periodontal infections can be influential in contributing to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus.

Author contributions

Drs. Taylor and Borgnakke both searched the literature for reports for possible inclusion in this manuscript. Both authors reviewed reports, conferred on which articles to include, and completed article assessment forms, designed by Dr. Taylor, to summarize the content of relevance to this literature review for each included report. Dr. Taylor designed the format for the tables and both authors contributed contents in the tables. Both authors drafted sections of the manuscript and contributed in responding to reviewers' comments, participated in final review of the proofs, and approved the proofs for publication.

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