Periodontal disease and diabetes mellitus

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ABSTRACT

Periodontal disease (PD) is one of the most commonly known human chronic disorders. The relationship between PD and several systemic diseases such as diabetes mellitus (DM) has been increasingly recognized over the past decades. Objective: The purpose of this review is to provide the reader with knowledge concerning the relationship between PD and DM. Many articles have been published in the English and Portuguese literature over the last 50 years examining the relationship between these two chronic diseases. Data interpretation is often confounded by varying definitions of DM, PD and different clinical criteria were applied to determine the prevalence, extent and severity of PD, levels of glycemic control and diabetes-related complications. Methods: This paper provides a broad overview of the predominant findings from research conducted using the BBO (Bibliografia Brasileira de Odontologia), MEDLINE, LILACS and PubMed for Controlled Trials databases, in English and Portuguese languages published from 1960 to October 2012. Primary research reports on investigations of relationships between DM/DM control, PD/periodontal treatment and PD/DM/diabetes-related complications identified relevant papers and meta-analyses published in this period. Results: This paper describes the relationship between PD and DM and answers the following questions: 1- The effect of DM on PD, 2- The effects of glycemic control on PD and 3- The effects of PD on glycemic control and on diabetes-related complications. Conclusions: The scientific evidence reviewed supports diabetes having an adverse effect on periodontal health and PD having an adverse effect on glycemic control and on diabetes-related complications. Further research is needed to clarify these relationships and larger, prospective, controlled trials with ethnically diverse populations are warranted to establish that treating PD can positively influence glycemic control and possibly reduce the burden of diabetes-related complications.

Key words: Periodontal diseases. Diabetes mellitus. Diabetes mellitus, Type 1. Diabetes mellitus, Type 2. Gestational diabetes. Glycemic control. Diabetes complications.

INTRODUCTION

In the last decades health professionals have been often organized into many specialties and subspecialties directed to several body organs and systems. The human organism is a unity that is composed by an infinite number of biologic processes so strongly linked that abnormalities in any part of the body and/or its processes may have deep effects in many other body areas, exemplified in this review by two highly prevalent diseases: PD and DM.25

PD is a chronic infectious disease, caused by Gram-negative microorganisms. An imbalance between a localized infection and an exaggerated host inflammatory response plays a pivotal role in determining gingival tissue damage. Recent evidence suggests that the effect of PD might not be limited just to the oral cavity but it might have systemic consequences. Indeed, PD has also been associated with a moderate systemic inflammatory response. Although, the mechanisms behind this association remain unclear, PD might represent one distant source of low-grade systemic inflammation. This association could explain the increased risk of impaired metabolic control in diabetes-related
complications and the adverse effects of DM on periodontal health\textsuperscript{15}. There is strong evidence that the prevalence, severity and progression of PD are significantly higher in people with DM\textsuperscript{97,98,101}.

In this review we describe the common processes involved in PD and DM and briefly review the evidence produced to support an association between PD, DM and diabetes-related complications.

**Periodontal disease**

PD is a chronic bacterial infection that affects both the gingiva and the bone that supports the teeth and is caused by anaerobic Gram-negative microorganisms that are present in the bacterial plaque that adheres to the teeth\textsuperscript{96}.

PD is a very prevalent condition. In the United States, over half the population aged 18 years or more have PD in its early stages, increasing to up to 75\% after the age of 35 years; its mild to moderate forms are present in 30\% to 50\%, and the severe generalized form in 5\% to 15\% of the general adult population\textsuperscript{25}. PD has even higher prevalence in minorities, in poor and developing countries and a considerable global variation\textsuperscript{77,96}.

The presence of anaerobic Gram-negative bacteria causes a local inflammatory response that becomes chronic and progressive; this inflammation of the gingiva causes alveolar bone destruction and loss of the tissue attachment to the teeth, caused by components of microbial plaque that have the capacity to induce an initial infiltrate of inflammatory cells, such as lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs)\textsuperscript{93}.

Some microbial components, especially lipopolysaccharide (LPS), activate macrophages that synthesize and secrete a great variety and amount of pro-inflammatory molecules, such as the cytokines interleukin-1 (IL-1) and tumor necrosis factor-\textalpha (TNF-\textalpha); prostaglandins, especially prostaglandin E2 (PGE2); and some other enzymes\textsuperscript{93}.

Bacterial toxins can also activate T lymphocytes to produce IL-1 and lymphotoxin (LT), a molecule with properties that are similar to those of TNF-\textalpha. These cytokines show potent pro-inflammatory and catabolic activities, and have important roles in periodontal tissue destruction caused by collagenolytic enzymes such as metalloproteinases (MMPs)\textsuperscript{93}. These collagenolytic enzymes are activated by reactive oxygen species and elevate the levels of interstitial collagenase in inflamed gingival tissue\textsuperscript{99}.

The attachment loss deepens the sulcus, creating a periodontal pocket that contains thousands of millions of bacterial cells. This stage is the transition between gingivitis and periodontitis, the most common PDs\textsuperscript{26,50}.

When bacterial biofilms on the teeth are not disrupted on a regular basis, the emergences of Gram-negative anaerobic bacterial species activate several host processes that will interfere in the extent and severity of the disease\textsuperscript{95}.

Recently, many advances have occurred in the knowledge of the nature of the infectious agents involved in PD. Approximately 500 different bacterial entities and various human viruses have already been associated with the formation of dental microbial plaque\textsuperscript{1}.

The most frequently recognized periodontal pathogens belong to three microaerophilic species (\textit{Actinobacillus actinomycetemcomitans}, \textit{Campylobacter rectus}, and \textit{Eikenella corrodens}) and seven anaerobic species (\textit{Porphyromonas gingivalis}, \textit{Bacteroides forsythus}, \textit{Treponema denticola}, \textit{Prevotella intermedia}, \textit{Fusobacterium nucleatum}, \textit{Eubacterium}, and \textit{spirochetes})\textsuperscript{92}. Various herpes viruses, such as the human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV-1), have recently also emerged as pathogens in cases of destructive PD\textsuperscript{99}.

Many conditions can predispose and/or facilitate the occurrence of PD such as smoking\textsuperscript{7,32,35,105}, genetic influences\textsuperscript{8,49,62}, estrogen deficiency\textsuperscript{30,32,35}, estrogen excess\textsuperscript{99}, dyslipidemia\textsuperscript{58,66,111} and obesity\textsuperscript{2,27}. The prevalence of obesity is increasing worldwide. This epidemic is also associated with an increased occurrence of obesity-related diseases like hypertension, cardiovascular disease, metabolic syndrome and DM that are also linked to PD\textsuperscript{2,27}.

**Diabetes mellitus**

DM encompasses a group of genetically and clinically heterogeneous metabolic disorders characterized by hyperglycemia that results from a defective insulin secretion and/or activity\textsuperscript{89}.

DM is classified according to its etiology as type 1 (T1D), type 2 (T2D), gestational diabetes (GDM) and other specific types. T1D results from the destruction of beta-cells within the islets of Langerhans of the pancreas, which results in a complete insulin deficiency; it can be immune-mediated or have an idiopathic etiology. T2D ranges from an insulin resistance which progresses into an insulin deficiency due to a secondary failure in the pancreatic beta-cells. GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Lastly, the category “other specific types” comprehends a group of several types of DM with different etiologies\textsuperscript{21}.

Developed countries have a higher prevalence of DM than developing countries and more women than men are affected with DM. T2D constitutes 90\% of the cases. In 1995 the prevalence of DM in adults all over the world was estimated to be around 4.0\% and it was expected to rise to 5.4\%.
by the year 2025. Numerically it means a rise from 135 million in 1995 to 300 million in the year 2025. The majority of this increase will occur in developing countries. An increase of 42% (from 51 to 72 million) is expected in developed countries and an increase of 170% (from 84 to 228 million) in the developing world. Therefore, it is expected that by the year 2025, 75% of people with DM will be living in developing countries where the majority of people with DM are aged between 45-64 years old. In developed countries, the majority of people with DM are older than 65 years. DM will be increasingly occurring in urban areas47.

People with diabetes and with chronically poor metabolic control can experience micro-vascular and macro-vascular complications leading to a significant burden for the individual and for the society. This burden includes direct costs of medical care and indirect costs, such as loss of productivity, which result from diabetes-related morbidity and premature mortality38.

Health care expenses for people with diabetes is more than two-times higher than the expenses for people without diabetes; the direct and indirect expenditures attributable to diabetes in 2007 in the USA were estimated at US$174 billion, with slightly more spent on chronic complications attributable to DM than properly on DM care4. The International Diabetes Federation estimated that DM costs account for 5-10% of the total healthcare budget in many countries40.

In Brazil, the per capita total, direct medical, direct nonmedical and indirect costs of patients with T1D were US$ 1,741.42, US$ 1,319.15, US$ 61.47 and US$ 360.81, respectively. The total direct non-medical costs were US$ 195,461.54, spent with transportation for the patients and caregivers39. Total annual costs for care of outpatients with T2D were US$ 2,108 per patient, out of which US$ 1,335 per patient of direct costs (63.3%) and US$ 773 per patient of indirect costs (36.7%). Patients with both micro-vascular and macro-vascular complications had higher costs (US$ 3,199 per patient) compared to those with either micro-vascular (US$ 2,062 per patient) or macro-vascular (US$ 2,517 per patient) complications only. The greatest amount of direct costs was attributed to medication (48.2%)6.

Effects of diabetes mellitus on periodontal disease

The search conducted for this review used the BBO (Bibliografia Brasileira de Odontologia), MEDLINE, LILACS and PubMed for Controlled Trials databases, in English and Portuguese languages published from 1960 to October 2012. Primary research reports on investigations of relationships between DM/DM control, PD/periodontal treatment and PD/DM/diabetes-related complications identified relevant papers and meta-analyses published in this period. This review does not provide an assessment of the quality of the reports. The identified reports are displayed in figures organized according to the following groups: 1- The effects of DM on PD; 2- The effects of glycemic control on PD and 3- The effects of PD on glycemic control and on diabetes-related complications.

The studies listed in Figure 1 compared periodontal status in individuals with and without DM in the majority of the reports. These studies were classified according to the study design, type of diabetes, sample number, age range, evaluation of PD and other diabetes-related variables. The majority of the studies were cross-sectional (21/29) and limited in the possibility of providing a causal-effect relationship.

The link between DM and the adverse effects on PD has been extensively described41,90. We have found that 27 in 29 studies showed supportive evidence of the adverse impact of DM on periodontal health.

There were four studies of T1D; one study reported more extensive radiographic bone loss in patients with T1D compared to the controls102, Lalla, et al.54 (2006) in a case-control study found that periodontal destruction can start very early in life in patients with T1D and becomes more prominent as children become adolescents44. In a population aged 4 to 33 years, Cianciola, et al.13 (1982) reported a significantly higher prevalence of PD in T1D than in non-diabetic siblings and non-diabetic unrelated controls. The prevalence of PD among 11- to 18-year-old teenagers with DM was 9.8% as compared to 1.7% in controls without DM. An accelerated periodontal destruction was found in children and teens with DM, with poor metabolic control13. In an adult population aged 40-69 years, 58.4% of patients with long standing T1D exhibited severe PD as opposed to 7.1% of controls without DM103.

Regarding the relationship between T2D and PD, we identified fourteen reports. Two reports were comprised of patients aged 15 years or older20,70, and twelve8,10,12,13,19,59,60,74,80,100,106,113 included only adults. Twelve of these fourteen studies reported significantly poorer periodontal health in subjects with T2D, whereas a significantly poorer greater prevalence was found in one study8 and no significant difference was found in another study113.

Six reports consist of analyses in which subjects with T1D and T2D were analyzed together without distinction of diabetes type. Four studies included children and adolescents6,46,53,85 and another two included only adult subjects17,73. Five of these six studies reported greater prevalence, extent, or severity of PD in subjects with DM5,17,46,53,85. One report did not find significant differences in PD.
### Table: Effects of diabetes mellitus on periodontal disease

| Reference                  | Year | Study design | Diabetes type | Number of subjects (DM/control) | Age (years) | Periodontal evaluation                                                                 | Other diabetes related variables considered                                                                 | Conclusions                                                                                     |
|----------------------------|------|--------------|---------------|---------------------------------|-------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Cianciola, et al.13         | 1982 | Cross-sectional | 1            | 263/208                         | 4 to 33     | Prevalence and severity of PD                                                            | Diabetes duration                                                                                      | Prevalence and severity of PD in T1D is more strongly related to chronological age than diabetes duration |
| Emrich, et al.18            | 1991 | Cross-sectional | 2            | 1,342/1,877                     | 15 to >55   | Probing attachment level, alveolar bone loss, age, sex, calculus index, plaque index, gingival index, fluorosis | Diabetes control                                                                                     | T2D increases the risk of PD independently of age, sex, and hygiene or other dental measures |
| Thorstensson, et al.10       | 1993 | Cross-sectional | 1            | 83/99                           | 40 to 69    | Gingival conditions, probing pocket depth and alveolar bone level                         | Diabetes duration                                                                                      | Age of onset appears to be an important risk factor for PD                         |
| Shlissman, et al.19         | 1990 | Cross-sectional | 1 and 2      | 736/2,483                       | 5 to 245    | Probing attachment level and radiographic bone loss                                      | Biennial oral glucose tolerance test                                                                  | Subjects with DM had a higher prevalence of PD; DM may be a risk factor for PD     |
| Nelson, et al.35            | 1990 | Longitudinal  | 2            | 1,363/910                       | ≥15         | Tooth loss and interproximal crest alveolar bone loss                                    | Biennial oral glucose tolerance test                                                                  | PD in subjects with DM is 2.6 times more prevalent than in non-diabetic controls   |
| Taylor, et al.100           | 1998 | Longitudinal  | 2            | 24/362                          | 15 to 57    | Severity of bone loss                                                                    | -                                                                                                       | DM2 is associated with the incidence of alveolar bone loss and increased rate of alveolar bone loss progression |
| Tervonen, et al.60          | 2000 | Cross-sectional | 1            | 35/10                           | 29          | Bone loss                                                                               | Glycemic control; duration of diabetes; diabetes severity                                             | Increased bone loss in subjects with complicated T1D already at an early age       |
| Sandberg, et al.10          | 2000 | Cross-sectional | 2            | 102/102                         | 64          | Gingivitis and bone loss                                                                 | Glycemic control; duration of diabetes; diabetes severity                                             | Subjects with T2D in some oral conditions exhibited poorer oral health             |
| Taylor GW97                 | 2001 | Review       | 1,2 and GDM | Mixed ages                      | -           | Evaluation of a bidirectional relationship between DM and PD                             | -                                                                                                       | The majority of the studies provided consistent evidence of a greater prevalence, severity, extent or progression of PD in subjects with DM |
| Orbak, et al.14             | 2002 | Cross-sectional | 2            | 40/20                           | 41          | Gingivitis                                                                             | Glycemic control; diabetes complications                                                              | T2D and smoking are high-risk factors for PD                                       |
| Tsai, et al.86              | 2002 | Cross-sectional | 2            | 50/3,841                        | >45         | Loss of periodontal attachment                                                           | Glycemic control                                                                                      | Positive association between poorly controlled T2D and severe PD                   |
| Ziebinski, et al.11         | 2002 | Cross-sectional | 2            | 32/40                           | >60         | Pocket depth                                                                            | Glycemic control; duration of diabetes                                                                | No differences in oral health were found between subjects with T2D and those in the control group |
| Arrieta-Blanco, et al.5     | 2003 | Cross-sectional | 1 and 2     | 70/74                           | 11 to 81    | Pocket depth; loss of periodontal attachment; bone loss                                 | Glycemic control; duration of diabetes; diabetes severity                                             | The gingivitis index was higher and the treatment was more complex in subjects with DM         |
| Endean, et al.20            | 2004 | Cross-sectional | 2            | 289/1,706                       | 15 to >45   | Pocket depth; tooth loss                                                                  | None                                                                                                   | The severity of PD and tooth loss was greater in subjects with DM than in controls |
| Lu and Yang24               | 2004 | Cross-sectional | 2            | 72/82                           | 54          | Gingivitis and loss of periodontal attachment                                             | Glycemic control; duration of diabetes; diabetes severity                                             | In subjects with T2D, PD is more severe than in healthy individuals               |
| Campus, et al.30            | 2005 | Cross-sectional | 2            | 71/141                          | 35 to 75    | Gingivitis and pocket depth                                                             | Glycemic control                                                                                      | Subjects with T2D have a susceptibility for more severe PD                          |
| Chuang, et al.32            | 2005 | Cross-sectional | 2            | 43/85                           | 28 to 85    | Pocket depth                                                                             | Glycemic control; end-stage renal disease                                                              | Diabetic uremic patients undergoing hemodialysis exhibited a higher risk for dental decay and xerostomia |
| Ogunbodede, et al.73        | 2005 | Cross-sectional | 1 and 2     | 65/54                           | 25 to 82    | Pocket depth                                                                             | Duration of diabetes                                                                                   | Oral health of a subject with DM with adequate metabolic control, may not be different from that of a non-diabetic          |
| Mattout, et al.60           | 2006 | Cross-sectional | 2            | 71/2,073                        | 35 to 75    | Gingivitis; pocket depth; loss of periodontal attachment                               | Fasting blood glucose                                                                                 | PD is more severe in subjects with T2D                                          |

Figure 1: Effects of diabetes mellitus on periodontal disease

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between subjects with and without DM when an adequate metabolic control was found in the former group.73

Regarding GDM, five reports were analyzed. One was conducted only with women with GDM that were compared to a control group between the 34-36th gestation weeks. The results of the study suggest that gingivitis seems to be more prevalent in women with GDM compared to healthy pregnant women and the plaque accumulation seems to be the main cause of gingival inflammation.65 Another study found that all types of DM increase the risk of PD, including GDM.61 Two other studies conducted in the USA collected data from over 4,000 women with a history of GDM. One report included ages 15-44112 and the other, ages 20-59112. Both reports concluded there is a strong relationship between GDM and PD. PD was found in 45% of pregnant women with GDM vs. 13% in the healthy pregnant women, with an adjusted odds ratio of 9.11. In non-pregnant women, 40% of women with T1D or T2D, 25% of those with a history of GDM, and 14% of healthy women had PD. The odds ratio for those with T1D and T2D was 2.7663. Novak, et al.71 (2006) found the prevalence of PD to be higher in women with a history of GDM and concluded that these women may be at greater risk for developing more severe PD, than women without a history of GDM. Finally, Taylor96 (2001) and Mealey61 (2006) in two extensive literature reviews found a bidirectional interrelationship between all types of DM, including GDM and PD.

Effects of glycemic control on periodontal disease

Current evidence also supports poorer glycemic control contributing to poorer periodontal health. We have identified fourteen studies reporting this relationship. Two of these studies included subjects with T1D exclusively, seven studies subjects with T2D exclusively and five a combination of subjects with either T1D, T2D, GDM and others (Figure 2). One prospective study conducted with T1D did not show any association between the degree of glycemic control and PD but a positive association with local oral hygiene measures49, and another study, that was cross-sectional, has regarded this association.102 Five of the seven reports published regarding the association between glycemic control and PD in T2D40,43,59,75,106 have found this association and two did not.80,91. We have found five studies providing information on the differences in periodontal health in groups of mixed types of diabetes5,37,45,61,68, three have found this association7,61,68 and two did not.35,39. Among these fourteen studies, eleven were cross-sectional that imposes some limitations on the cause-effect inference; two were prospective and one was an...
extensive literature review. Otherwise, nine of these reports support the evidence of greater prevalence, extent and severity of PD and also provide evidence that glycemic control worsens in parallel with the worsening of PD.

**Effects of periodontal disease on glycemic control and on diabetes-related complications**

Substantial evidence has been demonstrating DM as a risk factor for the impairment of periodontal health and a growing body of evidence has been supporting PD as having an adverse effect on glycemic control and on the pathophysiology of diabetes-related complications. The inflamed periodontal tissue may serve as a chronic source of bacteria, bacterial products and many inflammatory mediators such as TNF-α, IL6, and IL1 that have been shown to have important effects on lipid and glucose metabolism and have also been reported to be insulin antagonists and related to insulin resistance that is predominantly found in T2D and GDM.

As shown in Figure 3, data interpretation is often confounded by varying definitions of DM and PD and different clinical criteria applied to determine the prevalence, extent, severity of PD, levels of glycemic control and diabetes-related complications; there is also marked heterogeneity in the studies’ designs, conduct, length of follow-up, types of participants, and periodontal treatment protocols.

Evidence regarding the effects of PD on glycemic control comes from observational and treatment studies (Figure 3). The treatment studies are a set of reports that include ten randomized clinical trials (RCTs), twelve non-RCTs, four meta-analyses, one literature review, one longitudinal study, one transversal study, one retrospective study, one prospective study and two clinical cases discussions.

The RCTs used control groups that were either treated controls, non-treated controls or controls that did not change their usual dental care. Among the ten RCTs, eight reported a beneficial effect for periodontal therapy and two did not. One of the RCTs, recently conducted, showed significant improvement in HbA1c levels but did not result in a statistically significant improvement in serum levels of inflammatory markers such as hs-CRP, d-8-iso, MMP-2 and MMP-9.

An important source of variation in the RCTs is the use of antibiotics with the non-surgical periodontal therapy. This fact brings a lot of confusion in the interpretation of the results of these trials in such a way, that to date, there is no clear 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 group of twenty-three periodontal treatment studies that were not RCTs, seventeen reported a beneficial effect on glycemic control and six did not. Only ten of these studies had controls or comparison groups and six of the eight studies that used systemic antibiotics reporting a beneficial effect on glycemic control.

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, which present the world’s highest reported prevalence of periodontal disease and diabetes mellitus.

### Table 1: Effects of glycemic control on periodontal disease

| Reference                        | Year | Study design | Diabetes type | Age group | Control group | Effect |
|----------------------------------|------|--------------|---------------|-----------|---------------|--------|
| Sastrowijoto, et al.82           | 1990 | Prospective  | 1             | Adults    | No            | No     |
| Tervonen, et al.102              | 2000 | Cross-sectional | 1           | Adults    | Yes           | Yes    |
| Sandberg, et al.80               | 2000 | Cross-sectional | 2           | Adults    | Yes           | No     |
| Tsai, et al.106                  | 2002 | Cross-sectional | 2           | Adults    | Yes           | Yes    |
| Arrieta-Blanco, et al.5          | 2003 | Cross-sectional | 1 and 2     | Mixed ages| Yes           | No     |
| Guzman, et al.37                 | 2003 | Cross-sectional | 1 and 2     | Adults    | No            | Yes    |
| Karikoski and Murtomaa45         | 2003 | Prospective  | 1, 2 and others | Adults | No            | No     |
| Lu and Yang59                    | 2004 | Cross-sectional | 2           | Adults    | Yes           | Yes    |
| Negishi, et al.68                | 2004 | Cross-sectional | 1 and 2     | Adults    | No            | Yes    |
| Campus, et al.10                 | 2005 | Cross-sectional | 2           | Adults    | Yes           | Yes    |
| Chuang, et al.12                 | 2005 | Cross-sectional | 2           | Adults    | No            | No     |
| Peck, et al.75                   | 2006 | Cross-sectional | 2           | Adults    | No            | Yes    |
| Jansson, et al.43                | 2006 | Cross-sectional | 2           | Adults    | No            | Yes    |
| Mealey, et al.61                 | 2006 | Review        | 1.2 and GDM  | Mixed ages| Yes/No        | Yes    |
### Effects of diabetes mellitus on periodontal disease

| Reference          | Year | Study design | Diabetes type | Subjects DM/Control | Age (years) | Study duration | Periodontal treatment | Control group | Metabolic control | Effects on metabolic control and on diabetes-related complications |
|--------------------|------|--------------|---------------|--------------------|-------------|----------------|-----------------------|---------------|-------------------|------------------------------------------------------------------|
| Williams and Mahan,109 | 1960 | Clinical cases | -             | 9/0                | 20 - 32     | 3 - 7 m        | Extractions; scaling and probing; gingivectomy; systemic antibiotics | No control group | Insulin requirement; diabetes control | 7 in 9 subjects had significant reduction in insulin requirements |
| Wolf J102          | 1977 | Non-RCT      | 1 and 2       | 117/0              | 16 - 60     | 8 - 12 m       | Scaling; home care instructions on oral hygiene; periodontal surgery; extractions; endodontic treatment; restorations; denture replacement or repair | No control group | Blood glucose levels; 24 hour glycosuria; insulin dose | The treatment of periodontal inflammation and periapical lesions does little to improve diabetes control |
| Miller, et al.54   | 1992 | Non-RCT      | 1             | 10/0               | Unknown     | 8 wk           | Scaling; systemic doxycycline | No control group | HbA1c; glycosated albumin | Decrease in HbA1c and glycosated albumin in patients with improved gingival inflammation; patients with no improvement in gingival inflammation had either no change or increase in HbA1c after treatment |
| Seppala, et al.59  | 1994 | Non-RCT      | 1             | 38 (1 year); 22 (2 years) ** | 35 - 56     | 1 - 2 y        | Scaling; surgery and extraction | No control group | HbA1c; blood glucose levels | Improvement of HbA1c levels in poorly controlled and in well controlled T1D |
| Aldridge, et al.1  | 1995 | RCT          | 1             | 16/15              | 16 - 40     | 2 m            | Oral hygiene instructions; scaling | No treatment | HbA1c; fructosamine | Periodontal treatment showed no effect on improving HbA1c |
| Aldridge, et al.1  | 1995 | (Study 2)    | RCT           | 12/10              | 20 - 60     | 2 m            | Oral hygiene instructions; scaling; extractions and root canal therapy | No treatment | HbA1c | Periodontal treatment showed no effect on improving HbA1c |
| Grossi, et al.34   | 1996 | RCT          | 2             | 89/24              | 25 - 65     | 12 m           | Ultrasonic bactericidal curettage with irrigation using either water, chlorhexidine or povidone-iodine with or without systemic doxycycline | HbA1c | The three groups receiving doxycycline and ultrasonic bacterial curettage showed significant reductions in mean HbA1c after three months |
| Smith, et al.35    | 1996 | Non-RCT      | 1             | 18/0               | 26 - 57     | 2 m            | Scaling; oral hygiene instructions | No control group | HbA1c | Periodontal treatment showed no statistically significant effect on improving HbA1c |
| Westfall, et al.10 | 1996 | Non-RCT      | 1 and 2       | 20/20              | 45 - 65     | 5 y            | Oral hygiene instructions; scaling; periodic prophylaxis; surgery at sites with bleeding on probing; periodontal pocket depth ≥ 5 mm | Same treatment as subjects with T1D | HbA1c | The mean value of glycosated HbA1c between baseline until 24 months was not significantly different from that between 24-60 months |
| Taylor, et al.59   | 1996 | Prospective cohort | 2               | 49 and 55 subjects with severe and less severe periodontitis and no treatment | 18 - 67     | 2 - 4 y        | Not applicable | No control group | HbA1c | Subjects with severe periodontitis were about 6 times more likely to have poor glycemic control at follow-up |
| Grossi, et al.36   | 1997 | RCT          | 2             | 89/24              | 25 - 65     | 6 m            | Periodontal treatment included ultrasonic scaling and curettage combined with one of four different antimicrobial regimens | No treatment | Serum glucose levels; HbA1c | Effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a reduction in levels of HbA1c |
| Christgau, et al.11 | 1998 | Non-RCT      | 1 and 2       | 20/20              | 30 - 66     | 2 m            | Scaling; subgingival irrigations with chlohexidine; oral hygiene instructions; extractions | Same treatment as subjects with DM | HbA1c | No effect on HbA1c |
| Collin, et al.36   | 1998 | Retrospective cohort | 2               | 25/40 - no subjects received treatment | 58 - 77     | 2 - 3 y        | Not applicable | No treatment | HbA1c | In subjects with T2D the HbA1c levels are significantly increased in those with advanced periodontitis |
| Iwamoto, et al.41  | 2001 | Non-RCT      | 2             | 13/0               | 19 - 65     | 1 m            | Local minocycline in every periodontal pocket and mechanical debridement once a week for a month | No control group | HbA1c | Anti-infectious treatment is effective in improving metabolic control |
| Stewart, et al.41  | 2001 | Non-RCT      | 2             | 38/36              | 62 - 67     | 18 m           | Scaling; subgingival curettage and root planing; oral hygiene instructions | No treatment | HbA1c; changes in medications doses | Periodontal therapy was associated with improved glycemic control |

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| Study | Year | Type | Control | Sample Size | Age Range | Intervention | Outcome Measure | Results |
|-------|------|------|---------|-------------|------------|--------------|----------------|---------|
| Rodrigues, et al. | 2003 | RCT | Same as treatment group | 2 | 15/15 | Unknown | 3 m Scaling; systemic amoxicillin/clavulanic acid; oral hygiene instructions at baseline and every 2 w | HbA1c and fasting plasma glucose | Periodontal therapy was associated with improved glycemic control in treatment group. |
| Skaleric, et al. | 2004 | RCT | 2 | 2 15/15 Unknown | 3 m Scaling; systemic amoxicillin/clavulanic acid; oral hygiene instructions at baseline and every 2 w | HbA1c; fasting plasma glucose | Periodontal therapy was associated with improved glycemic control in treatment group. |
| Kiran, et al. | 2005 | RCT | 2 | 2 22/22 | 55-80 | Scaling and minocycline microspheres in pockets ≥5 mm at baseline and at 12 w | HbA1c Decreased HbA1c in test and control groups; treatment with minocycline is significantly more effective than scaling alone. |
| Promsudthi, et al. | 2005 | Non-RCT | 2 | 2 27/25 | 55-80 | Mechanical periodontal treatment and systemic doxycycline for 15 d | HbA1c; fasting plasma glucose | No association between periodontal treatment with adjunctive antimicrobial treatment and changes in HbA1c levels. |
| Janket, et al. | 2005 | Meta-analysis | 1 and 2 | 456 Mixed ages | Scaling; antibiotic | HbA1c | Decrease in HbA1c of 0.66% in those patients with type 2 diabetes without antibiotic use, and of 0.71% in those that used antibiotics. |
| Talbert, et al. | 2006 | Non-RCT | 2 | 2 25/0 | 16-64 | Scaling | HbA1c; fasting glucose levels and fasting plasma insulin | Treatment did not decrease the levels of HbA1c. |
| Schara, et al. | 2006 | Non-RCT | 1 | 10/0 | 38 | Scaling and local chlorhexidine | HbA1c | Decrease in HbA1c after three months of treatment, but no decrease 6 months after the end of the study. |
| Faria-Almeida, et al. | 2006 | Non-RCT | 2 | 10/10 | 35-70 | Scaling | HbA1c | Significant decrease in HbA1c levels. |
| Jansson, et al. | 2006 | Transversal | 2 | 38/153 | 55 | No treatment | No control group | The best predictor for severe PD in subjects with T2D is smoking followed by HbA1c levels; T2D subjects are at increased risk for PD. |
| Jones, et al. | 2007 | RCT | 2 | 82/83 | 59 | Scaling; doxycycline 100 mg daily for 14 days; chlorhexidine 30 ml during 4 m | HbA1c; insulin use | Periodontal and systemic therapies improved glycemic control. |
| Demmer, et al. | 2008 | Longitudinal | 2 | 9,296 | 25 - 74 | No treatment | No control group | Subjects with PD showed a two-fold increase in the chance of having DM; patients with advanced PD show a higher risk for T2D. |
| Darré, et al. | 2008 | Meta-analysis | 1 and 2 | 9 studies (485) Mixed ages | Periodontal treatment | HbA1c | A significant average decrease of 0.40% in the HbA1c levels; the most important reductions in HbA1c levels were observed in two studies that did not use antibiotics. |
| Lamster, et al. | 2008 | Review | - | Mixed ages | No treatment | HbA1c | Studies showed a realtionship between DM and PD. |
| Teeuw, et al. | 2010 | Meta-analysis | 2 | 5 studies (199/183) Mixed ages | Periodontal treatment with and without antibiotic or oral hygiene | HbA1c | A significant decrease in HbA1c levels; the most important reductions in HbA1c levels were observed in two studies that did not use antibiotics. |
| Simpson, et al. | 2011 | Meta-analysis | 1 and 2 | - | Periodontal treatment with and without antibiotic or oral hygiene | HbA1c | A significant decrease in HbA1c levels; the most important reductions in HbA1c levels were observed in two studies that did not use antibiotics. |

Abbreviations: RCT = randomized controlled trial; Non-RCT = non-randomized controlled trial; Treatment; D = days; Wk = weeks; M = months; Y = years; HbA1c = glycated hemoglobin; PD = periodontal disease; DM = diabetes mellitus; T2D = diabetes mellitus type 2; GDM = gestational diabetes mellitus.
DM\textsuperscript{16}, found that subjects with T2D in good to moderate control and with severe periodontitis at baseline were approximately six times more likely to have poor glycemic control at a 2-year follow-up than those without severe periodontitis at baseline\textsuperscript{26}. Collin, et al.\textsuperscript{14} (1998) in another observational study of 25 adults with T2D, aged 58-77 years, also reported an association between advanced periodontal disease and impaired metabolic control\textsuperscript{14}.

Recently, some important trials have recognized that poor glycemic control is a major determinant for the development of the chronic complications of DM. The Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications (EDIC) Trial, the long-term follow-up study of the DCCT, both conducted with T1D and the United Kingdom Prospective Diabetes Study (UKPDS) conducted with T2D, demonstrated that attaining and maintaining good glycemic control could reduce the risk for and/or postpone the progression of micro-vascular complications in patients with T1D and T2D\textsuperscript{18,67,107}.

Initially, the UKPDS observed a statistically non-significant 16% reduction (P=0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death. Recently, it was observed that a long-standing good metabolic control can bring significant long-term consequences including the reduction in the risks of fatal or nonfatal myocardial infarction and sudden death. The epidemiological analysis from the UKPDS showed a continuous association between the risk of cardiovascular complications and glycemic control; every percentage point decrease in HbA1c, was associated with a 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and a 18% reduction in combined fatal and nonfatal myocardial infarction\textsuperscript{18}.

Some observational studies regarding the association between PD and the risk for DM complications have given strong evidence for this association. In a study conducted in Sweden, with 39 case-control pairs of individuals with T1D and T2D for a median follow-up time of six years, Thorstensson, et al.\textsuperscript{104} (1996) observed a significantly higher prevalence of proteinuria and cardiovascular complications such as stroke, transient ischemic attacks, angina, myocardial infarction and intermittent claudication in the case group than in controls. These findings suggest that an association between renal disease, cardiovascular disease and its complications and severe periodontitis seems to exist\textsuperscript{104}.

Saremi, et al.\textsuperscript{85} (2005), studied the contribution of PD to the mortality associated with T2D in the Gila River Indian Community in Arizona, USA, on behalf of the National Institute of Diabetes and Digestive and Kidney Diseases, addressing nephropathy and cardiovascular disease. This was a prospective longitudinal study with a cohort of 628 individuals, aged approximately 35 years old, for a median follow-up of eleven years (range 0.3 to 16). During the study period 204 subjects died. Individuals with severe PD had 3.2 times greater risk for cardio-renal mortality (i.e., ischemic heart disease and diabetic nephropathy combined) compared with the reference group (no, mild, or moderate PD combined), after adjustment for several major risk factors of cardio-renal mortality such as age, sex, diabetes duration, HbA1c, body mass index (BMI), hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macro-albuminuria, and smoking\textsuperscript{81}.

Another study conducted by Shultis, et al.\textsuperscript{86} (2007), in the same community investigated the effect of periodontitis on overt nephropathy and end-stage renal disease (ESRD) in a group of 529 subjects with T2D, aged approximately 25 years old. After adjusting for age, sex, diabetes duration, BMI, and smoking, they found that periodontitis and edentulism were significantly associated with the risk of overt nephropathy and ESRD. The incidence of macro-albuminuria 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\textsuperscript{86}.

Summary and conclusions
The clinical and epidemiological evidence found in the literature we reviewed provides support for the concept that DM can have adverse effects on PD, that PD worsens in parallel with glycemic control and finally that PD is associated with an increase in the risk for diabetes-related complications. However, further prospective, rigorous, controlled trials with a larger number of patients, in ethnically diverse populations are warranted to establish these relationships and that treating PD can positively influence glycemic control and possibly reduce the burden of diabetes-related complications.

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