www.scielo.br/jaos
http://dx.doi.org/10.1590/1678-7757201302106

Periodontal disease and diabetes mellitus

Carlos Antonio NEGRATO[1], Olinda TARZIA[2], Lois JOVANOVIČ[3], Luiz Eduardo Montenegro CHINELLATO[4]

1- PhD in Medical Sciences, Research Support Center, Diabetics Association of Bauru, São Paulo, Brazil.
2- PhD in Oral Biochemistry, Bauru School of Dentistry, University of São Paulo, Bauru, SP, Brazil.
3- MD, CEO & Chief Scientific Officer - Sansum Diabetes Research Institute, Santa Barbara, USA.
4- DDS, MSc, PhD, Full Professor. Department of Stomatology, Bauru School of Dentistry, University of São Paulo, Bauru, SP, Brazil.

Corresponding address: Profa. Dra. Olinda Tarzia - Rua Rodrigo Romeiro, 4-45 - apto 21 - Centro - 17015-420 - Bauru - SP - Fone-Fax: 14 3223-1140 - e-mail: tarzia@uol.com.br

Received: December 15, 2011 - Modification: September 5, 2012 - Accepted: December 11, 2012

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[15]. There is strong evidence that the prevalence, severity and progression of PD are significantly higher in people with DM[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[69].

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[25]. PD has even higher prevalence in minorities, in poor and developing countries and a considerable global variation[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)[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-α (TNF-α); prostaglandins, especially prostaglandin E2 (PGE2); and some other enzymes[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-α. 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)[93]. These collagenolytic enzymes are activated by reactive oxygen species and elevate the levels of interstitial collagenase in inflamed gingival tissue[56].

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[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[25].

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[3].

The most frequently recognized periodontal pathogens belong to three microaerophilic species (*Actinobacillus actinomycetemcomitans, Campylobacter rectus,* and *Eikenella corrodens*) and seven anaerobic species (*Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella intermedia, Fusobacterium nucleatum, Eubacterium,* and *spirochetes*)[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[90].

Many conditions can predispose and/or facilitate the occurrence of PD such as smoking[7,32,35,105], genetic influences[9,49,62], estrogen deficiency[30,32,35], estrogen excess[39], dyslipidemia[58,66,111] and obesity[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[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[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[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 areas[47].

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 mortality[4,38].

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 care[4]. The International Diabetes Federation estimated that DM costs account for 5-10% of the total healthcare budget in many countries[40].

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 caregivers[29]. 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 described[61,96]. 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 controls[102], 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 adolescents[54]. 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 control[13]. 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 DM[103].

Regarding the relationship between T2D and PD, we identified fourteen reports. Two reports were comprised of patients aged 15 years or older[20,70], and twelve[8,10,12,13,19,59,60,74,80,100,106,113] 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 study[8] and no significant difference was found in another study[113].

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 adolescents[6,46,53,85] and another two included only adult subjects[17,73]. Five of these six studies reported greater prevalence, extent, or severity of PD in subjects with DM [5,17,46,53,85]. One report did not find significant differences in PD

Figure 1- Effects of diabetes mellitus on periodontal disease

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.[19]	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.[103]	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
Shlossman, et al.[85]	1990	Cross-sectional	1 and 2	736/2,483	5 to ≥45	Probing attachment loss 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.[70]	1990	Longitudinal	2	1,363/910	≥15	Tooth loss and interproximal crestal alveolar bone loss	-	PD in subjects with DM is 2.6 times more prevalente 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.[102]	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.[80]	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 GW[97]	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.[74]	2002	Cross-sectional	2	40/20	41	Gingivitis	Glycemic control; diabetes complications	T2D and smoking are high-risk factors for PD
Tsai, et al.[106]	2002	Cross-sectional	2	502/3,841	>45	Loss of periodontal attachment	Glycemic control	Positive association between poorly controlled T2D and severe PD
Zielinski, et al.[113]	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 Yang[59]	2004	Cross-sectional	2	72/92	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.[10]	2005	Cross-sectional	2	71/141	35 to75	Gingivitis and pocket depth	Glycemic control	Subjects with T2D have a susceptibility for more severe PD
Chuang, et al.[12]	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

Continues on the next page

Continuation

Borges-Yánez, et al.[8]	2006	Cross-sectional	2	247/78	>60	Loss of periodontal attachment	Fasting blood glucose	Poorly significant greater prevalence of PD in T2D
Xiong, et al.[112]	2006	Cross-sectional	1, 2 and GDM	256/4,234	15 to 44	Pocket depth or loss of periodontal attachment	Diabetes type	Positive association between PD, GDM and pregestational diabetes (T1D and T2D)
Novak, et al.[71]	2006	Cross-sectional	2 and GDM	113/4,131	20 to 59	Gingivitis and pocket depth and loss of periodontal attachment	Glycemic control; duration of diabetes	Women with GDM may be at greater risk for developing more severe PD than women without GDM
Mittas, et al.[65]	2006	Cross-sectional	GDM	64/88	28	Gingivitis	None	Gingival inflammation seems to be more prevalent in women with GDM
Mealey, et al.[61]	2006	Review	1, 2 and GDM	-	Mixed ages	Relationship between PD and DM	-	All types of DM increase the risk of PD
Jansson, et al.[43]	2006	Transversal	2	191/0	Mixed ages	PD	Glycemic control	Subjects with T2D are at increased risk for PD
Khader, et al.[46]	2006	Meta- analysis (1970 to 2003)	1 and 2	23 studies (total of 19,245)	5 to 78	PD	Severity of PD	Subjects with DM had a significantly higher severity but the same extent of PD than nondiabetics
Lalla, et al.[54]	2006	Case-control	1	182 /160	6 to 18	Gingivitis	Evolution of PD severity	Periodontal destruction can start very early in life in subjects with T1D
Lalla, et al.[53]	2007	Cross-sectional	1 and 2	350/350	6 to 18	Gingivitis and pocket depth and loss of periodontal attachment	Glycemic control; duration of diabetes	Positive association between T1D and an increased risk for PD even very early in life
Demmer, et al.[17]	2008	Longitudinal	1 and 2	652/9,296	25 to 74	Presence of PD and its severity	-	PD is an independent predictor of incident DM2

PD= periodontal disease - DM=diabetes mellitus - T1D=diabetes mellitus type 1 - T2D=diabetes mellitus type 2 - GDM=gestational diabetes mellitus

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 15-44[112] and the other, ages 20-59[112]. 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 2.76[63]. 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, Taylor[96] (2001) and Mealey[61] (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 measures[82], 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 T2D[10,43,59,75,106] have found this association and two did not[12,80]. We have found five studies providing information on the differences in periodontal health in groups of mixed types of diabetes[5,37,45,61,68]; three have found this association[37,61,68] and two did not[5,45]. 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[24,31,36,57] and have also been reported to be insulin antagonists and related to insulin resistance that is predominantly found in T2D and GDM[23,36,63,76].

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[61,72,76,96].

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[33,34,44,48,51,52,79,88] and two did not[1]. 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[52].

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[98].

Among the group of twenty-three periodontal treatment studies that were not RCTs, seventeen reported a beneficial effect on glycemic control[14,16,17,22,41-43,55,64,83,84,87,94,99,101,109,110] and six did not[11,78,91,95,108]. Only ten of these studies had controls or comparison groups[11,14,22,43,78,84,94,99,101,108]. Like the RCTs, there was marked variation in the use of adjunctive antibiotics, with six of the eight studies that used systemic antibiotics reporting a beneficial effect on glycemic control[41,42,64,83,87,109].

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

Figure 2- Effects of glycemic control on periodontal disease (GDM= gestational diabetes mellitus)

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 Murtomaa[45]	2003	Prospective	1, 2 and others	Adults	No	No
Lu and Yang[59]	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

Figure 3- Effects of periodontal disease on glycemic control and diabetes-related complications

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 J[110]	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; restaurations; 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.[64]	1992	Non-RCT	1	10/0	Unknown	8 wk	Scaling; systemic doxycycline	No control group	HbA1c; glycated albumin	Decrease in HbA1c and glycated 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.[84]	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
Aldrige, et al.[1]	1995 (Study 1)	RCT	1	16/15	16 - 40	2 m	Oral hygiene instructions; scaling	No treatment	HbA1c; fructosamine	Periodontal treatment showed no effect on improving HbA1c
Aldrige, et al.[1]	1995 (Study 2)	RCT	1	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 polvidone-iodine with or without systemic doxycycline	Ultrasonic curettage with irrigation using water and placebo	HbA1c	The thrre groups receiving doxycycline and ultrasonic bacterial curettage showed significant reductions in mean HbA1c after three months
Smith, et al.[91]	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
Westfelt, et al.[108]	1996	Non-RCT	1 and 2	20/20	45 - 65	5 y	Oral hygiene instructions; scaling; periodic prophylaxy; surgery at sites with bleeding on probing; periodontal pocket depth > 5 mm	Same treatment as subjects with T1D	HbA1c	The mean value of glycated HbA1c between baseline untill 24 months was not significantly different from that between 24-60 months
Taylor, et al.[99]	1996	Prospective cohort	2	49 and 56 subjects with severe and lees 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.[33]	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 chlorhexidine; oral hygiene instructions; extractions	Same treatment as subjects with DM	HbA1c	No effect on HbA1c
Collin, et al.[14]	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 debridment once a week for a month	No control group	HbA1c	Anti-infectious treatment is effective in improving metabolic control
Stewart, et al.[94]	2001	Non-RCT	2	36/36	62 - 67	18 m	Scaling; subgingival curettage and root planing; oral hygiene instructions	No treatment	HbA1c; changes in medications doses	Periodontal theraphy was associated with improved glycemic control

Continues on the next page

Continuation

Rodrigues, et al.[79]	2003	RCT	2	15/15	Unknown	3 m	Scaling; systemic amoxicillin/ clavulanic acid; oral hygiene instructions at baseline and every two w	Same as treatment group, except no medication	HbA1c and fasting plasma glucose	Periodontal therapy was associated with improved glycemic control in treatment group
Skaleric, et al.[88]	2004	RCT	1	10/10	26 - 58	24 wk	Scaling and minocycline microspheres in pockets ≥5 mm at baseline and at 12 w	Scaling	HbA1c	Decreased HbA1c in test and control groups; treatment with minocycline is significantly more effective than sacaling alone
Kiran, et al.[48]	2005	RCT	2	22/22	31 - 79	3 m	Scaling; oral hygiene instructions	No treatment	HbA1c; fasting and 2-h post-prandial glucose levels	Decreased HbA1c and 2-h post-prandial glucose levels in treatment group
Promsudthi, et al.[78]	2005	Non-RCT	2	27/25	55 - 80	3 m	Mechanical periodontal treatment and systemic doxycycline for 15 d	No treatment	HbA1c and fasting plasma glucose	No association between periodontal treatment with adjunctive antimicrobial treatment and changes in HbA1c levels
Janket, et al.[42]	2005	Meta- analysis	1 and 2	456	Mixed ages	25 y	Scaling; antibiotic	No treatment	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.[95]	2006	Non-RCT	2	25/0	16 - 64	3 m	Scaling	No control group	HbA1c; fasting glucose levels and fasting plasma insulin	Treatment did not decrease the levels of HbA1c
Schara, et al.[83]	2006	Non-RCT	1	10/0	38	12 m	Scaling and local chlorhexidine	No treatment	HbA1c	Decrease in HbA1c after three months of treatment, but no decrease 6 months after the end of the study
Faria-Almeida, et al.[22]	2006	Non-RCT	2	10/10	35-70	6 m	Scaling	Scaling	HbA1c	Significant decrease in HbA1c levels
Jansson, et al.[43]	2006	Transversal	2	38/153	55	2y	No treatment	No control group	HbA1c	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.[44]	2007	RCT	2	82/83	59	4 m	Scaling; doxycycline 100 mg daily for 14 days; chlorhexidine 30 ml during 4 m	Usual care	HbA1c; insulin use	Periodontal and systemic therapies improved glycemic control
Demmer, et al.[17]	2008	Longitudinal	2	9,296	25 - 74	20 y	No treatment	No control group	-	Subjects with PD showed a two-fold increase in the chance of having DM; patients with advanced PD show greater risk for T2D
Darré, et al.[16]	2008	Meta- analysis	1 and 2	9 studies (485)	Mixed ages	-	Periodontal treatment	No treatment	HbA1c	Significant decrease in HbA1c levels
Lamster, et al.[55]	2008	Review	1 and 2	-	Mixed ages	6 y	-	No treatment	-	37/44 cross-sectional studies and 7/7 prospective studies showed a realtionship between DM and PD
Teeuw, et al.[101]	2010	Meta- analysis	2	5 studies (199/183)	Mixed ages	3 - 9 m	Periodontal treatment	No 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
Simpson, et al.[87]	2011	Meta- analysis	1 and 2	-	18-80	-	Periodontal treatment with and without antibiotics; oral hygiene instructions	No treatment	HbA1c	Improvement in glycemic control after periodontal treatment
Koromantzos, et al.[51]	2011	RCT	2	30/30	40 - 75	6 m	Oral hygiene instructions; non-surgical periodontal treatment every 7 d	Ultrasound prophylaxy	HbA1c	Significant decrease in HbA1c levels in the treatment group
Koromantzos, et al.[52]	2012	RCT	2	30/30	40 - 75	6 m	Oral hygiene instructions; non-surgical periodontal tretment every 7 d	Ultrasound prophylaxy	HbA1c	Effective non-surgical periodontal treatment of subjects with T2D and moderate to severe PD improved significantly HbA1c levels but did not result in a statistically significant improvement in serum levels of inflammatory markers

Abbreviations: RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial-treatment study; D, days; Wk, weeks; M, months; Y, years; HbA1c, glycated hemoglobin - PD= periodontal disease - DM=diabetes mellitus - T1D=diabetes mellitus type 1 - T2D=diabetes mellitus type 2 - GDM=gestational diabetes mellitus

DM[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[96]. Collin, et al.[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[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[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[28].

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.[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[104].

Saremi, et al.[80] (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[81].

Another study conducted by Shultis, et al.[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[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.

REFERENCES

1- Aldridge JP, Lester V, Watts TL, Collins A, Viberti G, Wilson RF. Single-blind studies of the effects of improved periodontal health on metabolic control in type 1 diabetes mellitus. J Clin Periodontal. 1995;22:271-5.

2- Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. J Periodontal. 2003;74:610-5.

3- Amar S, Han X. The impact of periodontal infection on systemic diseases. Med Sci Monit. 2003;9:RA291-9.

4- American Diabetes Association. Economic costs of diabetes in the US in 2007. Diabetes Care. 2008;31:596-615.
5- Arrieta-Blanco JJ, Bartolomé-Villar B, Jiménez-Martinez E, Saavedra-Vallejo P, Arrieta-Blanco FJ. Dental problems in patients with diabetes mellitus (II): gingival index and periodontal disease. Medicina Oral. 2003;8:233-47.
6- Bahia LR, Araujo DV, Schaan BD, Dib SA, Negrato CA, Leão MPS, et al. The costs of type 2 diabetes mellitus outpatient care in the Brazilian public health system. Value Health. 2011;14(5 Suppl 1):S137-40.
7- Bergström J, Preber H. Tobacco use as a risk factor. J Periodontal. 1994;65(Suppl. 5):545-50.
8- Borges-Yáñez SA, Irigoyen-Camacho ME, Maupomé G. Risk factors and prevalence of periodontitis in community-dwelling elders in Mexico. J Clin Periodontal. 2006;33:184-94.
9- Burt B, Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: epidemiology of periodontal diseases. J Periodontal. 2005;76:1406-19.
10- Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. Diabetes and periodontal disease: a case-control study. J Periodontal. 2005;76:418-25.
11- Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S. Healing response to non-surgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological, and immunologic results. J Clin Periodontal. 1998;25:112-24.
12- Chuang SF, Sung JM, Kuo SC, Huang JJ, Lee SY. Oral and dental manifestations in diabetic and non-diabetic uremic patients receiving hemodialysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:689-95.
13- Cianciola LJ, Park BH, Bruck E, Mosovich L, Genco RJ. Prevalence of periodontal disease in insulin-dependent diabetes mellitus (juvenile diabetes). J Am Dent Assoc. 1982;104:653-60.
14- Collin HL, Uusitupa M, Niskanen L, Kontturi-Närhi V, Markkanen H, Koivisto AM, et al. Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus. J Periodontal. 1998;69:962-6.
15- D'Aiuto F, Graziani F, Tetè S, Gabriele M, Tonetti MS. Periodontitis: from local infection to systemic diseases. Int J Immunopathol Pharmacol. 2005;18(Suppl 3):1-11.
16- Darré L, Vergnes JN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: a meta-analysis of interventional studies. Diabetes Metab. 2008;34(5):497-506.
17- Demmer RT, Jacobs DR Jr., Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care. 2008;31:1373-9.
18- The Diabetes Control and Complications Trial Study Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-86.
19- Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. J Periodontal. 1991;62:123-31.
20- Endean C, Roberts-Thomson K, Wooley S. Anangu oral health: the status of the Indigenous population of the Anangu Pitjantjatjara lands. Aust J Rural Health. 2004;12:99-103.
21- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1998;21(Suppl.1):S5-19.
22- Faria-Almeida R, Navarro A, Bascones A. Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. J Periodontal. 2006;77:591-8.
23- Feingold KR, Grunfeld C. Role of cytokines in inducing hyperlipidemia. Diabetes. 1992;41:97-101.
24- Feingold KR, Soued M, Serio MK, Moser AH, Dinarello CA, Grunfeld C. Multiple cytokines stimulate hepatic lipid synthesis in vivo. Endocrinology. 1989;125:267-74.
25- Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, et al. The American Journal of Cardiology and Journal of Periodontology editor's consensus: periodontitis and atherosclerotic cardiovascular disease. J Periodontal. 2009;80:1021-32.
26- Geerts SO, Legrand V, Charpentier J, Albert A, Rompen EH. Further evidence of the association between periodontal conditions and coronary artery disease. J Periodontal. 2004;75:1274-80.
27- Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontal. 2005;76(Suppl. 11):2075-84.
28- Genuth S, Eastman R, Kahn R, Klein R, Lachin J, Lebovitz H, et al. Implications of the United Kingdom prospective diabetes study. Diabetes Care. 2003;26:S28-32.
29- Gomes MB, Mattos Matheus AS, Calliari LE, Luescher JL, Manna TD, Savoldelli RD, et al. Economic status and clinical care in young type 1 diabetes patients: a nationwide multicenter study in Brazil. Acta Diabetol. 2012; Jun 12. [Epub ahead of print].
30- Gomes-Filho IS, Passos JS, Cruz SS, Vianna MI, Cerqueira EM, Oliveira DC, et al. The association between postmenopausal osteoporosis and periodontal disease. J Periodontol. 2007;78:1731-40.
31- Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Ann Periodontal. 1998; 3:51-61.
32- Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, et al. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. J Periodontal. 1995;66:23-9.
33- Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontal. 1997;68:713-9.
34- Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. J Periodontal. 1996;67:1094-102.
35- Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontal 1994;65:260-7.
36- Grunfeld C, Soued M, Adi S, Moser AH, Dinarello CA, Feingold KR. Evidence for two classes of cytokines that stimulate hepatic lipogenesis: relationships among tumor necrosis factor, interleukin-1 and interferon-alpha. Endocrinology. 1990;127:46-54.
37- Guzman S, Karima M, Wang HY, Van Dyke TE. Association between interleukin-1 genotype and periodontal disease in a diabetic population. J Periodontal. 2003;74:1183-90.
38- Harris MI. Summary National Diabetes Data Group. Diabetes in America. 2nd ed. Washington DC: Government Printing Office; 1995. p 1-13.
39- Haytaç MC, Cetin T, Seydaoglu G. The effects of ovulation induction during infertility treatment on gingival inflammation. J Periodontal. 2004;75(6):805-10.
40- International Diabetes Federation. Diabetes Atlas. 3rd ed. Brussels: International Diabetes Federation; 2006.
41- Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontal. 2001;72:774-8.
42- Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA. Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. J Dent Res. 2005;84:1154-9.
43- Jansson H, Lindholm E, Lindh C, Groop L, Brattahall G. Type 2 diabetes and risk for periodontal disease: a role for dental health awareness. J Clin Periodontal. 2006;33:408-14.
44- Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, et al. Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontal. 2007;34:46-52.
45- Karikoski A, Murtomaa H. Periodontal treatment needs in a follow-up study among adults with diabetes in Finland. Acta Odontol Scand. 2003;61:6-10.

46- Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with non-diabetics: a meta-analysis. J Diabetes Complications. 2006;20:59-68.
47- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21:1414-31.
48- Kiran M, Arpak N, Unsal E, Erdoğan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. J Clin Periodontal. 2005;32(3):266-72.
49- Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, et al. The interleukin- 1 genotype as a severity factor in adult periodontal disease. J Clin Periodontal. 1997;24:72-7.
50- Kornman KS, Page RC, Tonetti MS. The host response to the microbial challenge in periodontitis: assembling the players. Periodontal 2000. 1997;14:33-53.
51- Koromantzos PA, Makrilakis K, Dereka X, Katsilambros N, Vrotsos IA, Madianos PN. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. J Clin Periodontal. 2011;38:142-7.
52- Koromantzos PA, Makrilakis K, Dereka X, Offenbacher S, Katsilambros N, Vrotsos IA, et al. Effect of non-surgical periodontal therapy on C-reactive protein, oxidative stress, and matrix metalloproteinase (MMP)-9 and MMP-2 levels in patients with type 2 diabetes: a randomized controlled study. J Periodontal. 2012;83:3-10.
53- Lalla E, Cheng B, Lal S, Kaplan S, Softness B, Greenberg E, et al. Diabetes mellitus promotes periodontal destruction in children. J Clin Periodontal. 2007;34:294-8.
54- Lalla E, Cheng B, Lal S, Tucker S, Greenberg E, Goland R, et al. Periodontal changes in children and adolescents with diabetes: a case-control study. Diabetes Care. 2006;29(2):295-9.
55- Lamster IB; Lalla E; Borgnakke WS; Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008;139(Suppl 5):19S-24S.
56- Lee W, Aitken S, Sodek J, McCulloch CA. Evidence of a direct relationship between neutrophil collagenase activity and periodontal tissue destruction *in vivo*: role of active enzyme in human periodontitis. J Periodontal Res. 1995;30:23-33.
57- Ling PR, Istfan NW, Colon E, Bistrian BR. Differential effects of interleukin-1 receptor antagonist in cytokine- and endotoxin-treated rats. Am J Physiol. 1995;268:E255-61.
58- Lösche W, Marshal GJ, Apatzidou DA, Krause S, Kocher T, Kinane DF. Lipoprotein-associated phospholipase A2 and plasma lipids in patients with destructive periodontal disease. J Clin Periodontal. 2005;32:640-4.
59- Lu HK, Yang PC. Cross-sectional analysis of different variables of patients with non-insulin dependent diabetes and their periodontal status. Int J Periodontics Restorative Dent. 2004;24:71-9.
60- Mattout C, Bourgeois D, Bouchard P. Type 2 diabetes and periodontal indicators: epidemiology in France 2002-2003. J Periodontal Res. 2006;41:253-8.
61- Mealey BL, Oates TW, American Academy of Periodontology. Diabetes mellitus and periodontal diseases. J Periodontal. 2006;77:1289-303.
62- Michalowicz BS, Aeppli D, Virag JG, Klump DG, Hinrichs JE, Segal NL, et al. Periodontal findings in adult twins. J Periodontal. 1991;62:293-9.
63- Michie HR. Metabolism of sepsis and multiple organ failure. World J Surg. 1996;20:460-4.
64- Miller LS, Manwell MA, Newbold D, Reding ME, Rasheed A, Blodgett J. The relationship between reduction in periodontal inflammation and diabetes control: a report of 9 cases. J Periodontal. 1992;63:843-8.
65- Mittas E, Erevnidou K, Koumantakis E, Papavasileiou S, Helidonis E. Gingival conditions of women with gestational diabetes on a Greek island. Spec Care Dentist. 2006;26:214-9.
66- Morita M, Horiuchi M, Kinoshita Y, Yamamoto T, Watanabe T. Relationship between blood triglyceride levels and periodontal status. Community Dent Health. 2004;21:32-6.
67- Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53.
68- Negishi J, Kawanami M, Terada Y, Matsuhashi C, Ogami E, Iwasaka K, et al. Effect of lifestyle on periodontal disease status in diabetic patients. J Int Acad Periodontal. 2004;6:120-4.
69- Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. Diabetol Metab Syndr. 2010;2:3.
70- Nelson RG, Shlossman M, Budding. LM, Pettitt DJ, Saad MF, Genco RJ, et al. Periodontal disease and NIDDM in Pima Indians. Diabetes Care. 1990;13:836-40.
71- Novak KF, Taylor GW, Dawson DR, Ferguson JE 2nd, Novak MJ. Periodontitis and gestational diabetes mellitus: exploring the link in NHANES III. J Public Health Dent. 2006;66:163-8.
72- Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontal. 1996;67:1103-13.
73- Ogunbodede EO, Fatusi OA, Akintomide A, Kolawole K, Ajayi A. Oral health status in a population of Nigerian diabetics. J Contemp Dent Pract. 2005;6:75-84.
74- Orbak R, Tezel A, Canakçi V, Demir T. The influence of smoking and non-insulin-dependent diabetes mellitus on periodontal disease. J Int Med Res. 2002;30:116-25.
75- Peck T, Price C, English P, Gill G. Oral health in rural South African type 2 diabetic patients. Trop Doct. 2006;36:111-2.
76- Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia. 1997;40:1286-92.
77- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366:1809-20.
78- Promsudthi A, Pimapansri S, Deerochanawong C, Kanchanavasita W. The effect of periodontal therapy on uncontrolled type 2 diabetes mellitus in older subjects. Oral Dis. 2005;11:293-8.
79- Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. J Periodontal. 2003;74:1361-7.
80- Sandberg GE, Sundberg HE, Fjellstrom CA, Wikblad KF. Type 2 diabetes and oral health: a comparison between diabetic and non-diabetic subjects. Diabetes Res Clin Pract. 2000;50:27-34.
81- Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, et al. Periodontal disease and mortality in type 2 diabetes. Diabetes Care. 2005;28:27-32.
82- Sastrowijoto SH, van der Velden U, van Steenbergen TJ, Hillemans P, Hart AA, de Gaaff J, et al. Improved metabolic control, clinical periodontal status and subgingival microbiology in insulin-dependent diabetes mellitus. A prospective study. J Clin Periodontal. 1990;17:233-42.
83- Schara R, Medvescek M, Skaleric U. Periodontal disease and diabetes metabolic control: a full-mouth disinfection approach. J Int Acad Periodontal. 2006;8:61-6.
84- Seppälä B, Ainamo J. A site-by-site follow-up study on the effect of controlled versus poorly controlled insulin-dependent diabetes mellitus. J Clin Periodontal. 1994;21:161-5.
85- Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes mellitus and periodontal disease. J Am Dent Assoc. 1990;121:532-6.
86- Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, et al. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care. 2007;30:306-11.
87- Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. Cochrane Database Syst Rev. 2010;12(5):CD004714.

88- Skaleric U, Schara R, Medvescek M, Hanlon A, Doherty F, Lessem J. Periodontal treatment by Arestin and its effects on glycemic control in type 1 diabetes patients. J Int Acad Periodontal. 2004;6:160-5.
89- Skyler J, Oddo C. Diabetes trends in the USA. Diabetes Metab Res Ver. 2002;18:S21-6.
90- Slots J, Kamma JJ, Sugar C. The herpesvirus-*Porphyromonas gingivalis*-periodontitis axis. J Periodontal Res. 2003;38:312-23.
91- Smith GT, Greenbaum CJ, Johnson BD, Persson GR. Short-term responses to periodontal therapy in insulin-dependent diabetic patients. J Periodontal. 1996;67:794-802.
92- Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontal. 1998;25:134-44.
93- Sorsa T, Ingman T, Suomalainen K, Haapasalo M, Konttinen YT, Lindy O, et al. Identification of proteases from periodontopathogenic bacteria as activators of latent human neutrophils and fibroblast-type interstitial collagenases. Infect Immun. 1992;60:4491-5.
94- Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. J Clin Periodontal. 2001;28:306-10.
95- Talbert J, Elter J, Jared HL, Offenbacher S, Southerland J, Wilder RS. The effect of periodontal therapy on TNF-alpha, IL-6 and metabolic control in type 2 diabetics. J Dent Hyg. 2006;80:7.
96- Taylor GW. Periodontal treatment and its effects on glycemic control: a review of the evidence. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87:311-6.
97- Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Ann Periodontol. 2001;6(1):99-112.
98- Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral Dis. 2008;14:191-203.
99- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontal. 1996;67:1085-93.
100- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontal. 1998;69(1):76-83.
101- Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care. 2010;33(2):421-7.
102- Tervonen T, Karjalainen K, Knuuttila M, Huumonen S. Alveolar bone loss in type 1 diabetic subjects. J Clin Periodontal. 2000;27:567-71.
103- Thorsternsson H, Hugoson A. Periodontal disease experience in adult long-duration insulin-dependent diabetics. J Clin Periodontal. 1993;20:352-8.
104- Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontal. 1996;23:194-202.
105- Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. J Periodontal. 2000;71:743-51.
106- Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol. 2002;30:182-92.
107- UK Prospective Diabetes Study. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53.
108- Westfelt E, Rylander H, Blohmé G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. J Clin Periodontal. 1996;23:92-100.
109- Williams RC Jr, Mahan CJ. Periodontal disease and diabetes in young adults. J Am Med Assoc 1960;172:776-8.
110- Wolf J. Dental and periodontal conditions in diabetes mellitus. A clinical and radiographic study. Proc Finn Dent Soc. 1977;73:1-56.
111- Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT. Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. Am J Epidemiol. 2000;151:273-82.
112- Xiong X, Buekens P, Vastardis S, Pridjian G. Periodontal disease and gestational diabetes mellitus. Am J Obstet Gynecol. 2006;195:1086-9.
113- Zielinski MB, Fedele D, Forman LJ, Pomerantz SC. Oral health in the elderly with non-insulin-dependent diabetes mellitus. Spec Care Dentist. 2002;22:94-8.