Periodontal disease and diabetes-Review of the literature

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Abstract

Aims: To provide updated knowledge on the relationship between periodontal disease and diabetes from an oral health perspective.

Methods: A review of the English-language literature was performed, gathering articles on the two diseases published over the past 10 years.

Results: Both diseases result from the confluence of various triggering and modifying factors, and there are inter-individual differences in the risk of their development. Recent research has shown that diabetes may increase the risk of periodontitis, and it has been proposed that chronic periodontal disease may influence the natural course of diabetes. There appears to be an association among oral infections, impaired sugar metabolism, and atherosclerosis, indicating a theoretical link between metabolic syndrome and periodontal disease.

Clinical implications: Control of periodontal disease may enhance glycemic control in patients with type 2 diabetes. In turn, improved glycemic control may contribute to a better control of periodontal disease.

Key words: Diabetes mellitus, metabolic syndrome, periodontal disease, cardiovascular disease.

Introduction

This review outlines the characteristics of diabetes and periodontal disease, explores their known interrelationships, and discusses the scientific evidence, mainly focusing on clinical research.

The relationship between periodontitis and diabetes has been extensively investigated over the past few decades (1). Nevertheless, the impact of periodontal treatment on glycemic control in diabetics has not been fully elucidated. Although there have been numerous scientific studies on the influence of periodontal treatments on glycemic control, there is limited knowledge on the effects of glycemic control on periodontal status. This review not only shows data about recent knowledge of these two pathologies, but also highlights the need for further research to elucidate this interaction.

The aim of the review was to provide updated knowledge on these topics from an oral health perspective. We reviewed all articles related to these two diseases published in English over the past 10 years, using the National Library of Medicine Entrez PubMed search engine for the literature search.

Diabetes mellitus

Diabetes mellitus is a metabolic disease usually characterized by the classic triad of polydipsia, polyuria and polyphagia, consequences of homeostasis disruption due to impaired glucose metabolism. It is difficult to establish the prevalence in the general population, which has been estimated at 1- 6% according to the diagnostic criteria used. Approximately 90% of cases correspond to patients with non-insulin dependent type-2 diabetes (2).

The impaired metabolism of glucose, lipids, and proteins in diabetes produces alterations in macro- and micro-vascular circulation that are associated with the five classic complications of the disease, i.e., retinopathy, neuropathy, nephropathy, cardiovascular complications, and delayed wound-healing (1). Periodontal disease has been proposed as the sixth complication of diabetes, based on the highly frequent presence of both diseases in the same patient (2-4). However, some aspects of this association remain controversial.

Classification

There are two main types of diabetes, insulin-dependent type-1 diabetes and non-insulin-dependent type-2 diabetes. Despite their designations, this classification does not solely depend on the need for exogenous insulin, which can sometimes also be required by type-2 patients (5). Type-1 diabetes is produced by the destruction of insulin-producing cells, whereas type-2 results from the combination of an increase in cell resistance to endogenous insulin with a defective secretion of this substance. Most dental researchers have addressed type-1 diabetes, and studies of type-2 diabetes from an oral health perspective have only been published since the mid-1990s.

Etiology and pathogenesis

The following two mechanisms have been proposed to explain the classic complications of diabetes (2).

1) Polyol pathway.

According to this theory, glucose is converted into sorbitol by the action of aldose reductase, which is implicated as the toxin in almost all of these complications.

2) Production of advanced glycosylation end products (AGEs).

This second theory proposes that glucose binds to proteins, lipids, and nucleic acids, giving rise to AGEs that alter their functions. Thus, the binding of glucose to hemoglobin, collagen, or albumin produces complications according to the organ in which AGEs are deposited (e.g., kidney, nervous system, vascular system, or retina, among others).

Periodontal disease

Periodontal disease is an entity of localized infections that involve tooth supporting tissues, the structures that make up the periodontium (i.e., gingiva, periodontal ligament, root cementum, and alveolar bone). The designation periodontal disease includes both reversible (gingivitis) and irreversible (periodontitis) processes. In periodontitis, there is destruction of the connective tissue of the tooth attachment apparatus accompanied by apical migration of the apparatus and eventual tooth loss.

The first clinical manifestation of periodontal disease is the appearance of periodontal pockets, which offer a favorable niche for bacterial colonization. It can be diagnosed by clinical examination with periodontal probe to determine pocket depths in combination with X-ray imaging, using microbiological techniques for a precise analysis of the infectious agents.

The clinical importance of periodontal disease derives in part from its very high prevalence. Although variable data have been published, most studies in the USA, for example, have reported that half of the population has some history of gingivitis and that 14% of them suffer from periodontal disease (3). In fact, the figures for periodontal disease may underestimate its true prevalence, since earlier studies had found that 25-36% of the population was affected. Estimations of the epidemiology of this disease appear to depend on the diagnostic approach adopted (2).

Classification

Variability in the diagnosis of the disease is in part caused by the lack of an adequate classification. Several attempts have been made to classify periodontal disease according to its etiology and clinical manifestations (6), considering periodontal disease as an entity independent from the patient that is capable of producing signs and symptoms (7,8). The 1999 American Association of Periodontology (AAP) classification, currently the most widely used, identifies six categories: gingival disease, chronic periodontitis, aggressive periodontitis, periodontitis as manifestation of systemic disease, necrotizing periodontal disease, and periodontal abscess (6).

Drawbacks of both the 1989 and 1999 AAP proposals are that periodontal disease cannot be classified according to its etiology, and there are no well-defined clinical criteria for its diagnosis, leaving this decision to the healthcare professional (8).

Etiology and pathogenesis

According to current concepts of the multifactorial etiology of periodontal disease, it is caused by the interaction among single or multiple microbial agents (necessary but not sufficient primary etiologic factors), a host with some degree of susceptibility, and environmental factors with an influence on both. Although a single model of the etiopathogeny of periodontal disease has

yet to be validated, it is broadly accepted that periodontal disease results from action of the bacterial biofilm on the periodontium of the susceptible individual. Bacteria are able to survive and grow in the complex ecosystem of this biofilm because of their production of virulence factors. These factors also confer a greater resistance to host defense mechanisms, i.e., they increase the capacity of the bacteria to overcome the inflammatory reaction and immune response to antigen presentation (9).

Although there have been some reports of tissue damage caused by the presence of bacteria in situ, i.e., in the affected tissue itself, it is more commonly observed at some distance from the bacteria, demonstrating their capacity for indirect action. Bacteria appear to act directly during the first moments of infection. However, most of their activity is indirect, via cell and humoral components of specific and non-specific host responses to protect the biofilm (10).

According to a review by Offenbacher in 1996, the presence of bacteria in the periodontal pocket triggers a reaction that starts with intervention of the neutrophil-antibody-complement axis, stimulating different cell types (11). Thus, neutrophils attempt to phagocyte and lyse bacteria to prevent lateral and apical expansion of the bacterial plaque, while the complement system provides a rapid increase in the anti-inflammatory response and in antibodies produced by plasma cells during a previous exposure. If this reaction (i.e., the inflammatory response) is sufficient to control the disease, a limited gingivitis is the result and the defensive response of the organism has been adequate to prevent propagation of the infection. In certain circumstances, however, microorganisms can evade the defense systems or are so virulent that they can overcome them and invade the tissue. A second line of defense is then activated in the immune response, composed of macrophages, lymphocytes, and cytokines able to act against the pathogens in a more specific manner (11).

Diabetes as a risk factor for periodontal disease

Many authors have described diabetes as a risk factor for periodontal disease. Hence, Mealey concluded that diabetic patients had a three-fold higher risk of periodontal disease compared with non-diabetic patients after controlling for age, sex, and other confounding factors (5).

For diabetes to be acknowledged as a risk factor it must meet the risk analysis criteria set out by Johnson & Hill, especially the two following conditions (12):

1) biological plausibility that the factor can cause a given disease by a known action mechanism, and
2) demonstration in prospective studies that the factor chronologically precedes the disease.

Longitudinal and cross-sectional studies are still needed to confirm this association. There must be known

mechanism(s) by which the factor can give rise to the effect, as we shall discuss in more detail below. Consequently, the evidence is still weak and no causal relationship between periodontal disease and diabetes has been established.

Interrelationship between diabetes and periodontal disease

Diabetes mellitus is, as previously stated, a systemic disease associated with serious complications that can affect the quality of life and life expectancy of the patient (12,13). There can be damage to the eyes and the nervous, cardiovascular, and renal systems and impairment of wound healing (2). Besides these well-documented secondary effects, there are reports of an increased risk of periodontal disease or of its greater severity in patients with diabetes (3,12,14). For example, studies on Pima Indians in Arizona showed that loss of periodontal attachment and bone loss were greater in diabetic versus non-diabetic individuals within different age groups (15,16).

Possible mechanisms underlying this association between periodontal disease and diabetes are currently under investigation and remain somewhat controversial. Some authors have described a possible common origin of the two diseases (17), whereas others consider that diabetes produces a hyper-inflammatory phenotype in certain cells due to the action of AGEs (4,12,18). We briefly discuss some of the mechanisms proposed to underlie interaction between diabetes and periodontal disease.

Both diabetes and periodontal disease are considered to have a hereditary component (18), and a large number of cases have been related to a given family pattern. However, it has not yet proved possible to relate these diseases to any specific genetic mutation or disorder, and both diseases can therefore be described as polygenic.

Genetic factors evidently play a major role in susceptibility to these diseases. However, the complex interactions in periodontal disease between host response mechanisms and the action of pathogenic microorganisms hamper clarification of the role of genetic factors (17). Nevertheless, an association has been observed between both diseases and an HLA genotype. The HLA molecule (human major histocompatibility locus molecule) is genetically determined on chromosome 6, and disorders in this chromosome appear to predispose the host to both diabetes and periodontitis by altering antigen presentation to T cells and therefore the specific immune response of the patient (17). However, more studies are required in this area before conclusions can be drawn.

The role of the immune system in the etiopathogeny of diabetes and periodontal disease is well documented (17). No doubt remains about the importance of the con-

trolled release of cytokines and soluble factors that limit the noxious effects of both diseases.

A further possible connection between the diseases appears to be the hyper-inflammatory phenotype observed in the patients. Patients with diabetes type-1 or -2 or periodontal disease show an imbalance or hyper-release of soluble cytokines against the attack of coadjuvant factors (13). The other risk factors include tobacco use or stress for periodontal disease and the action of viruses or toxic agents for diabetes. In response to the presence of these modifying factors, cells of both diabetic and periodontal patients release an increased amount of certain cytoactive chemicals e.g., prostaglandin E2 (PGE2), interleukin 1 (IL-1), and tumor necrosis factor-alpha (TNF-α). This up-regulation of immune response mediators has been demonstrated in vitro and in comparisons between diseased animals and healthy controls and may represent another possible explanation for the association between the two diseases (5).

The first hypothesis on the diabetes-periodontal disease relationship derives from a combination of the above theories. Thus, it is proposed that a faulty combination of genes in chromosome 6 renders the host more susceptible to external factors that can give rise to diabetes and/or periodontal diseases if immunological and other defense mechanisms fail (17).

Besides the mainly genetic theories discussed above, other explanations of the interaction between the two diseases have been proposed based on the binding of AGEs to their cell receptors (RAGEs) (4), which are present in certain diabetic patients, e.g., in endothelial or phagocytic cells (15). Hence, AGEs may be deposited on mononuclear or polymorphonuclear cells, inhibiting their chemotactic and phagocytic capacities and permitting the advance of gram-negative anaerobic bacteria, which would explain the higher prevalence and severity of periodontal disease in diabetic patients (4). According to this theory, AGE-stimulated macrophages and polymorphonuclear cells show a hyper-response to the progression of bacterial biofilm, releasing a larger amount of cytokines and soluble mediators and producing a greater destruction of connective tissue in these patients (Fig. 1).

Binding between AGEs and their receptors has also been observed in fibroblasts, which would have repercussions for collagen, the main component of periodontal tissue. Accordingly, interference with the collagen turnover would impair wound-healing in diabetic patients and may reduce the resistance of periodontal tissues to bacterial attack (2). It has also been demonstrated that AGEs increase collagenase and other enzyme activity in connective tissue, thereby contributing to tissue destruction.

Matrix metalloproteinases (MMPs) are locally increased in periodontal disease-affected gingival pock-
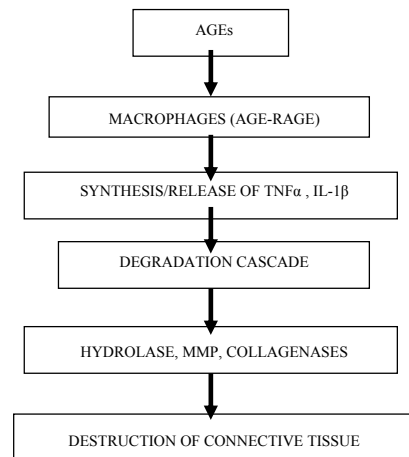
Fig. 1. Model depicting how diabetes mellitus could contribute to the development of periodontal disease. The binding of AGEs to their receptors triggers a cascade of events that produce the destruction of connective tissue. AGE= advanced glycation end product, RAGE = receptor for AGE, TNFα = tumor necrosis factor alpha, IL-1β = interleukin-1 beta, MMP = matrix metalloproteinase. Modified from Grossi and Genco (3).

ets, and advanced periodontal disease has been associated with elevated salivary MMP levels. Periodontal patients also have increased serum MMPs, which may be specifically due to infection with certain periodontal pathogens. It has been proposed that MMP-9 may link periodontal disease with cardiopathogenesis.(19)

To summarize, it has been shown, in a biologically plausible manner, how the host defense capacity can be altered in diabetes. The bacterial species in the periodontium are the same in diabetic and non-diabetic patients, suggesting that the increased periodontal disease risk in diabetic patients derives from an AGE-generating immunologic disorder (2). In turn, periodontal pathogens cause the up-regulation of cytokines and tissue degrading enzymes, which may also have systemic consequences (20).

Periodontal disease as a risk factor for diabetes
Recognition of subgingival plaque as a microbial biofilm has substantially added to our understanding of the pathophysiology of periodontal disease. In microbial biofilms, bacteria are embedded in an extracellular matrix and adhere to one another and/or to a surface (19). Bacterial adhesion is essential to establish the subgingival biofilm, and the pathogenic potential of this biofilm is determined by the growth and maturation of the bacteria in question. These bacteria constantly expel part of their cell structure components into the crevicular space. The cell wall structures of Gram-negative
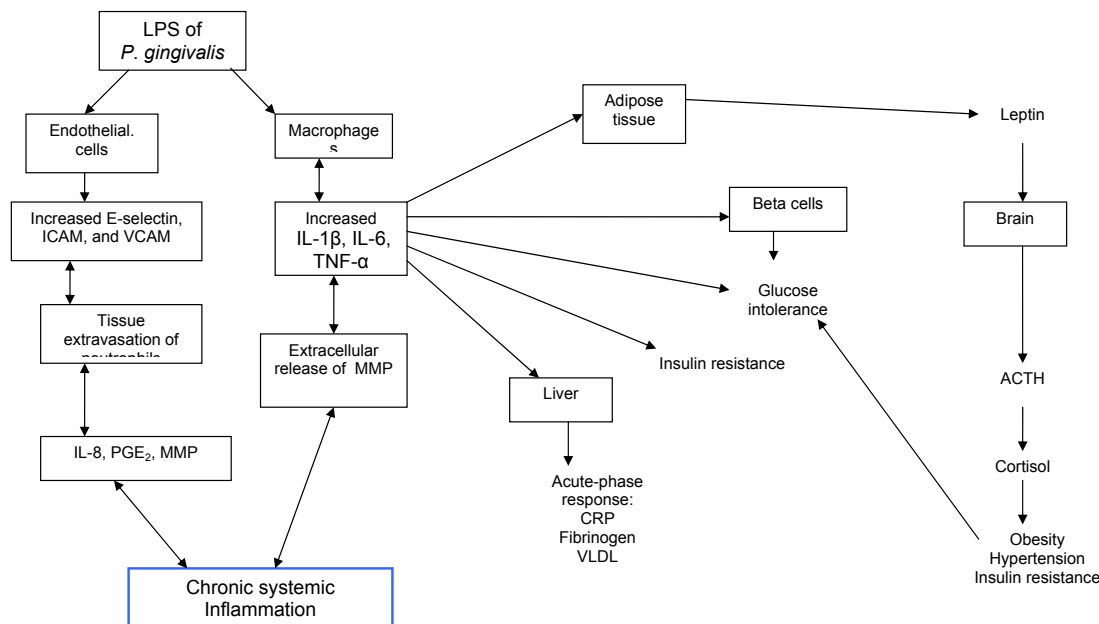
Fig. 2. Model depicting how periodontal infection could contribute to systemic inflammation, impairing sugar balance and diabetes. Several expected tissue reactions may have two-way interactions. LPS = lipopylosaccharide, ICAM = intercellular adhesion molecule, VCAM = vascular cell adhesion molecule, IL-8, IL-1β, -6 = interleukin-8, -1β, -6, PGE2 = prostaglandin E2, MMP = matrix metalloproteinase, CRP = C-reactive protein, VLDL = very low-density lipoprotein, ACTH = adreno-corticotropic hormone. Modified from Grossi.

bacteria are of major importance in the pathogenesis of periodontal disease. These structures are lipopolysaccharides and vesicles with protein content that form part of the normal turnover of the cell wall of these microorganisms and can activate the innate host response. The structure of the biofilm provides highly favorable conditions for the survival of the bacteria that form it, despite an intact host immune system. The virulence factors of these microorganisms are responsible for triggering the sequence of pathogenic events in periodontal disease. Periodontal micro-organisms, in particular Porphyromonas gingivalis (P.g.) and Tannerella forsythia (T.f.), were found to increase MMP-9 in gingival crevicular fluid and serum (20).

According to the pathogenic model proposed in (Fig. 2), periodontal disease might increase the already elevated cytokine levels in diabetic patients and thereby contribute to systemic inflammation.

Excessive formation and accumulation of AGEs in tissues is the most common cause of diabetic complications. The binding of these molecules to neutrophils produces a hyperinflammatory state that amplifies the response to cytokines. These previously activated neutrophils also show a heightened response on making contact with LPS of gram-negative bacteria (e.g., P.g.) in the subgingival biofilm, and the consequent triggering of the inflammatory cascade increases the destruction of periodontal connective tissue and the severity of diabetes (14).

Periodontal treatment and glycemic control in diabetics

Although the relationship between diabetes and periodontal disease is not questioned in the current literature, the effect of the metabolic control of diabetes on periodontal disease and the effect of periodontal treatment on metabolic control in diabetic patients remains controversial. (Table 1) summarizes recent meta-analyses on this issue.

In general, however, periodontal treatment is a high priority in patients for whom periodontal disease may pose a health risk, and this includes diabetic patients. Protocols have been described for the treatment and prevention of infections in diabetic patients, mainly to control acute infections; the treatment of chronic infections appears to be significantly less effective.

Studies of mechanical treatment combined with systemic antibiotic therapy

A number of recent studies evaluated whether the use of systemic antibiotics improved the periodontal prognosis and metabolic control in diabetic patients. Mechanical periodontal therapy with 100 mg doxycycline produced a 0.6% reduction in HbA1c in type-2 diabetic patients.

Tetracyclines and their derivatives appear to play a relevant role in the inhibition of tissue destruction enzymes. Hence, doxycycline appears to be a potent modifier of the response to periodontal treatment in diabetic patients by inhibiting non-enzymatic glycosylation of extracellular proteins, suggesting that it has a similar effect on hemoglobin glycosylation.

Table 1. Characteristics and findings of intervention studies published on the periodontal disease – diabetes axis. Adapted from Janket.(20).

Authors (Publication year)	Study Design	Diabetes type/ Mean age ± SD	Sample Size	Study Duration	Intervention	Outcome Measures	Results
Seppälä & Ainamo (1994)	Longitudinal intervention studies with self as control	IDDM, Ages 35-56 yrs	38, 22	1 year 2 years	1. Non-surgical debridement 2. Oral surgery as needed	1. Periodontal health 2. HbA1c	1. Poor glycemic control→ poor periodontal health. 2. HbA1c did not change.
Aldridge et al. (1995)	Controlled single-blind trials with random assignment	IDDM, Ages 16-40	23 pts with periodontitis, 12 exp, 10 controls	6 weeks	1. Non-surgical debridement	1. Periodontal health 2. HbA1c	1. Periodontal health →significantly improved; 2. HbA1c; Exp 9.8→10.4, Contr 9.7→9.5
Grossi et al. (1997)	RCT with 5 subgroups: 1. H_2O+doxycycline; 2. 0.12% CHX+doxycycline 3. 0.05 povodine iodine +doxycycline 4. 0.12% CHX+ placebo 5. H_2O + placebo	Type 2; Ages 25-65	Total 113 (20-plus in subgroups)	3, 6 and 12 months	1. Non-surgical debridement; Additional CHX or doxycycline (as described in design column)	1. Periodontal health 2. HbA1c	Δ HbA1c% varied by group: 1. 10.5±0.6→9.56 2. 10.4±0.6→9.89 3. 10.3±0.6→9.79 4. 10.7±0.4→10.5 5. 9.2±0.5→8.9
Christgau et al. (1998)	Prospective parallel trial	Type 1 =7; Type 2 =13; Ages (cases)30-66, (controls)30-67	20 diabetic patients; 20 controls	2 weeks 4 months	Phase I, Non-surgical debridemente; Phase II, Non-surgical debridement plus 0.12%CHX irrigation +1% CHX gel placement	1. Periodontal health 2. HbA1c	1. Periodontal health improved over time; 2. HbA1c did not change.
Rodrigues et al (2003)	Clinical trial with two parallel groups	Type 2, non-smokers, duration DM≤ 5 years	30 (15 :SRP+amoxicillin, 15 SRP).	3 months	1. OHI for all ; 2. SRP for all; 3. group 1 received amoxycillin 875 mg b. i. d.	1. Probing pocket depth 2. Attachment loss; 3. HbA1c; 4. Fasting blood glucose (FBG)	1. Probing depth decreased; 2. No change in AL; 3. HbA1c change: group 1:9.5±2.4 to 9.2±1.6%; group 2: 8.8±1.8 to 7.6±1.4%; 4. No changes in FGB.
Faria-Almeida et al. (2006)	Parallel, comparative longitudinal clinical study	Type 2 Ages 35-70 years	10 (diabetic group); 10 (controls, non-diabetic periodontal patients)	3 and 6 months	1. Non-surgical debridement	1. Probing pocket depth 2. Attachment loss; 3. HbA1c; 4. Fasting blood glucose (FBG)	1. Probing depth and AL both decreased. 2. HbA1c change (diabetic group): 7.2 ± 1.3% to 6.5 ± 1.1%(3 months); 5.9 ± 0.6% (6 months). 3. FGB did not change (diabetic group).

Table 2. Suggestions for future research on periodontal disease – diabetes.

Study question	Type of research needed
Prevalence of periodontal disease in diabetic populations.	Clinical and epidemiological studies in wide samples of both type-1 and type-2 diabetic patients.
Periodontal disease and metabolic syndrome.	Clinical and epidemiological studies with adequate samples, probably requiring a multi-center approach.
Effect of periodontal treatment on sugar metabolism.	Clinical intervention studies with randomized controlled trial design to assess different treatment modes.
Periodontal pathogens and diabetes.	Clinical, microbiological, and biochemical studies.
Genetics of periodontal disease and diabetes.	Molecular biological studies to assess the role of genetics in the development of the diseases.

Conclusions

Results of published research in type-1 diabetic patients do not allow definitive conclusions to be drawn on the effects of periodontal treatment on glycemic control. This may be explained by the different etiologies of type 1 and type 2 diabetes and by the strict control maintained during insulin treatment. Thus, researchers have found no differences in HbA1c after periodontal treatment of type-1 diabetic patients. Therefore, studies on the interrelationship between diabetes and periodontal disease should focus on type-2 diabetes, since the two entities are usually found in the same sub-population. The meta-analysis was only able to confirm an improvement in metabolic control by the application of doxycycline gel. We therefore strongly support the call for further research to elucidate this issue before definitive conclusions can be drawn.

Given the interrelationship between diabetes and periodontal disease, it is important to establish a good communication between the specialist responsible for a diabetic patient and the patient's dentist. Although the association between these diseases is now accepted as a reality, the clinical implications need to be adequately investigated. Importantly, the possibility of the simultaneous presence of the two diseases should be borne in mind to ensure their early diagnosis.

In view of the very high prevalence of both diseases and their potentially severe repercussions, the medical specialist should play a leading role in encouraging diabetic patients to visit their dentists regularly to control detrimental factors, such as the sustained presence of bacterial plaque in the periodontal pocket. Likewise, oral health personnel should bear in mind that impaired sugar metabolism and diabetes can affect the outcome and severity of periodontal disease. (Table 2) outlines the types of study required to advance our knowledge and understanding of this issue.

References with links to Crossref - DOI

References

1. Mealey BL, Oates TW; American Academy of Periodontology. Diabetes mellitus and periodontal diseases. J Periodontol. 2006;77:1289-303.
2. Mealey BL. Diabetes and periodontal disease: two sides of a coin. Compend Contin Educ Dent. 2000;21:943-6, 948, 950.
3. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. Ann Periodontol. 1998;3:3-12.
4. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Ann Periodontol. 1998;3:51-61.
5. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. Ann Periodontol. 1998;3:3-12.
6. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4:1-6.
7. Van der Velden U. Purpose and problems of periodontal disease classification. Periodontol 2000. 2005;39:13-21.
8. Baelum V, Lopez R. Defining and classifying periodontitis: need for a paradigm shift? Eur J Oral Sci. 2003;111:2-6.
9. Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: current concepts. J Periodontol. 1992;63:322-31.
10. Liljenberg B, Lindhe J, Berglundh T, Dahlén G, Jonsson R. Some microbiological, histopathological and immunohistochemical characteristics of progressive periodontal disease. J Clin Periodontol. 1994;21:720-7.
11. Offenbacher S. Periodontal diseases: pathogenesis. Ann Periodontol. 1996;1:821-78.
12. Pihlstrom BL. Periodontal risk assessment, diagnosis and treatment planning. Periodontol 2000. 2001;25:37-58.
13. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: recent concepts involving serum lipids. J Periodontol. 2000;71:1375-84.
14. Serrano-Ríos M, Corbatón A. Diabetes mellitus, heart failure and mortality. Med Clin (Barc). 2005;125:182-3.
15. Lalla E, Lamster IB, Schmidt AM. Enhanced interaction of advanced glycation end products with their cellular receptor RAGE: implications for the pathogenesis of accelerated periodontal disease in diabetes. Ann Periodontol. 1998;3:13-9.
16. Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes mellitus and periodontal disease. J Am Dent Assoc. 1990;121:532-6.
17. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. J Periodontol. 1991;62:123-31.
18. Soskolne WA, Klinger A. The relationship between periodontal diseases and diabetes: an overview. Ann Periodontol. 2001;6:91-8.
19. Bascones A, Gamonal J, Gomez M, Silva A, Gonzalez MA. New knowledge of the pathogenesis of periodontal disease. Quintessence Int. 2004;35:706-16.

20. 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.