AAP-Commissioned Review

Diabetes Mellitus and Periodontal Diseases

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Background: The purpose of this review is to provide the reader with practical knowledge concerning the relationship between diabetes mellitus and periodontal diseases. Over 200 articles have been published in the English literature over the past 50 years examining the relationship between these two chronic diseases. Data interpretation is often confounded by varying definitions of diabetes and periodontitis and different clinical criteria applied to prevalence, extent, and severity of periodontal diseases, levels of glycemic control, and complications associated with diabetes.

Methods: This article provides a broad overview of the predominant findings from research published in English over the past 20 years, with reference to certain "classic" articles published prior to that time.

Results: This article describes current diagnostic and classification criteria for diabetes and answers the following questions: 1) Does diabetes affect the risk of periodontitis, and does the level of metabolic control of diabetes have an impact on this relationship? 2) Do periodontal diseases affect the pathophysiology of diabetes mellitus or the metabolic control of diabetes? 3) What are the mechanisms by which these two diseases interrelate? and 4) How do people with diabetes and periodontal disease respond to periodontal treatment?

Conclusions: Diabetes increases the risk of periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. Less clear is the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs. Inflammatory periodontal diseases may increase insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal diseases and diabetes. *J Periodontol 2006;77:1289-1303.*

KEY WORDS

Diabetes mellitus; inflammation; insulin resistance; obesity; periodontal diseases.

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METHODS

The information presented in this review is based on a survey of English language literature primarily over the last 20 years, although certain "classic" articles are referenced from before the 1980s. The literature search was conducted using the National Library of Medicine's Entrez PubMed search engine. The article does not contain an exhaustive article-by-article review of the literature but, instead, provides a broad overview of the predominant findings from research. The article does not seek to analyze statistically any of the data from the reviewed articles, but relies on the original data analysis and author interpretation. Several references are cited from the medical literature and are not meant to be inclusive of all or even a substantial part of the medical literature available on the subject of diabetes mellitus. Diabetes mellitus is a clinically and genetically

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heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids, and proteins.[1] The characteristic feature of diabetes is an abnormal elevation in blood glucose levels. Hyperglycemia is due to a deficiency of insulin secretion caused by pancreatic β-cell dysfunction and/or insulin resistance in liver and muscle.[2] This metabolic dysregulation is often associated with alterations in adipocyte metabolism. Diabetes is a syndrome in which chronic hyperglycemia leads to long-term damage to various organs including the heart, eyes, kidneys, nerves, and vascular system.

DIABETES EPIDEMIOLOGY AND CLASSIFICATION

Diabetes affects ~21 million Americans, including over 9% of the adult population.[3,4] Approximately 6 million of these individuals have the disease but are undiagnosed.[5] The prevalence of diabetes is increasing annually in the United States and varies by age and racial category, with older individuals, Native Americans, Hispanics, and non-Hispanic blacks more commonly having diabetes than younger individuals and non-Hispanic whites. The incidence of diabetes is also increasing annually. In 2002, ~1.3 million new cases of diabetes were diagnosed, an increase of 500,000 new cases per year since 1998, when the incidence was 800,000 cases.[5] The rise in prevalence and incidence of diabetes is directly related to increasing obesity rates in the American population.[5] About 85% to 90% of diabetic cases are type 2 diabetes, whereas type 1 diabetes constitutes 5% to 10% of patients. Gestational diabetes and secondary forms of diabetes associated with other conditions such as pancreatic disease, drug therapies, and endocrine disorders account for the remainder of cases.

The current classification of diabetes is based upon the pathophysiology of each form of the disease.[2] Type 1 diabetes results from cellular mediated autoimmune destruction of pancreatic β-cells, usually leading to total loss of insulin secretion. Markers of autoimmune destruction have been identified and can be used for diagnosis or risk assessment.[2] Type 1 diabetes is usually present in children and adolescents, although some studies demonstrated 15% to 30% of all cases being diagnosed after 30 years of age.[6] In older type 1 patients, the β-cell destruction occurs more slowly than in children, with a less abrupt onset of symptoms. This demonstrates that the pace and extent of cellular destruction can occur at a different rate from patient to patient. The lack of insulin production in patients with type 1 diabetes makes the use of exogenous insulin necessary to sustain life, hence the former name "insulin-dependent diabetes."[2] In the absence of insulin, these patients develop ketoacidosis, a life-threatening condition.

Type 2 diabetes, previously called non–insulin-dependent diabetes, results from insulin resistance, which alters the use of endogenously produced insulin at the target cells.[1,2] Type 2 patients have altered insulin production as well; however, autoimmune destruction of β-cells does not occur as it does in type 1, and patients retain the capacity for some insulin production. Because the type 2 patient still produces insulin, the incidence of ketoacidosis is very low compared to type 1; however, ketoacidosis can occur in association with the stress of another illness such as infection. Type 2 patients can be undiagnosed for many years because the hyperglycemia appears gradually and often without symptoms.[7] In many patients, especially early in the disease process, pancreatic insulin production is actually increased to compensate for insulin resistance. As the condition progresses, pancreatic insulin production may diminish over time due to the prolonged increase in secretory demand caused by the insulin resistance.[8] Insulin secretion becomes insufficient to compensate for insulin resistance. Although type 2 patients do not need insulin treatment to survive, insulin is often taken as part of the medical management of type 2 diabetes.

Most patients with type 2 diabetes are obese or have an increased percentage of body fat distributed predominantly in the abdominal region.[1] The normal body mass index (BMI) is under 25 kg/m^2, whereas a BMI between 25 and 30 kg/m^2 is defined as overweight, and a BMI of over 30 kg/m^2 is defined as obese. Adipose tissue plays an important role in the development of insulin resistance.[9] Elevated circulating levels of free fatty acids (FFA) derived from adipocytes contribute to insulin resistance by inhibiting glucose uptake, glycogen synthesis, and glycolysis and by increasing hepatic glucose production.[10] Insulin resistance often improves with weight reduction and pharmacological treatment but is generally not restored to normal.

Gestational diabetes complicates ~4% of all pregnancies in the Unites States, but the prevalence can range from 1% to 14% of pregnancies, depending on the population studied.[11] Gestational diabetes usually has its onset in the third trimester of pregnancy, and adequate treatment will reduce perinatal morbidity. Most women with gestational diabetes return to a normoglycemic state after parturition; however, a history of gestational diabetes significantly increases the risk of subsequently developing type 2 diabetes. Under normal conditions, insulin secretion is increased by 1.5- to 2.5-fold during pregnancy, reflecting a state of insulin resistance.[12] A woman with a limited β-cell reserve may be incapable of increasing insulin production to compensate for her insulin-resistant state, resulting in hyperglycemia.

Some individuals have glucose levels that do not meet the criteria for diabetes but are too high to be considered normal. Members of this group have a condition called "prediabetes," a term which encompasses both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).[2] These patients are usually normoglycemic but demonstrate elevated blood glucose levels under certain conditions. People whose hyperglycemia is limited to periods of fasting have impaired fasting glucose, whereas those whose hyperglycemia occurs after a glucose load have impaired glucose tolerance. Both impaired fasting glucose and impaired glucose tolerance are strong predictors for future development of type 2 diabetes; furthermore, impaired glucose tolerance is a significant predictor of myocardial infarction and stroke.[13]

DIABETES: DIAGNOSTIC CRITERIA AND EVALUATION OF GLYCEMIC CONTROL

In 1998, the World Health Organization adopted the diagnostic parameters for diabetes established by the American Diabetes Association.[14] Currently, there are three ways to diagnose diabetes.[2] Because a single abnormal laboratory test is not sufficient to establish a diagnosis, any positive laboratory value must be confirmed on a different day: 1) symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (≥11.1 mmol/l). Casual is defined as any time of day without regard to the time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss; 2) fasting plasma glucose ≥126 mg/dl (≥7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours; and 3) 2-hour postload glucose ≥200 mg/dl (≥11.1 mmol/l) during an oral glucose tolerance test. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

The normal fasting plasma glucose level is <100 mg/dl (5.6 mmol/l). Impaired fasting glucose is diagnosed when the fasting plasma glucose level is ≥100 mg/dl but ≤125 mg/dl (between 5.6 and 6.9 mmol/l). Impaired glucose tolerance can only be diagnosed after an oral glucose tolerance test. A normal 2-hour postload glucose level is <140 mg/dl (7.8 mmol/l). Impaired glucose tolerance is diagnosed when the 2-hour postload plasma glucose concentration is ≥140 mg/dl but ≤199 mg/dl (between 7.8 and 11.1 mmol/l) (Table 1).

In a patient with diagnosed diabetes, the hemoglobin A1c test (HbA1c) is used to monitor the patient's overall glycemic control. It is not recommended for diagnosis because there is not a gold standard assay for the HbA1c and because many countries do not have ready access to the test. Glycohemoglobin is formed continuously in erythrocytes as the product of a non-enzymatic reaction between glucose and the hemoglobin protein, which carries oxygen. The binding of glucose to hemoglobin is highly stable; therefore, hemoglobin remains glycated for the life span of the erythrocyte, ~123 ± 23 days.[15] The HbA1c test is used to measure glycohemoglobin levels and provides an estimate of the average blood glucose level over the preceding 30- to 90-day period. Higher average blood glucose levels are reflected in higher HbA1c values[16] (Table 2). The normal HbA1c is <6%[2] (Table 3). HbA1c levels correlate well with the development of diabetic complications and may become established as a test for the diagnosis of diabetes at some time in the future.[17]

Table 1.

2005 American Diabetes Association Criteria for the Diagnosis of Diabetes Mellitus, IGT, and IFG

	Normal	Diabetes	IGT	IFG
Fasting plasma glucose (mg/dl)	<100	≥126		100 to 125
Casual plasma glucose (mg/dl)		≥200 plus symptoms of diabetes		
2-hour PG* (mg/dl)	<140	≥200	140 to 199	

Adapted from reference 2.
* 2-hour postload glucose (PG) using the 2-hour oral glucose tolerance test.

Table 2.

Correlation Between HbA1c Levels and Mean Plasma Glucose Levels

HbA1c (%)	Mean Plasma Glucose (mg/dl)
6	135
7	170
8	205
9	240
10	275
11	310
12	345

The HbA1c test provides an estimate of the average glucose level over the 30 to 90 days preceding the test. It does not account for short-term fluctuations in plasma glucose levels. Adapted from reference 16.

Table 3.

American Diabetes Association Recommendations for HbA1c Levels

HbA1c (%)	Interpretation
<6	Normal value
<7	Treatment goal for patient with diabetes; diet, exercise, and/or medications should control glucose levels well enough to maintain HbA1c values <7%
>8	Physician intervention in diabetes management regimen is recommended to improve glycemic control

Adapted from reference 2.

In the presence of hyperglycemia, other serum proteins beside hemoglobin are also glycated. Measurement of these glycated proteins can be used as an alternative to the HbA1c for assessment of glycemic control over time.[2] For example, albumin is a serum protein with a half-life of 2 to 3 weeks. The fructosamine test measures glycated albumin, and this test reflects glycemic control over a shorter interval (weeks) than the HbA1c test (months). The fructosamine test is sometimes used when an objective measurement that reflects a shorter period of time is needed, for example, during pregnancy, initiation of a new therapy, or a medical illness. It may also be used in instances when the HbA1c test may not be reliable, such as when anemia is present. The normal range for the fructosamine test is between 200 and 300 μmol/l.

EFFECTS OF DIABETES ON THE PERIODONTIUM

Examination of the available data reveals strong evidence that diabetes is a risk factor for gingivitis and periodontitis, and the level of glycemic control appears to be an important determinant in this relationship.[18,19] One must use caution in evaluating the research because studies examined diverse populations, often lacked controls or had small numbers of subjects, defined diabetes and glycemic control in various ways, and used different periodontal parameters to describe the clinical conditions present.

Although some authors have not found a significant association between diabetes and gingival inflammation,[20] in many studies, the prevalence and severity of gingivitis has been demonstrated to be higher in individuals with diabetes. In children with type 1 diabetes, the prevalence of gingivitis was greater than in non-diabetic children with similar plaque levels.[21] Twice as many sites had gingival inflammation in children with diabetes compared to non-diabetic control children with similar plaque levels.[22] Poor metabolic control can increase the severity of gingival inflammation in diabetic children,[23] whereas improvement in glycemic control may be associated with decreased gingival inflammation.[24,25] In adults with type 1 diabetes, the overall degree of gingival inflammation was similar between diabetic subjects as a whole and non-diabetic control subjects with similar plaque accumulation.[26] However, when diabetic patients in this study were stratified according to their level of glycemic control, significantly greater gingival bleeding was seen in poorly controlled diabetic patients than in either well-controlled diabetic subjects or non-diabetic controls. The number of bleeding sites decreased as glycemic control improved.[26] Greater gingival inflammation was also seen in adults with type 2 diabetes than in non-diabetic controls, with the highest level of inflammation in subjects with poor glycemic control.[27] A longitudinal experimental gingivitis study[28] showed more rapid and pronounced development of gingival inflammation in relatively well-controlled adult type 1 diabetic subjects than in non-diabetic controls, despite similar levels of plaque accumulation and similar bacterial composition of plaque, suggesting a hyperinflammatory gingival response in diabetes. These studies suggest that the presence of diabetes is often, but not always, associated with increased gingival inflammation. In addition, the level of glycemic control may play a role in the gingival response to bacterial plaque in people with diabetes.

The preponderance of evidence suggests that diabetes also increases the risk of periodontitis. A thorough meta-analysis concluded that the majority of studies demonstrate a more severe periodontal condition in diabetic adults than in adults without diabetes.[18] These studies included over 3,500 diabetic adults and clearly demonstrated a significant association between periodontitis and diabetes.

Diabetes has been associated with an increased risk of periodontitis even at a young age. In a group of 263 type 1 diabetic patients compared to 59 non-diabetic siblings and 149 non-diabetic unrelated controls, periodontitis was not seen among any of the subjects under the age of 12.[21] However, between 13 and 18 years of age, 13.6% of the diabetic individuals had periodontitis, and the prevalence increased to 39% among those aged 19 to 32 years. By comparison, the prevalence in non-diabetic control subjects was <3%.

Epidemiologic studies in diabetic adults have often shown an increase in extent and severity of periodontitis.[29-32] In the Pima Indians of Arizona, a population with the highest occurrence of type 2 diabetes in the world, the prevalence and severity of attachment loss and bone loss was greater among diabetic subjects

than among non-diabetic control subjects in all age groups.[30,31] In a multivariate risk analysis, diabetic subjects had 2.8- to 3.4-fold increased odds of having periodontitis compared to non-diabetic subjects after adjusting for the effects of confounding variables such as age, gender, and oral hygiene measures. Smaller cross-sectional and case-control studies generally confirmed a greater risk of attachment loss and bone loss in diabetic adults.[27,33-37]

Longitudinal research has also shown an increased risk of progressive periodontal destruction in people with diabetes. In a study of the Pima Indians, the incidence and prevalence of periodontal disease were determined in 2,273 subjects 15 years of age or older.[38] The prevalence of periodontitis was 60% in subjects with diabetes and 36% in those without diabetes. The incidence was determined in a subset of 701 subjects 15 to 54 years old, with little or no evidence of periodontitis at baseline. Following these subjects for an average of over 2.5 years, the incidence of periodontitis was 2.6-fold higher in diabetic subjects than in non-diabetic patients.[38] In another 2-year longitudinal study, subjects with type 2 diabetes had a fourfold increased risk of progressive alveolar bone loss compared to non-diabetic subjects.[39]

The relationship between metabolic control of diabetes and periodontal disease is difficult to define conclusively.[19] Research suggests that this association is similar to the association between glycemic control and the classic complications of diabetes such as retinopathy and nephropathy; namely, there is significant heterogeneity in the diabetic population. Thus, although poor control of diabetes clearly increases the risk of diabetic complications, there are many poorly controlled diabetic individuals without major complications.[40,41] Conversely, good control of diabetes greatly decreases the risk of diabetic complications, but there are people with well-controlled diabetes who suffer major diabetic complications nonetheless. In a similar fashion, the body of evidence suggests that some diabetic patients with poor glycemic control develop extensive periodontal destruction, whereas others do not. On the other hand, many well-controlled diabetic patients have excellent periodontal health, but others develop periodontitis.

In a large epidemiologic study in the United States, adults with poorly controlled diabetes had a 2.9-fold increased risk of having periodontitis compared to non-diabetic adult subjects; conversely, well-controlled diabetic subjects had no significant increase in the risk of periodontitis.[42] In a cross-sectional study of patients who had type 1 diabetes for a mean duration of over 16 years, subjects with poor glycemic control had more interproximal attachment loss and bone loss than well-controlled subjects.[43] Similar results have been found in other studies in which the percentage of deep periodontal pockets and the prevalence of severe attachment loss increased as the glycemic control worsened.[44,45] Type 1 diabetic subjects with poor metabolic control over the preceding 2 to 5 years had a significantly greater prevalence of deep probing depths and advanced attachment loss than subjects with good glycemic control.[32] Likewise, poorly controlled diabetic subjects had significantly greater bone loss and attachment loss than well-controlled diabetic subjects over a 2- to 3-year follow-up period.[46,47] In longitudinal Pima Indian studies, poor glycemic control of type 2 diabetes was associated with an 11-fold increased risk of progressive bone loss compared to non-diabetic controls, whereas well-controlled diabetic subjects had no significant increase in risk.[39] Thus, metabolic control of diabetes may be an important variable in the onset and progression of periodontal disease.

Other studies have given only marginal support to the relationship between glycemic control and the extent or severity of periodontitis, whereas some have shown no relationship. In a study of 118 diabetic subjects and 115 healthy controls, deeper probing depths and greater gingival inflammation, bleeding on probing, and attachment loss were seen in those with diabetes; however, the level of glycemic control among the diabetic subjects did not correlate to the periodontal parameters measured.[33] Another study found a trend toward an increasing prevalence of alveolar bone loss as glycemic control worsened.[36] The mean percentage of sites with >15% bone loss went from 28% in well-controlled type 1 diabetic subjects to 44% in poorly controlled subjects. However, the difference did not reach statistical significance, perhaps due to the small size of the study population. Some studies found no evidence of a relationship between glycemic control and periodontal status.[48,49]

MECHANISMS BY WHICH DIABETES MAY INFLUENCE THE PERIODONTIUM

To validate a relationship between diabetes and periodontal diseases, biologically plausible mechanisms must be evident to explain the pathobiology of the interactions. A large evidence base is available to describe these potential mechanisms, many of which are strikingly similar to those associated with the classic diabetic complications, including retinopathy, nephropathy, neuropathy, macrovascular diseases, and altered wound healing. The strength of the evidence has led some to suggest that periodontitis should be listed among the ''classic'' complications of diabetes.[50]

Although bacteria are necessary for periodontal diseases to occur, there are few differences in the subgingival microflora between diabetic and non-diabetic patients with periodontitis, although some early

studies reported higher proportions of *Capnocytophaga* species in those with diabetes.[51] Most culture studies show that the bacterial microflora at periodontally diseased sites in diabetic subjects is similar to the microflora at similarly diseased sites in non-diabetic subjects.[49,52] Likewise, no significant differences in the subgingival microflora were seen between type 1 diabetic children and their non-diabetic siblings.[20] These studies involved the use of culture techniques to identify bacteria; it is unknown whether newer identification techniques will confirm the similarity in the subgingival bacterial microflora between people with and without diabetes. However, the apparent lack of significant differences in potential pathogens suggests that alterations in the host immunoinflammatory response may have a major influence on the increased prevalence and severity of periodontal destruction seen in diabetes.

The function of immune cells, including neutrophils, monocytes, and macrophages, is altered in diabetes.[51] Neutrophil adherence, chemotaxis, and phagocytosis are often impaired, which may inhibit bacterial killing in the periodontal pocket and significantly increase periodontal destruction.[53,54] Although the function of neutrophils is often diminished in diabetes, the monocyte/macrophage cell line may exhibit upregulation in response to bacterial antigens. The hyperresponsiveness of monocytes/macrophages results in significantly increased production of proinflammatory cytokines and mediators.[55-57] Peripheral blood monocytes from diabetic subjects produce elevated levels of tumor necrosis factor-alpha (TNF-α) in response to antigens from *Porphyromonas gingivalis* compared to monocytes from non-diabetic control subjects.[55] These findings are supported in a diabetic animal model in which *P. gingivalis* inoculation produced a prolonged inflammatory response.[56] Interestingly, this prolonged inflammatory response was found to be independent of the pathogenic components of the inoculated organisms and directly related to TNF stimulation. Because gingival crevicular fluid is a serum transudate, elevated serum levels of inflammatory mediators associated with diabetes are reflected in similarly increased levels of these mediators in gingival crevicular fluid.[57] The level of inflammatory cytokines in the gingival crevicular fluid is also related to glycemic control of diabetes. In a study of diabetic subjects with periodontitis, those with HbA1c levels over 8% had crevicular fluid levels of interleukin-1 beta (IL-1β) almost twice as high as subjects with HbA1c levels <8%.[58] The net effect of these host defense alterations in diabetes is an increase in periodontal inflammation, attachment loss, and bone loss.

The increased levels of periodontal attachment and bone loss seen in diabetic patients may be associated with the alterations in connective tissue metabolism that uncouple the resorptive and formative responses. Impaired osseous healing and bone turnover in association with hyperglycemia have been demonstrated in a number of studies.[59-63] The effects of a hyperglycemic state include inhibition of osteoblastic cell proliferation and collagen production that result in reduced bone formation and diminished mechanical properties of the newly formed bone.[64-67] Interestingly, using a murine model, the reduced expression of two genetic markers of osteoblastic differentiation, Cbfa1 and Dlx5, found in response to hyperglycemia were reversed with insulin treatment controlling the hyperglycemia.[66]

There is additional evidence emerging that decreases in matrix-producing cells critical to maintaining the periodontium, including fibroblasts and osteoblasts, occur due to an increased rate of apoptosis in a hyperglycemic state in response to *P. gingivalis* infection.[68-70] Together, the diminished levels of proliferation and differentiation and increased levels of cell death provide a compelling argument for the greater propensity of diabetic patients to have more severe periodontal attachment loss due to inadequacies in the formative aspects of connective tissue metabolism relative to the degradation and remodeling of tissues of the attachment apparatus.

Increased plasma glucose levels are also reflected in elevated gingival crevicular fluid glucose levels in diabetic individuals.[71] Because the periodontal pocket is a site of persistent bacterial wounding, an intact wound-healing response is critical to maintain tissue health. High glucose levels in the gingival crevicular fluid may directly hinder the wound-healing capacity of fibroblasts in the periodontium by inhibiting attachment and spreading of these cells that are critical to wound healing and normal tissue turnover.[72]

Microvascular changes are a hallmark of many diabetic complications.[73] The structural changes that characterize diabetic angiopathy include abnormal growth and impaired regeneration of vessels. The changes seen in the microvasculature of the retina, glomerulus, and other end organs in people with diabetic complications also occur in the periodontium.[74,75] In individuals with sustained hyperglycemia, proteins become irreversibly glycated to form advanced glycation end products (AGEs).[76] These stable carbohydrate-containing proteins have multiple effects on cell-to-cell and cell-to-matrix interactions and are commonly thought to be a major link between the various diabetic complications. The formation of AGEs also occurs in the periodontium, and higher levels of periodontal AGE accumulation are found in those with diabetes than in non-diabetic subjects.[77] AGEs often form on collagen, increasing collagen cross-linking and resulting in the formation

of highly stable collagen macromolecules. These molecules accumulate in tissues due to their resistance to normal enzymatic degradation and tissue turnover.[76] AGE-modified collagen accumulates in the walls of larger blood vessels, thickening the vessel wall and narrowing the lumen. In addition, AGE-modified vascular collagen has an affinity for low-density lipoprotein (LDL) and causes the accumulation of LDL in the vessel wall, contributing to atherosclerotic changes characteristic of macrovascular complications of diabetes.[78] The basement membranes of endothelial cells also accumulate AGE-modified collagen macromolecules, which can result in increased basement membrane thickness in the microvasculature, altering normal homeostatic transport across the membrane.[78] This increased basement membrane thickness is seen in the blood vessels of the periodontium in people with diabetes.[74] AGE formation is also associated with increased production of vascular endothelial growth factor (VEGF), a multifunctional cytokine that induces neovascularization and plays a major role in microvascular complications of diabetes.[79,80] Elevated VEGF has been detected in serum of diabetic individuals and in all major tissues affected by diabetic vasculopathies. A recent study found elevated VEGF expression in the gingival tissues of diabetic subjects compared to non-diabetic controls, again demonstrating the similarities between the periodontium and other end organs affected by diabetes.[81]

AGE-collagen levels have been well correlated with duration of diabetes, diabetic complications, and glycemic control.[82] Furthermore, improved glycemic control has been associated with reduced AGE-collagen formation.[83,84] Mechanistically, AGE–bone collagen may influence cellular, structural, and functional characteristics leading to alterations in bone metabolism.[85-87] Altered levels of glycation in bone collagen appear to affect bone turnover, such that bone formation is reduced with elevated levels of AGE collagen.[88] This effect has been associated with altered osteoblastic differentiation and extracellular matrix production.[89,90]

The effects of AGE-collagen are not as clear regarding bone resorption. Although several studies documented increased levels of osteoclast numbers, resorptive markers, and bone resorption,[91-93] there are a number of studies that suggest decreased bone resorption may occur.[94-96] As such, the role of AGEs on the resorptive aspects of bone metabolism are likely most relevant to the inflammatory response.

AGEs activate a receptor known as "receptor for AGEs" (RAGE) found on the surface of smooth muscle cells, endothelial cells, neurons, and monocytes/macrophages.[97] This receptor is found in the periodontium, and a 50% increase in mRNA for RAGE was identified in the gingival tissues of type 2 diabetic subjects compared to non-diabetic controls.[77,98] Hyperglycemia results in increased RAGE expression and AGE-RAGE interaction on the endothelium, causing an increase in vascular permeability and thrombus formation.[73,97] The AGE-RAGE interaction on monocytes increases cellular oxidant stress and activates the transcription factor nuclear factor-kappa B (NF-κB), which alters the phenotype of the monocyte/macrophage and results in the increased production of proinflammatory cytokines such as IL-1β and TNF-α.[78,97] This increased production of proinflammatory cytokines is critical to the chronic inflammatory process in the formation of atheromatous lesions in the larger blood vessels.[99] Increased oxidant stress has also been demonstrated in the gingiva of diabetic subjects in association with an increased accumulation of AGEs.[77] It is this interaction between the receptor RAGE and AGEs in periodontal tissues that is thought to explain, in part, the marked elevation in gingival crevicular fluid levels of IL-1β, TNF-α, and prostaglandin E_2 (PGE_2) seen in diabetic subjects compared to non-diabetic individuals.[58] These proinflammatory cytokines contribute to the pathogenesis of periodontal diseases and probably play a major role in patients with diabetes, especially when glycemic control is poor. In diabetic animal models, blocking the receptor RAGE decreases TNF-α, IL-6, and matrix metalloproteinase (MMP) levels in the gingiva, diminishes AGE accumulation in periodontal tissues, and decreases alveolar bone loss in response to *P. gingivalis*.[100]

Changes in collagen synthesis, maturation, and homeostatic turnover are common in diabetes. These changes can contribute to the pathogenesis of periodontal diseases and to alterations in wound healing because collagen is the major structural protein in the periodontium. Human gingival fibroblasts produce decreased amounts of collagen and glycosaminoglycans in high-glucose environments.[101] Diabetic animals exhibit a decreased rate of collagen production that can be restored by the administration of insulin to normalize plasma glucose levels.[102] In addition to decreased synthesis, newly formed collagen is susceptible to degradation by MMPs such as collagenase, which are elevated in diabetic tissues, including the periodontium.[103,104] In diabetes, a greater proportion of tissue collagenase is in an active form compared to non-diabetic individuals, in whom a greater proportion is in latent form.[104] In contrast to the effects that elevated MMPs have on newly synthesized collagen, existing collagen becomes highly cross-linked in the presence of AGEs, decreasing its solubility.[76] The result of these changes in collagen metabolism is an alteration in normal homeostatic collagen turnover in which recently synthesized collagen is rapidly

degraded by elevated levels of active MMPs, whereas highly cross-linked AGE-modified collagen macromolecules accumulate in the tissues. This change in homeostasis may alter wound healing responses to chronic microbial wounding of the periodontium.

EFFECTS OF PERIODONTAL DISEASES ON THE DIABETIC STATE

Periodontal diseases can have a significant impact on the metabolic state in diabetes. The presence of periodontitis increases the risk of worsening of glycemic control over time. For example, in a 2-year longitudinal trial, diabetic subjects with severe periodontitis at baseline had a six-fold increased risk of worsening of glycemic control over time compared to diabetic subjects without periodontitis.[105] Periodontitis may also be associated with an increased risk of other diabetic complications, as seen in a longitudinal case-control study in which 82% of diabetic patients with severe periodontitis experienced the onset of one or more major cardiovascular, cerebrovascular, or peripheral vascular events compared to only 21% of diabetic subjects without periodontitis.[106] Because cardiovascular diseases are so widely prevalent in people with diabetes, a recent longitudinal trial examined the effect of periodontal disease on overall mortality and cardiovascular disease–related mortality in more than 600 subjects with type 2 diabetes.[107] In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than in subjects with no periodontitis or mild periodontitis, and the mortality rate from diabetic nephropathy was 8.5 times higher in the severe periodontitis group after accounting for other known risk factors. The overall mortality rate from cardio-renal disease was 3.5 times higher in subjects with severe periodontitis.

Intervention trials have been performed to assess the potential effects of periodontal therapy on glycemic control in people with diabetes. The first such study, a case series published in 1960, showed that type 1 diabetic patients with periodontitis had a reduction in required insulin doses following scaling and root planing, localized gingivectomy, and selected tooth extraction combined with systemic procaine penicillin G and streptomycin.[108] In more recent times, treatment has usually consisted of scaling and root planing either alone or in combination with adjunctive systemic tetracycline antibiotics. Tetracyclines decrease the production of MMPs such as collagenase and are a logical choice for study because collagenase production is often elevated in diabetic patients.[109]

Several studies of type 1 and type 2 diabetic subjects with severe periodontitis have shown improvements in glycemic control following scaling and root planing combined with systemic doxycycline therapy.[110-112] In these studies, periodontal treatment was associated with a reduction in HbA1c levels of ~10% between pretreatment baseline values and 2- to 3-month post-treatment values. Another study in older, poorly controlled type 2 diabetic subjects who received scaling and root planing plus adjunctive doxycycline showed a significant improvement in periodontal health but only a non-significant reduction in HbA1c values.[113] Some studies in which patients received scaling and root planing without adjunctive systemic antibiotics likewise showed improved periodontal health but no significant change in glycemic control.[114,115] Conversely, other studies showed significant improvement in glycemic control when periodontal therapy consisted of scaling and root planing alone.[116,117] One study even showed better improvement in glycemic control in a diabetic group treated with scaling and root planing alone compared to diabetic subjects treated with scaling and root planing plus systemic amoxicillin/clavulanic acid.[118]

The effect of periodontal therapy on glycemic control is often mirrored by changes in clinical parameters of periodontal inflammation. For example, in a study of well-controlled type 2 diabetic patients with gingivitis or mild periodontitis, periodontal treatment was limited to scaling and root planing without systemic antibiotics.[117] A control group of diabetic subjects with a similar periodontal status received no treatment. Three months after therapy, the treated subjects had a 50% reduction in the prevalence of gingival bleeding, from 55% of sites at baseline to 24% of sites post-treatment. These same subjects had a significant reduction in mean HbA1c from 7.3% to 6.5%. As expected, the untreated control group had no change in gingival bleeding 3 months after baseline (51% of sites at baseline; 52% post-treatment), nor did they have any improvement in HbA1c (baseline, 7.0%; follow-up, 7.3%). Thus, significant changes in glycemic control may accompany clinically evident improvement in gingival inflammation following periodontal therapy.

These conflicting data are difficult to interpret, especially given the wide range of medical treatment regimens used by study populations, which may confound changes related to resolution of periodontal inflammation.[119] In most studies, there is significant variation in glycemic control changes of individual subjects after periodontal therapy. For example, responses can range from major reductions in HbA1c values of 1 to 2 absolute percentage points or more, whereas in other subjects receiving the same therapy, HbA1c values may change little or may even worsen.[116] A recent meta-analysis of 10 intervention trials included 456 patients.[119] After periodontal therapy, the weighted average decrease in absolute HbA1c values was ~0.4%, but this was not found to

be statistically significant. The addition of adjunctive systemic antibiotics to the mechanical therapy regimen resulted in an average absolute reduction of 0.7%. Again, this reduction did not achieve a level of statistical significance. The authors of this meta-analysis pointed out numerous problems with existing studies including inadequate sample sizes, mixing of subjects with type 1 and type 2 diabetes, and confounding effects of smoking, body mass index, and medications, among others. Further studies are required to determine whether periodontal therapy provides a significant benefit on glycemic control.

MECHANISMS BY WHICH PERIODONTAL DISEASES MAY INFLUENCE DIABETES

Periodontal diseases may induce or perpetuate an elevated systemic chronic inflammatory state.[120] Acute bacterial and viral infections are known to increase insulin resistance in people without diabetes, a condition which often persists for weeks to months after clinical recovery from the illness.[121,122] Such illnesses and resultant increases in insulin resistance in people with diabetes greatly aggravate glycemic control. Chronic Gram-negative periodontal infections may also result in increased insulin resistance and poor glycemic control.[123] Treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control. The previously discussed intervention studies that showed improved glycemic control following periodontal therapy support such a hypothesis.

Studies suggest that periodontitis patients, particularly those colonized by Gram-negative organisms such as *P. gingivalis, Tannerella forsythensis*, and *Prevotella intermedia*, have significantly higher serum markers of inflammation such as C-reactive protein (CRP), IL-6, and fibrinogen than subjects without periodontitis.[124-126] Systemic dissemination of these organisms or their products may induce a bacteremia or endotoxemia, inducing an elevated inflammatory state and stimulating increased levels of serum inflammatory markers. In one study, the simple act of chewing caused systemic endotoxemia in 40% of subjects with periodontitis compared to only 12% of periodontally healthy subjects; additionally, the concentration of endotoxin in the bloodstream was five-fold higher in those with periodontitis.[127] Periodontal treatment not only reduces clinically evident inflammation, but may also result in decreased serum levels of IL-6 and CRP.[128] This evidence suggests that periodontal diseases have systemic effects that extend beyond the local periodontal environment.

The potential impact of elevated systemic proinflammatory mediators in subjects with diabetes is tremendous. Systemic inflammation is significantly elevated in the presence of obesity, insulin resistance, hyperglycemia, and diabetes.[1] High serum levels of the acute-phase reactants CRP and fibrinogen are seen in people with insulin resistance and obesity.[9,129] Insulin resistance and obesity are recognized as chronic inflammatory states and share many of the pathophysiologic features of atherosclerosis.[9,99] Obesity, atherosclerosis, and insulin resistance are strongly linked to the actions of the proinflammatory cytokines IL-6 and TNF-α and their resultant stimulation of acute phase reactant production in the liver.[130] The hallmark of type 2 diabetes is an increase in insulin resistance, which is also strongly linked to obesity.[7]

Obesity alters the normal metabolic and endocrine function of adipose tissue, resulting in increased production of fatty acids, hormones, cytokines, and acute phase reactants.[131] Adipose tissue has a major endocrine function, producing a wide array of hormones commonly called "adipokines."[132] Changes in body-fat content result in alterations of adipokine production and function. These hormones, including leptin, resistin, and adiponectin, among others, participate in regulation of appetite, energy use, insulin sensitivity, blood pressure, angiogenesis, and immune function.[132] An increased body mass index is associated with an increase in the number and size of adipocytes, which are cells with high metabolic activity that produce large quantities of TNF-α and IL-6. In fact, adipose tissue produces about one-third of the total circulating serum level of IL-6.[133] Although the exact physiologic pathways have not been fully delineated, obesity may increase insulin resistance by causing elevated production of TNF-α and IL-6 and decreased production of adiponectin.[9,134] TNF-α can induce insulin resistance at the receptor level by preventing autophosphorylation of the insulin receptor and suppressing second messenger signaling through the inhibition of the enzyme tyrosine kinase.[131] Infusion of TNF-α in healthy humans directly induces insulin resistance in skeletal muscle and reduces glucose uptake and use.[135] Blocking TNF-α with pharmacologic agents has been shown to reduce serum insulin levels and improve insulin sensitivity in some subjects[136] but not in others.[137] Adiponectin antagonizes many of the effects of TNF-α and improves insulin sensitivity.[138] As body mass increases, adiponectin production decreases; thus, obesity results in elevated TNF-α levels and decreased adiponectic levels, both of which result in insulin resistance.[138] IL-6 stimulates TNF-α production; therefore, increased production of IL-6 from adipocytes in obese individuals causes elevated TNF-α production, which may further exacerbate insulin resistance. The increased production of TNF-α and IL-6 also stimulates greater hepatic CRP production, which may also increase insulin resistance.[9,139]

Multiple mechanisms are involved in regulation of insulin sensitivity and resistance, including

adipokines, genetic factors, environmental stresses, and inflammatory mediators. As an inflammatory condition, periodontal diseases may also play a role in this process. Elevated circulating levels of several proinflammatory cytokines have been found in individuals with periodontitis.[124-126] Obesity has been associated with an increased risk of periodontal disease.[140-142] Compared to subjects with a BMI ≤20 kg/m^2, the risk of periodontitis increased three-fold in Japanese subjects with a BMI between 25 and 30 kg/m^2 and over eight-fold in subjects with a BMI ≥30 kg/m.^{2} The relationship between obesity and periodontitis may be mediated by insulin resistance.[140] A recent examination of Third National Health and Nutrition Examination Survey (NHANES III) data for non-diabetic subjects revealed a positive association between BMI and clinical attachment loss.[140] Interestingly, overweight individuals (BMI ≥27) with elevated insulin resistance had a significant odds ratio of 1.48 for severe periodontal disease compared to overweight individuals without insulin resistance. Subjects in the highest quartile of body mass (BMI ≥30.8 kg/m^2) also showed significantly elevated serum levels of TNF-α and soluble TNF-α receptors compared to those in the lowest quartile of body mass, with a BMI <24.6 kg/m.^{2} These data suggest that increased BMI is associated with both systemic inflammation and periodontal disease.

In addition to the elevated systemic inflammatory state associated with obesity and insulin resistance, people with diabetes often have a shift in monocyte/macrophage phenotype, which results in the overproduction of these same inflammatory cytokines in response to periodontal pathogens.[55] Diabetic patients who also have periodontitis may present with an even greater systemic inflammatory condition with elevated serum levels of IL-6, TNF-α, and CRP, which can worsen insulin resistance and thereby aggravate glycemic control. This could explain why periodontitis increases the risk of poor glycemic control in patients with type 2 diabetes.[105] It may also explain why improvement in glycemic control has followed periodontal therapy in some studies of diabetic subjects.[110-112,116,117] In a small study of 13 type 2 diabetic subjects with periodontitis, periodontal treatment consisting of mechanical debridement and local delivery of minocycline resulted in a significant reduction in serum TNF-α levels that was accompanied by a significant reduction in mean HbA1c levels from 8.0% to 7.1%.[143] Reductions in HbA1c values were strongly correlated with the reductions in serum TNF-α levels across the patient population. Thus, periodontal treatment may reduce inflammation locally and also decrease serum levels of the inflammatory mediators that cause insulin resistance, thereby positively affecting glycemic control.

EFFECTS OF DIABETES ON THE RESPONSE TO PERIODONTAL THERAPY

Only limited evidence is available to evaluate the comparative response to periodontal therapy in diabetic and non-diabetic patients with periodontitis. In well-controlled diabetic subjects, the clinical and microbiologic response to scaling and root planing appears similar to that in non-diabetic individuals.[115,144] Although many diabetic patients show improvement in clinical parameters of disease immediately after therapy, patients with poorer glycemic control may have a more rapid recurrence of deep pockets and a less favorable long-term response.[145] In one longitudinal study, 20 diabetic and 20 non-diabetic subjects received scaling and root planing, modified Widman flap surgery at sites with residual probing depths ≥5 mm, and regular maintenance therapy.[146] Five years after the baseline examination, diabetic and non-diabetic subjects had a similar percentage of sites demonstrating gain, loss, or no change in clinical attachment. The HbA1c values revealed that most of the diabetic subjects in this study were well controlled or moderately controlled at baseline.[146] Further longitudinal studies of various periodontal treatment modalities are needed to determine the healing response in individuals with diabetes compared to individuals without diabetes.

CONCLUSIONS

Periodontal diseases and diabetes mellitus are closely associated and are highly prevalent chronic diseases with many similarities in pathobiology. Related antecedent conditions including obesity and insulin resistance may play an important role in this relationship. Inflammation is a critical player in the association, and its importance is just now coming to light. Diabetes clearly increases the risk of periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. Less clear is the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs. It is possible that periodontal diseases may serve as initiators or propagators of insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal diseases and diabetes.

REFERENCES

1. Mealey BL, Ocampo GL. Diabetes mellitus. *Periodontol 2000* 2006; in press.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Position statement. *Diabetes Care* 2005;29(Suppl. 1):S37-S42.
3. Mokdad AH, Ford ES, Bowman BA, et al. The continuing increase of diabetes in the U.S. *Diabetes Care* 2001;24:412.

4. National Center for Health Statistics. United States, 2005. Chartbook on Trends in the Health of Americans, Table 55. Hyattsville, MD: National Center for Health Statistics; 2005.
5. Centers for Disease Control and Prevention. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/estimates.htm. Accessed December 27, 2005.
6. Laakso M, Pyorala K. Age at onset and type of diabetes. *Diabetes Care* 1985;8:114-117.
7. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-194.
8. Rhodes CJ. Type 2 diabetes – A matter of β-cell life and death? *Science* 2005;307:380-384.
9. Festa A, D'Agostino R Jr., Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000;102:42-47.
10. Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* 2000;11:351-356.
11. Saydah SH, Chandra A, Eberhardt MS. Pregnancy experience among women with and without gestational diabetes in the U.S. 1995 national survey of family growth. *Diabetes Care* 2005;28:1035-1040.
12. Kirwan JP, Varastehpour A, Jing M, et al. Reversal of insulin resistance postpartum is linked to enhanced skeletal muscle insulin signaling. *J Clin Endocrinol Metab* 2004;89:4678-4684.
13. DECODE Study Group. Glucose tolerance and mortality: Comparison of WHO and American Diabetes Association diagnostic criteria. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis of diagnostic criteria in Europe. *Lancet* 1999;354:617-621.
14. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.
15. Virtue MA, Furne JK, Nuttall FQ, Levitt MD. Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. *Diabetes Care* 2004;27:931-935.
16. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c: Analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25:275-278.
17. Davidson MB, Schriger DL, Peters AL, Lorber B. Glycosylated hemoglobin as a diagnostic test for type 2 diabetes mellitus. *JAMA* 2000;283:606-607.
18. Papapanou PN. Periodontal diseases: Epidemiology. *Ann Periodontol* 1996;1:1-36.
19. Mealey BL, Moritz AJ. Hormonal influences: Effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. *Periodontol 2000* 2003;32:59-81.
20. Sbordone L, Ramaglia L, Barone A, Ciaglia RN, Iacono VJ. Periodontal status and subgingival microbiota of insulin-dependent juvenile diabetics: A 3-year longitudinal study. *J Periodontol* 1998;69:120-128.
21. Cianciola L, Park B, Bruck E, Mosovich L, Genco R. Prevalence of periodontal disease in insulin-dependent diabetes mellitus (juvenile diabetes). *J Am Dent Assoc* 1982;104:653-660.
22. de Pommereau V, Dargent-Pare C, Robert JJ, Brion M. Periodontal status in insulin-dependent diabetic adolescents. *J Clin Periodontol* 1992;19:628-632.
23. Gusberti F, Syed S, Bacon G, Grossman N, Loesche W. Puberty gingivitis in insulin-dependent diabetic children. I. Cross-sectional observations. *J Periodontol* 1983;54:714-720.
24. Sastrowijoto S, van der Velden U, van Steenbergen T, et al. Improved metabolic control, clinical periodontal status, and subgingival microbiology in insulin-dependent diabetes mellitus. A prospective study. *J Clin Periodontol* 1990;17:233-242.
25. Karjalainen K, Knuuttila M. The onset of diabetes and poor metabolic control increases gingival bleeding in children and adolescents with insulin-dependent diabetes mellitus. *J Clin Periodontol* 1996;23:1060-1067.
26. Ervasti T, Knuuttila M, Pohjamo L, Haukipuro K. Relation between control of diabetes and gingival bleeding. *J Periodontol* 1985;56:154-157.
27. Cutler CW, Machen RL, Jotwani R, Iacopino AM. Heightened gingival inflammation and attachment loss in type 2 diabetics with hyperlipidemia. *J Periodontol* 1999;70:1313-1321.
28. Salvi GE, Kandylaki M, Troendle A, Persson GR, Lang NP. Experimental gingivitis in type 1 diabetics: A controlled clinical and microbiological study. *J Clin Periodontol* 2005;32:310-316.
29. Bacic M, Plancak D, Granic M. CPITN assessment of periodontal status in diabetic patients. *J Periodontol* 1988;59:816-822.
30. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin dependent diabetes mellitus. *J Periodontol* 1991;62:123-131.
31. Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes mellitus and periodontal disease. *J Am Dent Assoc* 1990;121:532-536.
32. Tervonen T, Oliver R. Long-term control of diabetes mellitus and periodontitis. *J Clin Periodontol* 1993;20:431-435.
33. Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR. Periodontal status of diabetic and nondiabetic men: Effects of smoking, glycemic control, and socioeconomic factors. *J Periodontol* 1996;67:1185-1192.
34. Collin HL, Uusitupa M, Niskanen L, et al. Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus. *J Periodontol* 1998;69:962-966.
35. Moore PA, Weyant RJ, Mongelluzzo MB, et al. Type 1 diabetes mellitus and oral health: Assessment of periodontal disease. *J Periodontol* 1999;70:409-417.
36. Tervonen T, Karjalainen K, Knuuttila M, Huumonen S. Alveolar bone loss in type 1 diabetic subjects. *J Clin Periodontol* 2000;27:567-571.
37. Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. Diabetes and periodontal disease: A case-control study. *J Periodontol* 2005;76:418-425.
38. Nelson RG, Shlossman M, Budding LM, et al. Periodontal disease and NIDDM in Pima Indians. *Diabetes Care* 1990;13:836-840.
39. Taylor GW, Burt BA, Becker MP, et al. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. *J Periodontol* 1998;69:76-83.

40. Diabetes Control and Complications Trial 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;329:977-986.
41. U.K. Prospective Diabetes Study (UKPDS) Group. 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;352:837-853.
42. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the U.S. adult population. *Community Dent Oral Epidemiol* 2002;30:182-192.
43. Safkan-Seppala B, Ainamo J. Periodontal conditions in insulin-dependent diabetes mellitus. *J Clin Periodontol* 1992;19:24-29.
44. Tervonen T, Knuuttila M. Relation of diabetes control to periodontal pocketing and alveolar bone level. *Oral Surg Oral Med Oral Pathol* 1986;61:346-349.
45. Guzman S, Karima M, Wang H-Y, Van Dyke TE. Association between interleukin-1 genotype and periodontal disease in a diabetic population. *J Periodontol* 2003;74:1183-1190.
46. Seppala B, Seppala M, Ainamo J. A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease. *J Clin Periodontol* 1993;20:161-165.
47. Seppala B, Ainamo J. A site-by-site follow-up study on the effect of controlled versus poorly controlled insulin-dependent diabetes mellitus. *J Clin Periodontol* 1994;21:161-165.
48. Barnett M, Baker R, Yancey J, MacMillan D, Kotoyan M. Absence of periodontitis in a population of insulin-dependent diabetes mellitus patients. *J Periodontol* 1984;55:402-405.
49. Sastrowijoto S, Hillemans P, van Steenbergen T, Abraham-Inpijn L, de Graaff J. Periodontal condition and microbiology of healthy and diseased periodontal pockets in type 1 diabetes mellitus patients. *J Clin Periodontol* 1989;16:316-322.
50. Löe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993;16(Suppl. 1): 329-334.
51. American Academy of Periodontology. Diabetes and periodontal diseases (position paper). *J Periodontol* 1999;70:935-949.
52. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ. Microbiological and immunological studies of adult periodontitis in patients with non-insulin dependent diabetes mellitus. *J Periodontol* 1988;59:23-31.
53. Manouchehr-Pour M, Spagnuolo PJ, Rodman HM, Bissada NF. Comparison of neutrophil chemotactic response in diabetic patients with mild and severe periodontal disease. *J Periodontol* 1981;52:410-415.
54. McMullen JA, Van Dyke TE, Horoszewicz HU, Genco RJ. Neutrophil chemotaxis in individuals with advanced periodontal disease and a genetic predisposition to diabetes mellitus. *J Periodontol* 1981;52:167-173.
55. Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP, Offenbacher S. Monocytic TNF-α secretion patterns in IDDM patients with periodontal diseases. *J Clin Periodontol* 1997;24:8-16.
56. Naguib G, Al-Mashat H, Desta T, Graves D. Diabetes prolongs the inflammatory response to a bacterial stimulus through cytokine dysregulation. *J Invest Dermatol* 2004;123:87-92.
57. Salvi GE, Yalda B, Collins JG, et al. Inflammatory mediator response as a potential risk marker for periodontal diseases in insulin-dependent diabetes mellitus patients. *J Periodontol* 1997;68:127-135.
58. Engebretson SP, Hey-Hadavi J, Ehrhardt FJ, et al. Gingival crevicular fluid levels of interleukin-1β and glycemic control in patients with chronic periodontitis and type 2 diabetes. *J Periodontol* 2004;75:1203-1208.
59. Loder RT. The influence of diabetes mellitus on the healing of closed fractures. *Clin Orthop* 1988;232: 210-216.
60. White CB, Turner NS, Lee GC, Haidukewych GJ. Open ankle fractures in patients with diabetes mellitus. *Clin Orthop* 2003;414:37-44.
61. Stuart MJ, Morrey BF. Arthrodesis of the diabetic neuropathic ankle joint. *Clin Orthop* 1990;253:209-211.
62. Inaba M, Nishizawa Y, Mita K, et al. Poor glycemic control impairs the response of biochemical parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in patients with type 2 diabetes. *Osteoporos Int* 1999;9:525-531.
63. Tisdel CL, Marcus RE, Heiple KG. Triple arthrodesis for diabetic peritalar neuroarthropathy. *Foot Ankle Int* 1995;16:332-338.
64. Beam HA, Parsons JR, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. *J Orthop Res* 2002;20:1210-1216.
65. Gooch HL, Hale JE, Fujioka H, Balian G, Hurwitz SR. Alterations of cartilage and collagen expression during fracture healing in experimental diabetes. *Connect Tissue Res* 2000;41:81-85.
66. Lu H, Kraut D, Gerstenfeld LC, Graves DT. Diabetes interferes with bone formation by affecting the expression of transcription factors that regulate osteoblast differentiation. *Endocrinology* 2003;144: 346-352.
67. Amir G, Rosenmann E, Sherman Y, Greenfeld Z, Ne'eman Z, Cohen AM. Osteoporosis in the Cohen diabetic rat: Correlation between histomorphometric changes in bone and microangiopathy. *Lab Invest* 2002;82:1399-1405.
68. He H, Liu R, Desta T, Leone C, Gerstenfeld L, Graves D. Diabetes causes decreased osteoclastogenesis, reduced bone formation, and enhanced apoptosis of osteoblastic cells in bacteria stimulated bone loss. *Endocrinology* 2004;145:447-452.
69. Liu R, Desta T, He H, Graves D. Diabetes alters the response to bacteria by enhancing fibroblast apoptosis. *Endocrinology* 2004;145:2997-3003.
70. Liu R, Bal HS, Desta T, Krothapalli N, Alyassi M, Luan Q, Graves DT. Diabetes enhances periodontal bone loss through enhanced resorption and diminished bone formation. *J Dent Res* 2006;85:510-514.
71. Ficara AJ, Levin MP, Grower MF, Kramer GD. A comparison of the glucose and protein content of gingival crevicular fluid from diabetics and nondiabetics. *J Periodontal Res* 1975;10:171-175.
72. Nishimura F, Takahashi K, Kurihara M, Takashiba S, Murayama Y. Periodontal disease as a complication of diabetes mellitus. *Ann Periodontol* 1998;3:20-29.
73. Wautier J-L, Guillausseau P-J. Diabetes, advanced glycation endproducts and vascular disease. *Vasc Med* 1998;3:131-137.
74. Frantzis TG, Reeve CM, Brown AL. The ultrastructure of capillary basement membranes in the attached

gingiva of diabetic and non-diabetic patients with periodontal disease. *J Periodontol* 1971;42:406-411.
75. Seppala B, Sorsa T, Ainamo J. Morphometric analysis of cellular and vascular changes in gingival connective tissue in long-term insulin-dependent diabetes. *J Periodontol* 1997;68:1237-1245.
76. Monnier VM, Glomb M, Elgawish A, Sell DR. The mechanism of collagen cross-linking in diabetes. A puzzle nearing resolution. *Diabetes* 1996;45(Suppl. 3):S67-S72.
77. Schmidt AM, Weidman E, Lalla E, et al. Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: A potential mechanism underlying accelerated periodontal disease associated with diabetes. *J Periodontal Res* 1996;31:508-515.
78. Schmidt AM, Yan SD, Wautier J-L, Stern D. Activation of receptor for advanced glycation end products. A mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circ Res* 1999;84:489-497.
79. Paques M, Massin P, Gaudric A. Growth factors and diabetic retinopathy. *Diabetes Metab* 1997;23:125-130.
80. Chiarelli F, Santilli F, Mohn A. Role of growth factors in the development of diabetic complications. *Horm Res* 2000;53:53-67.
81. Ünlu F, Gurdal Guneri P, Hekimgil M, Yesilbek B, Boyacioglu H. Expression of vascular endothelial growth factor in human periodontal tissues: Comparison of healthy and diabetic patients. *J Periodontol* 2003;74:181-187.
82. Monnier VM, Bautista O, Kenny D, et al. Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes. *Diabetes* 1999;48:870-880.
83. Odetti P, Traverso N, Cosso L, Noberasco G, Pronzato MA, Marinari UM. Good glycaemic control reduces oxidation and glycation end-products in collagen of diabetic rats. *Diabetologia* 1996;39:1440-1447.
84. Turk Z, Misur I, Turk N, Benko B. Rat tissue collagen modified by advanced glycation: Correlation with duration of diabetes and glycemic control. *Clin Chem Lab Med* 1999;37:813-820.
85. Wang X, Shen X, Li X, Agrawal CM. Age-related changes in the collagen network and toughness of bone. *Bone* 2002;31:1-7.
86. Vashisht D, Gibson GJ, Khoury JI, Schaffler MB, Kimura J, Fyhrie DP. Influence of nonenzymatic glycation on biomechanical properties of cortical bone. *Bone* 2001;28:195-201.
87. Verzijl N, DeGroot J, Ben ZC, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: A possible mechanism through which age is a risk factor for osteoarthritis. *Arthritis Rheum* 2002;46:114-123.
88. Gunczler P, Lanes R, Paoli M, Martinis R, Villaroel O, Weisinger JR. Decreased bone mineral density and bone formation markers shortly after diagnosis of clinical type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2001;14:525-528.
89. McCarthy AD, Etcheverry SB, Bruzzone L, Lettieri G, Barrio DA, Cortizo AM. Non-enzymatic glycosylation of a type I collagen matrix: Effects on osteoblastic development and oxidative stress. *BMC Cell Biol* 2001;2:16-21.
90. Santana RB, Xu L, Chase HB, Amar S, Graves DT, Trackman PC. A role for advanced glycation end products in diminished bone healing in type 1 diabetes. *Diabetes* 2003;52:1502-1510.
91. Takagi M, Kasayama S, Yamamoto T, et al. Advanced glycation endproducts stimulate interleukin-6 production by human bone-derived cells. *J Bone Miner Res* 1997;12:439-446.
92. Valerio G, Franzese A, Esposito-Del Puente A, et al. Increased urinary excretion of collagen crosslinks in type 1 diabetic children in the first 5 years of disease. *Horm Res* 1999;51:173-177.
93. Okazaki R, Totsuka Y, Hamano K, et al. Metabolic improvement of poorly controlled noninsulin-dependent diabetes mellitus decreases bone turnover. *J Clin Endocrinol Metab* 1997;82:2915-2920.
94. Okazaki R, Miura M, Toriumi M, et al. Short-term treatment with troglitazone decreases bone turnover in patients with type 2 diabetes mellitus. *Endocr J* 1999;46:795-801.
95. Erbagci AB, Araz M, Ergabci A, Tarakcioglu M, Namiduru ES. Serum prolidase activity as a marker of osteoporosis in type 2 diabetes mellitus. *Clin Biochem* 2002;35:263-268.
96. Cloos C, Wahl P, Hasslacher C, et al. Urinary glycosylated, free and total pyridinolines and free and total deoxypyridinoline in diabetes mellitus. *Clin Endocrinol (Oxf)* 1998;48:317-323.
97. Schmidt AM, Hori O, Cao R, et al. RAGE: A novel cellular receptor for advanced glycation end products. *Diabetes* 1996;45(Suppl. 3):S77-S80.
98. Katz J, Bhattacharyya I, Farkhondeh-Kish F, Perez FM, Caudle RM, Heft MW. Expression of the receptor of advanced glycation end products in gingival tissues of type 2 diabetes patients with chronic periodontal disease: A study utilizing immunohistochemistry and RT-PCR. *J Clin Periodontol* 2005;32:40-44.
99. Ross R. Atherosclerosis – An inflammatory disease. *N Engl J Med* 1999;340:115-126.
100. Lalla E, Lamster IB, Feit M, et al. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. *J Clin Invest* 2000;105:1117-1124.
101. Willershausen-Zonnchen B, Lemmen C, Hamm G. Influence of high glucose concentrations on glycosaminoglycan and collagen synthesis in cultured human gingival fibroblasts. *J Clin Periodontol* 1991; 18:190-195.
102. Ramamurthy NS, Zebrowski EJ, Golub LM. Insulin reversal of alloxan-diabetes induced changes in gingival collagen metabolism of the rat. *J Periodontal Res* 1974;9:199-206.
103. Ryan M, Ramamurthy NS, Sorsa T, Golub LM. MMP-mediated events in diabetes. *Ann N Y Acad Sci* 1999;878:311-334.
104. Sorsa T, Ingman T, Suomalainen K, et al. Cellular source and tetracycline inhibition of gingival crevicular fluid collagenase of patients with labile diabetes mellitus. *J Clin Periodontol* 1992;19:146-149.
105. Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol* 1996;67:1085-1093.
106. Thorstensson H, Kuylensteirna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol* 1996;23:194-202.
107. Saremi A, Nelson RG, Tulloch-Reid M, et al. Periodontal disease and mortality in type 2 diabetes. *Diabetes Care* 2005;28:27-32.

108. Williams RC Jr., Mahan CJ. Periodontal disease and diabetes in young adults. *JAMA* 1960;172:776-778.
109. Golub LM, Lee H-M, Ryan ME. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res* 1998;12: 12-26.
110. Miller LS, Manwell MA, Newbold D, et al. The relationship between reduction in periodontal inflammation and diabetes control: A report of 9 cases. *J Periodontol* 1992;63:843-848.
111. Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. *J Periodontol* 1996; 67:1094-1102.
112. Grossi SG, Skrepcinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. *J Periodontol* 1997;68:713-719.
113. 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;11:293-298.
114. Aldridge JP, Lester V, Watts TLP, 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 Periodontol* 1995;22: 271-275.
115. 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 immunological results. *J Clin Periodontol* 1998;25:112-124.
116. Stewart JE, Pager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol* 2001;28:306-310.
117. Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol* 2005;32: 266-272.
118. Rodrigues DC, Tabe MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003;74:1361-1367.
119. Janket S-J, 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;84:1154-1159.
120. Loos BG. Systemic markers of inflammation in periodontitis. *J Periodontol* 2005;76:2106-2115.
121. Sammalkorpi K. Glucose intolerance in acute infections. *J Intern Med* 1989;225:15-19.
122. Yki-Jarvinen H, Sammalkorpi K, Koivisto VA, Nikkila EA. Severity, duration and mechanism of insulin resistance during acute infections. *J Clin Endocrinol Metab* 1989;69:317-323.
123. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes and periodontal infections. *J Periodontol* 2005;76:2075-2084.
124. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol* 2001;72:1221-1227.
125. Loos BG, Craandiji J, Hoek FJ, Wertheim-van Dillen PME, van der Velden U. C-reactive protein and other markers of systemic inflammation in relation to cardiovascular diseases are elevated in periodontitis. *J Periodontol* 2000;71:1528-1534.
126. 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;151:273-282.
127. Geerts SO, Nys M, De Mol P, et al. Systemic release of endotoxins induced by gentle mastication: Association with periodontitis severity. *J Periodontol* 2002;73: 73-78.
128. D'Aiuto F, Parker M, Andreou G, et al. Periodontitis and systemic inflammation: Control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res* 2004;83:156-160.
129. Haffner S, Temprosa M, Crandall J, et al. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes* 2005;54:1566-1572.
130. Pickup JC, Crook MA. Is type 2 diabetes mellitus a disease of the innate immune system? *Diabetologia* 1998;41:1241-1248.
131. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 2003;24:278-301.
132. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: An update. *Clin Endocrinol (Oxf)* 2006;64:355-365.
133. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-α, in vivo. *J Clin Endocrinol Metab* 1997;82:4196-4200.
134. Kadowaki T, Yamauchi T. Adiponectin and adiponectine receptors. *Endocr Rev* 2005;26:439-451.
135. Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes* 2005;54: 2939-2945.
136. Gonzalez-Gay MA, DeMatias JM, Gonzalez-Juanatey C, et al. Anti-tumor necrosis-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006;24:83-86.
137. Dominguez H, Storgaard H, Rask-Madsen C, et al. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. *J Vasc Res* 2005;42:517-525.
138. Whitehead JP, Richards AA, Hickman IJ, Macdonald GA, Prins JB. Adiponectin – A key adipokine in the metabolic syndrome. *Diabetes Obes Metab* 2006;8: 264-280.
139. Natali A, Toschi E, Baldeweg S, et al. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. *Diabetes* 2006;55:1133-1140.
140. Saito T, Shimazaki Y, Sakamoto M. Obesity and periodontitis. *N Engl J Med* 1998;339:482-483.
141. Wood N, Johnson RB, Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III). *J Clin Periodontol* 2003;30:321-327.
142. Nishida N, Tanaka M, Hayashi N, et al. Determination of smoking and obesity as periodontitis risks

using the classification and regression tree method. *J Periodontol* 2005;76:923-928.
143. Iwamoto Y, Nishimura F, Nakagawa M, et al. The effects of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. *J Periodontol* 2001;72:774-778.
144. Tervonen T, Knuuttila M, Pohjamo L, Nurkkala H. Immediate response to non-surgical periodontal treatment in subjects with diabetes mellitus. *J Clin Periodontol* 1991;18:65-68.
145. Tervonen T, Karjalainen K. Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type 1 diabetes. *J Clin Periodontol* 1997;24:505-510.
146. Westfelt E, Rylander H, Blohme G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. *J Clin Periodontol* 1996; 23:92-100.

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