



The influence of diabetes on the periodontal tissues

MARIA EMANUEL RYAN, D.D.S., Ph.D.; OANA CARNU, D.M.D.; ANGELA KAMER, D.M.D., Ph.D.

The pathogenesis of periodontal disease is complex because it reflects a combination of the initiation and maintenance of the chronic inflammatory process by a diverse microbial flora and its numerous bacterial products.

The subsequent host response to this infection mediates a complex cascade of tissue-destructive pathways.¹

The majority of evidence demonstrates an increase in the prevalence and severity of periodontal disease in people with diabetes mellitus.

Additional factors contributing to this multifaceted local disease process in the oral cavity include a number of systemic diseases, especially diabetes, that can exaggerate the host response to the local microbial factors (for example, endotoxin), resulting in unusually destructive periodontal breakdown (Figure). Mechanisms underlying this interaction are emerging, despite methodological problems and faulty experimental design of research conducted in this area.^{2,3} In fact, aggressive periodontitis is recognized as the sixth complication of diabetes according to Löe,⁴ who concluded that multiple epidemiologic studies have

demonstrated that both type 1 and type 2 diabetes are predictors of periodontal disease when the systemic condition is poorly controlled. This article focuses on the role of diabetes as a significant contributing factor for periodontal disease.

PERIODONTAL DISEASES IN PEOPLE WITH DIABETES MELLITUS

Gingivitis. People with type 1 diabetes⁵ are at greater risk of developing gingivitis. Both children and adults with poor metabolic control show a tendency toward higher gingivitis scores.⁶⁻⁸ The prevalence of gingivitis in children and adolescents is nearly twice that observed in populations of children and adolescents without diabetes.⁹ Studies indicate that the severity

Background. The authors conducted a systematic review of the literature to assess the relationship between diabetes mellitus and periodontitis.

Types of Studies

Reviewed. The authors conducted searches to identify published human epidemiologic studies; cross-sectional observations; and longitudinal, cohort, case-control and other studies that describe variables associated with diabetes and periodontal disease. Some animal studies are reported to support human findings and explore mechanisms of action.

Results. The majority of evidence demonstrates an increase in the prevalence and severity of periodontal disease in people with diabetes mellitus. Interpretation of published results is complicated by a number of factors: small sample sizes; the absence of standard reporting of the type of diabetes; the presence of diabetes complications; the lack of longitudinal studies and control groups; and inadequate control of covariates such as age, duration of diabetes and level of control of diabetes.

Clinical Implications. Mechanisms underlying the accelerated periodontal disease associated with diabetes appear to reflect primarily abnormal host responses, rather than microbial shifts, resulting from diabetes. A better understanding of the mechanisms involved in the more aggressive periodontitis seen in patients with diabetes enables the practitioner to consider different therapeutic options for this growing patient population.

and extent of gingivitis are significantly increased in young patients with diabetes.⁹⁻¹³ The association of diabetes with gingivitis in children and adolescents is so widely accepted that diabetes mellitus-associated gingivitis is included as a specific entity in the most recent classification of periodontal diseases.^{14,15} In adults with type 2 diabetes, gingival inflammation may occur at higher rates than those in adults

without diabetes. Nearly 64 percent of patients with diabetes may have gingival inflammation compared with 50 percent of subjects without diabetes.¹⁶

It appears that the degree of metabolic control of diabetes is an important factor in the development and progression of gingivitis. Serum fructosamine levels, reflecting the patients' glycemic control over the preceding two to three weeks,¹⁷ are correlated positively with the degree of gingival bleeding¹⁸ and the severity of gingival inflammation¹⁹ in adults with type 2 and children with type 1 diabetes, respectively. The correlation between serum fructosamine levels and gingival inflammation in children recently was reported to be maintained into the adolescent years.²⁰ Values of glycosylated hemoglobin, or HbA_{1c} (reflecting blood glucose concentrations averaged over the previous six to eight weeks²¹), exceeding 10 percent (normal values are 4 to 6 percent) appear to particularly predispose children and adolescents to gingivitis.^{6,10,22} Notably, the presence of gingivitis in subjects with diabetes is not related to higher levels of plaque accumulation because the plaque index is not significantly increased in subjects with diabetes.^{20,23} The clinical correlate to all of these findings is that normalizing glycemic levels may significantly reduce the severity and extent of gingivitis in patients with diabetes.²²

Periodontitis. Unlike gingivitis, periodontitis is uncommon in children younger than 12 years, even among those with diabetes. In adolescence, periodontitis does occur, but the extent of attachment loss is usually minimal.⁵ The prevalence of periodontal disease in juveniles with type 1 diabetes has been reported to be 9.8 percent, compared with 1.7 percent in those without diabetes.¹¹ A study in Finland did not report this rapid periodontal destruction in adolescents.²³ The discrepancies between these two patient populations may be related to different levels of metabolic/glycemic control and other factors, such as different gene pools, which appear to have a strong relationship with rapid periodontal breakdown.²⁴

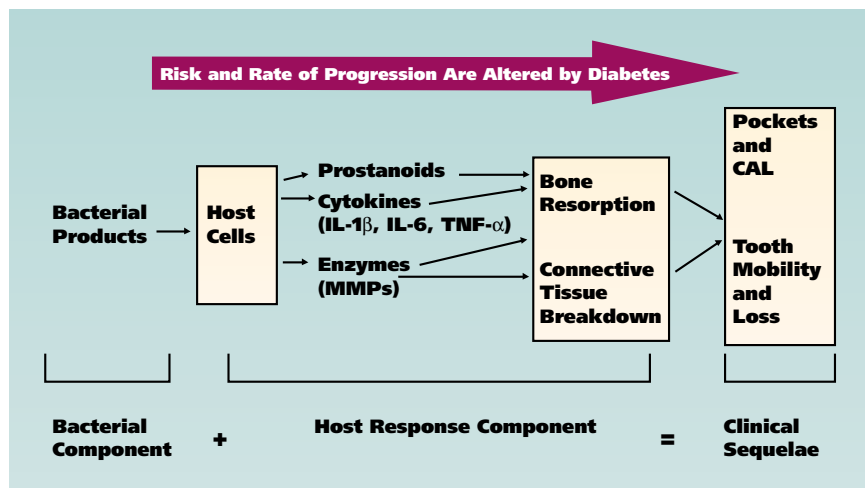


Figure. Simplified schematic depicting etiologic factors and cascade of events contributing to periodontitis that are altered by diabetes. IL-1 β : Interleukin-1 beta. IL-6: Interleukin-6. TNF- α : Tumor necrosis factor-alpha. MMPs: Matrix metalloproteinases. CAL: Clinical attachment loss.

The duration of diabetes appears to be an important factor in the evaluation of diabetes as a risk factor for periodontal disease. Patients who have had type 1 diabetes for more than 10 years lost more periodontal attachment than did those who have had type 1 diabetes for less than 10 years, particularly in patients aged 35 years and older.²⁵ Moreover, patients aged 40 to 50 years with type 1 diabetes of long duration exhibited significantly more sites with advanced periodontitis and bone loss than did age-matched controls without diabetes.²⁶ It also has been demonstrated²⁵ and confirmed⁸ that patients with type 1 diabetes with other complications of diabetes (for example, retinopathy and nephropathy) have significantly greater losses of periodontal attachment than do those without these complications. Other studies demonstrated that those patients with type 1 diabetes with periodontitis had a higher prevalence of ketoacidosis, retinopathy and neuropathy.²⁷ These studies strongly suggest that with increasing diabetes-related complications, patients are more likely to develop additional long-term complications.

Poor metabolic control appears to increase the likelihood of periodontitis among people with type 1 diabetes. More than one-quarter of subjects with type 1 diabetes with poor metabolic control had sites with attachment loss of 5 millimeters or greater, compared with 10 percent of the subjects with good metabolic control.²⁸ Subjects with poorly controlled diabetes had attachment loss of 2 mm or greater at an average of 24 percent of

sites, while patients with good-to-moderate diabetes control had similar levels of attachment loss at only 10 percent of sites.²⁹ The percentage of sites with attachment loss of 2 mm or greater in subjects without diabetes was similar to the percentage of sites in patients with well-controlled diabetes, suggesting that patients with well-controlled diabetes may not be at an increased risk of developing periodontal diseases. Metabolic control of type 2 diabetes is equally as important, based on data from the Third National Health and Nutrition Examination Survey, or NHANES III, which reported that the odds of having severe periodontal disease in patients with fair-to-good ($HbA_{1c} \leq 9$ percent) or poor ($HbA_{1c} > 9$ percent) glycemic control were approximately 50 percent or 200 percent higher than the odds among subjects without diabetes, respectively.³⁰ These findings suggest a dose-response relationship between periodontal disease risk and glycemic control.³⁰

Most of the studies on periodontal disease in patients with type 2 diabetes have been conducted on the Pima Indians from the Gila River Indian Community in Arizona. With 50 percent of its population older than 35 years of age having type 2 diabetes, the Pima Indians have the highest recorded prevalence of type 2 diabetes in the world.³¹ Tooth loss in Pima Indians with type 2 diabetes, as reported in 1990, was 15 times higher than that in those without diabetes.³² In general, diabetes increases the risk of developing periodontitis in the Pima Indian population by about threefold.³³ More specifically, there was a twofold greater risk of severe periodontitis in patients with poor glycemic control. Increasing duration of diabetes and the presence of retinopathy also imparted a significantly greater risk of developing periodontal disease.³ In this population, periodontitis occurred early in life, increased with age and was responsible for most tooth loss.

In a study of periodontal disease in a Mexican population of people with type 2 diabetes, researchers concluded that the number of years since diagnosis of diabetes was a more significant factor than the age of the person when considering the severity of periodontal disease.³⁴ Comparable results in patients with type 2 diabetes were reported in other studies from disparate geographic regions.^{16,30,35-37} The incidence of periodontal disease increased by nearly threefold in patients with type 2 diabetes compared with subjects without diabetes. The odds ratio, or OR, for periodontal disease among subjects with type 2

diabetes ranges from 2 to 4.^{30,33,37,38} Taylor and colleagues³⁹ reported that 67 percent of patients with type 2 diabetes had significant radiographic bone loss compared with 44 percent of subjects without diabetes, and that subjects with diabetes lost more bone than did subjects without diabetes over a two-year period. These findings suggest that periodontal disease in patients with diabetes may progress faster.³⁹

It also is known that risk factors for periodontal disease can be cumulative. For example, the ORs for periodontal disease in subjects who smoke have ranged from 2 to 7, although higher values have been reported.^{16,40} Patients with diabetes who are smokers may be at even greater risk of developing periodontal disease compared with non-smoking patients with diabetes.^{30,41} An OR for severe periodontal disease in patients who smoke and had better-controlled diabetes ($HbA_{1c} \leq 9$ percent) was 2.3, while patients who smoke and had poorly controlled diabetes ($HbA_{1c} > 9$ percent) had an OR of 4.6, suggesting a combined effect of smoking and glycemic control on developing periodontal disease.³⁰ Other subgroups of people with diabetes also are at higher risk of developing periodontitis (Box): those with poor oral hygiene, those with a long history of diabetes, those with other complications of the disease, those with a history of poorly controlled diabetes, teenagers and pregnant women.²

PERIODONTALLY RELEVANT HOST-RESPONSE ABNORMALITIES

Systemic diseases or disease processes that adversely affect host defense systems act as risk factors for gingivitis and periodontitis. Several altered host responses are associated with increased incidence and severity of periodontitis in diabetics.

Several studies have focused on the role of periodontal infection,²³ and the microflora of dental plaque in people with diabetes,⁴² but these have not been conclusive. Thus, it is unclear if an altered microflora contributes to the greater incidence and severity of periodontal infection and destruction in subjects with diabetes. Increased calculus formation, reported in patients with diabetes, may be due to an increased concentration of serum calcium in both parotid and submandibular saliva of subjects with type 1 diabetes.⁴³ The gingival crevicular fluid, or GCF, of patients with diabetes may exhibit glucose levels twice those of other patients,⁴⁴ and urea concentrations also may

be increased.⁴⁵ These changes, as well as basement membrane thickening and glycosylation of hemoglobin should promote a unique environment, resulting in shifts of the microbial flora. However, studies have reported essentially no differences between people with or without diabetes,^{42,46} suggesting that alterations in the host response to existing periodontal pathogens may be primarily responsible for the more aggressive periodontal destruction observed in patients with diabetes.

Vascular abnormalities. Early studies of the pathogenesis of periodontal disease in those with diabetes mellitus focused on basement membrane thickening and possible changes in the vasculature.^{47,48} These studies showed that degenerative vascular changes seen in other tissues and/or organs in patients with diabetes⁴⁹ also occurred in the gingival tissues. It was postulated that vascular changes interfere with both the delivery of nutrients and the migration of leukocytes to the gingival tissues, resulting in decreased oxygen diffusion and elimination of metabolic waste, contributing to an increased severity of periodontitis and decreased wound healing capacity.^{47,50} These vascular changes worsen with poor metabolic control and longer duration of the disease.⁵¹

Nonenzymatic glycosylation. A consequence of hyperglycemia in diabetes is the alteration of circulating and immobilized proteins. When proteins such as collagen, or lipids, are exposed to aldose sugars, they undergo nonenzymatic glycation⁵² and oxidation.⁵³ Initially, reversible alterations of the proteins exposed to sugars are seen, and, eventually, complex molecular rearrangements may occur, resulting in the irreversible formation of altered proteins known as advanced glycation end products, or AGEs. Glucose-derived cross-links can contribute to reduced collagen solubility and turnover rate in humans with diabetes.⁵⁴ Decreased solubility of gingival collagen in people with diabetes can be returned to near-normal levels by insulin treatment,⁵⁵⁻⁵⁷ presumably reflecting a reduction in glucose-derived cross-linking.⁵⁸ In addition, glycosylation of existing collagen at wound margins results in reduced solubility and delayed remodeling of the wound site.⁵⁹ Patients with diabetes have elevated levels of AGEs in their gingival tissues⁶⁰ that may be associated with a state of enhanced oxidant stress, a potential mechanism for accelerated tissue injury. Elevated levels of both AGEs and cross-links between collagen molecules in palatal biopsy spec-

BOX

IMPORTANT FACTORS TO CONSIDER IN ASSESSING THE PERIODONTAL STATUS OF PATIENTS WITH DIABETES.

- **Degree of Metabolic Control**
- **Duration of Disease**
- **Presence of Other Long-Term Complications**
(Retinopathy, angiopathy, nephropathy, neuropathy, delayed wound healing)
- **Concurrent Risk Factors**
(Plaque, smoking, stress, medications, hormonal variations [adolescence, pregnancy, menopause])

imens of patients with type 1 diabetes have been correlated with HbA_{1c} levels.²²

AGEs act on target cells via their recognition of cell-surface polypeptide receptors. The best characterized binding site for AGEs is a member of the immunoglobulin superfamily now called the receptor for AGE, or RAGE.⁶¹ AGEs can interact with RAGEs on cells, such as macrophages, stimulating the production of enzymes (for example, matrix metalloproteinases, or MMPs), adhesion molecules,⁶² cytokines (for example, tumor necrosis factor-alpha, or TNF- α ; interleukin-1 beta, or IL-1 β ⁶³; and interleukin-6, or IL-6),⁶⁴ as well as other mediators. This is of great interest because these mediators have been detected in the GCF of patients with poorly controlled diabetes. The overproduction of these products in response to the ligand-receptor interactions could help mediate and/or be in addition to alterations in collagen metabolism. AGE-modified proteins also are chemotactic for human monocytes.⁶³ This could magnify the inflammatory response, delaying wound repair and inducing connective-tissue damage and bone resorption.⁶⁰

Abnormalities of bone metabolism such as osteopenia and delayed fracture healing have been demonstrated in patients with diabetes.^{65,66} Because type I collagen makes up 90 percent of the bone matrix, it is possible that glycosylation of this collagen could affect osteoblast and osteoclast cell function and contribute to the development of diabetes-associated osteopenia.

Imbalances in lipid metabolism. Diabetes complications that have been attributed primarily to hyperglycemia may be caused by an imbalance in lipid metabolism characterized by increased serum levels of low-density lipoproteins, or LDL, triglycerides and fatty acids. Several researchers⁶⁷⁻⁷¹ correlated modifications in lipid metabolism with impaired function of monocytes and/or

macrophages in successive *in vitro* and *in vivo* studies. Monocyte-derived macrophages exposed to serum lipids following endotoxin stimulation exhibit suppression in growth factor production, expressing an inflammatory phenotype rather than a reparative or proliferative one. Several studies illustrate that hypertriglyceridemia induces an increased production of proinflammatory cytokines (TNF- α and IL-1 β) by monocytes. In addition, neutrophils exposed to triglycerides produce more IL-1 β and have altered chemotactic and phagocytic properties. Increased levels of pro-inflammatory cytokines have been observed not only in serum but also in GCF of hyperlipidemic subjects with type 2 diabetes. This disequilibrium between increased amounts of cytokines and reduced levels of growth factors with protective function may hinder repair ability and facilitate tissue breakdown.^{68,69}

Altered collagen metabolism. Accordingly, investigators have focused their efforts on various aspects of the host response in subjects with diabetes, including collagen metabolism, and have suggested new host modulatory approaches to address the altered host response.^{57,72} Several oral and extraoral diabetes-induced collagen abnormalities have been identified, including a large reduction in collagen synthesis and solubility in gingiva, skin and bone, and an even more profound increase in the urinary excretion of hydroxyproline, an amino acid marker of collagen and its breakdown fragments. These findings suggest that the disease increases the degradation of newly synthesized collagen in various connective tissues throughout the body.⁷³

Altered collagen metabolism may predispose people with diabetes not only to periodontal disease but also to other abnormalities of connective tissues, such as impaired wound healing. Elevations in GCF collagenase activity⁵⁷ and decreases in gingival fibroblast collagen synthesis⁷⁴ in patients with diabetes have been observed. The cellular source of the increased collagenase activity in the GCF of patients with type 1 diabetes was reported to be the neutrophil.⁷⁵ However, the fibroblasts may contribute to the excess collagenase; recent studies indicate that under the appropriate circumstances, fibroblasts (and other cells such as chondroblasts) can be induced to secrete a neutrophil-type of collagenase (that is, MMP-8).⁷⁶

Neutrophil dysfunction. Polymorphonuclear leukocyte, or PMN, functions, such as chemotaxis and phagocytosis, have been shown to be

decreased in patients with diabetes with periodontal disease.^{77,78} In addition, there is a strong correlation between PMN dysfunction and the severity of periodontal disease.⁷⁹ Reports of a genetic predisposition in subjects with diabetes to the development of periodontal disease⁸⁰ may be related to this reported PMN dysfunction. To support this hypothesis, a study has demonstrated that a diabetic patient's siblings who do not have diabetes also have depressed PMN function.⁸¹ However, this study and other studies have observed a decrease in PMN chemotaxis in patients with poorly controlled diabetes, and the severity of this PMN defect was correlated to the degree of glycemic control. In this regard, increased glucose levels found in the GCF of patients with poorly controlled diabetes may contribute to the suppression of PMN function.⁸² Defects other than PMN chemotaxis⁸³ and reduced phagocytosis⁷⁷ have been demonstrated in patients with diabetes mellitus, including impaired intracellular killing and impaired adherence.⁸⁴ These defects in the body's immune system may predispose people with diabetes to periodontal disease.

Altered monocytic response. Elevated levels of chemical mediators of inflammation known as prostanoids (prostaglandin E₂, or PGE₂) have been detected in the blood of patients with type 1 diabetes.⁸⁵ In addition, GCF-PGE₂ levels are substantially higher in patients with diabetes.⁸⁶ Furthermore, the GCF-PGE₂ levels at clinically healthy sites (that is, probing depths of 0-3 mm, no inflammation) of patients with diabetes are higher than the levels seen in similar sites in healthy patients who have a more prevalent form of periodontitis.⁸⁷ The significance of these elevated GCF-PGE₂ levels in patients with diabetes needs further evaluation by longitudinal studies to determine whether this abnormality predicts future unusually aggressive periodontal breakdown. It appears that increased local GCF-PGE₂ responses observed in patients with diabetes are coincident with an upregulated monocytic phenotype.⁸⁸ Thus, even low levels of endotoxin challenge within the periodontal pocket seem to induce high levels of PGE₂ secretion at these sites. In addition, adherent monocytes obtained from blood samples of patients with type 1 diabetes maintained in culture, when stimulated with bacterial endotoxin, secrete higher levels of PGE₂ in a dose-dependent manner, as compared with monocytes isolated from subjects without diabetes who have either healthy gingiva or adult periodontitis.⁸⁸

These clinical and basic science data have led to the proposition that therapies should include a systemic host-modulatory approach in addition to traditional techniques. This approach is in sharp contrast to approaches designed only to remove periodontal pathogens and address only the sites that are deemed to be active by rather crude diagnostic techniques, such as bleeding upon probing.

CONCLUSION

Diabetes is a complex disease characterized by numerous variables that can influence the development of complications, including periodontitis. Although the exact mechanisms of action are not fully understood, poor metabolic control, as well as extended duration of the hyperglycemic state, are risk factors for periodontitis and altered host function. Most likely, a combination of many factors ultimately leads to the increased prevalence and severity of periodontitis in patients with diabetes. These factors may act individually in an additive fashion or synergistically to contribute to periodontal disease. Continued scientific exploration is required to determine which factors should be the primary target for the treatment of periodontitis, as well as other complications, in this patient population. ■

Dr. Ryan is an associate professor, Department of Oral Biology and Pathology, School of Dental Medicine, State University of New York, Stony Brook University, South Campus, Stony Brook, N.Y. 11794-8702, e-mail "Maria.Ryan@stonybrook.edu". Address reprint requests to Dr. Ryan.

Dr. Carnu is a research assistant, Department of Oral Biology and Pathology, School of Dental Medicine, State University of New York at Stony Brook.

Dr. Kamer is an assistant professor, Department of Periodontics, New York University College of Dentistry.

Dr. Ryan is a consultant and is named on patents as an inventor of therapeutic applications of tetracycline discussed in this article. These patents have been fully assigned to the research foundation of Stony Brook University, State University of New York, Stony Brook, N.Y., and have been exclusively licensed to CollaGenex Pharmaceuticals, Newtown, Pa.

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