Periodontal disease and diabetes

A two-way street

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ABSTRACT

Background. The association between diabetes and inflammatory periodontal diseases has been studied extensively for more than 50 years. The author reviews the bidirectional relationships between diabetes and periodontal diseases.

Conclusions. A large evidence base suggests that diabetes is associated with an increased prevalence, extent and severity of gingivitis and periodontitis. Furthermore, numerous mechanisms have been elucidated to explain the impact of diabetes on the periodontium. While inflammation plays an obvious role in periodontal diseases, evidence in the medical literature also supports the role of inflammation as a major component in the pathogenesis of diabetes and diabetic complications. Research suggests that, as an infectious process with a prominent inflammatory component, periodontal disease can adversely affect the metabolic control of diabetes. Conversely, treatment of periodontal disease and reduction of oral inflammation may have a positive effect on the diabetic condition, although evidence for this remains somewhat equivocal.

Clinical Implications. Patients with diabetes who have periodontal disease have two chronic conditions, each of which may affect the other, and both of which require frequent professional evaluations, in-depth patient education and consistent educational reinforcement by health care providers.

Key Words. Diabetes mellitus; periodontal diseases; periodontal therapy; inflammation.

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Diabetes mellitus affects an estimated 20 million Americans, about 35 to 40 percent of whom have not received a diagnosis.[1] More than 9 percent of the adult population has diabetes, and both the incidence and prevalence are increasing every year.

The two main types of diabetes are classified primarily on the basis of their underlying pathophysiology.[2] Type 1 diabetes, which constitutes about 5 to 10 percent of all cases in the United States, results from autoimmune destruction of insulin-producing β-cells in the pancreas, leading to total loss of insulin secretion.[3] Insulin is used by the body to facilitate the transfer of glucose from the bloodstream into the target tissues, such as muscle, where glucose is used for energy (Figure). Because a person with type 1 diabetes no longer produces endogenous insulin, glucose is unable to enter target cells and remains in the bloodstream, resulting in sustained hyperglycemia. A patient with type 1 diabetes must take exogenous insulin to remain alive—hence, the former name "insulin-dependent diabetes."

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Type 2 diabetes, which constitutes about 85 to 90 percent of all cases, results from insulin resistance rather than from total absence of insulin production.[3] Autoimmune destruction of β-cells does not occur in type 2 diabetes, and patients retain the capacity to secrete some insulin, although production often diminishes over time. Patients with type 2 diabetes can remain undiagnosed for years because hyperglycemia appears gradually and often without symptoms.[3] Insulin resistance results in a decreased capacity to transfer glucose into target cells; thus, hyperglycemia develops.

STUDIES OF DIABETES AND PERIODONTAL DISEASES

The relationship between diabetes and periodontal diseases has been the subject of more than 200 articles published in English during the past 50 years. Interpretation of this research is made difficult by the numerous classifications for diabetes and periodontitis used over the years; varying clinical and radiographic criteria used to assess periodontal disease prevalence, extent and severity; evolving standards for the degree of glycemic control; and changing methods for assessing complications associated with diabetes. In addition, researchers and clinicians must use caution when comparing the results of different studies, because research has focused on assorted populations and often has included relatively few subjects or lacked controls.

Gingivitis. An overall assessment of the available data strongly suggests that diabetes is a risk factor for gingivitis and periodontitis.[4,5] In a classic study of diabetes and gingivitis reported more than 30 years ago, the prevalence of gingival inflammation was greater in children with type 1 diabetes than in children without diabetes who had similar plaque levels.[6] Ervasti and colleagues[7] observed greater gingival bleeding in patients with poorly controlled diabetes than in control subjects without diabetes or in subjects with well-controlled diabetes. Subjects with type 2 diabetes also had greater gingival inflammation than did control subjects without diabetes; the highest level of gingivitis was found in subjects with poor glycemic control.[8]

The onset of type 1 diabetes in children has been associated with increased gingival bleeding, while improved control of blood sugar levels after initiation of insulin therapy resulted in decreased gingivitis.[9] Using an experimental gingivitis protocol, a recent longitudinal study showed more rapid and severe gingival inflammation in adult subjects with type 1 diabetes than in control subjects without diabetes, despite similar qualitative and quantitative bacterial plaque characteristics, suggesting a hyperinflammatory gingival response in people with diabetes.[10]

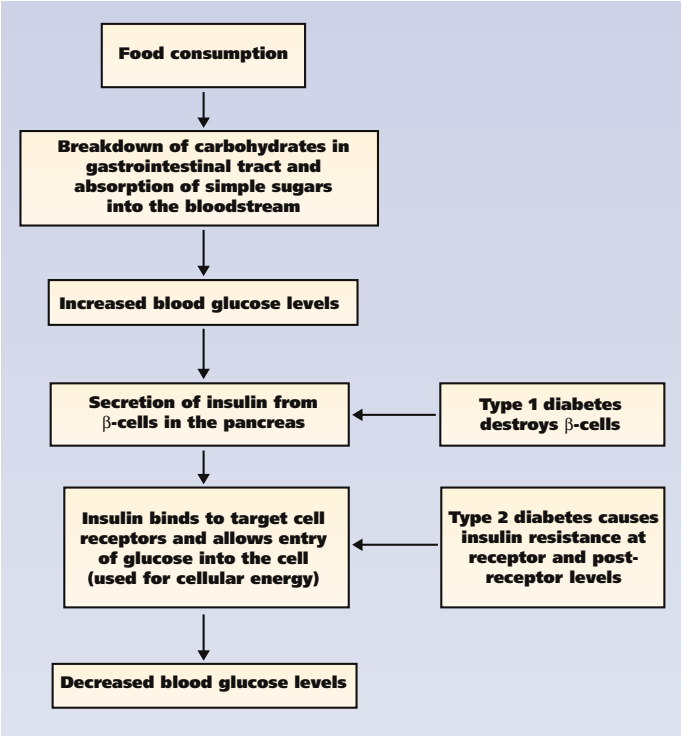

Figure. Carbohydrate metabolism, insulin and diabetes.

Periodontitis. Most of the evidence also suggests that diabetes increases the risk of developing periodontitis. In a classic cross-sectional study, type 1 diabetes was associated with a fivefold increased prevalence of periodontitis in teenagers.[6] A recent case-control study confirmed that attachment loss is more prevalent and extensive in children with diabetes than in children without diabetes.[11] In addition, epidemiologic research supports an increased prevalence and severity of attachment loss and bone loss in adults with diabetes.[12,13]

A multivariate risk analysis showed that subjects with type 2 diabetes had approximately threefold increased odds of having periodontitis compared with subjects without diabetes, after adjusting for confounding variables including age, sex and oral hygiene measures.[12,13] In a meta-analysis of studies conducted before 1996 that included more than 3,500 adults with diabetes, Papapanou[4] found a significant association

between diabetes and periodontitis. Diabetes also may increase the risk of experiencing continued periodontal destruction over time. For example, a two-year longitudinal study demonstrated a fourfold increased risk of progressive alveolar bone loss in adults with type 2 diabetes compared with that in adults who did not have diabetes.[14]

Like gingivitis, the risk of developing periodontitis may be greater in patients with diabetes who have poor glycemic control than that in patients with well-controlled diabetes. In the Third National Health and Nutrition Examination Survey, which included thousands of Americans, adults with poorly controlled diabetes had an almost threefold increased risk of having periodontitis compared with that in adult subjects without diabetes, while subjects with diabetes and good glycemic control had no significant increase in risk.[15] Poor glycemic control in patients with diabetes also has been associated with an increased risk of progressive loss of periodontal attachment and alveolar bone over time.[14,16] However, other studies have shown only a marginal or insignificant relationship between glycemic control and periodontal status.[17,18]

It is likely that there is individual patient variability in the degree to which glycemic control influences periodontal status. This is not surprising, given the multifactorial nature of periodontal diseases, in which systemic conditions play a modifying role rather than a primary, causative role. Dentists should be aware of the potential influence that poor glycemic control has on the periodontium of patients with diabetes, but they also should recognize that patients with well-controlled diabetes can have periodontal diseases just as patients with poorly controlled diabetes may have a healthy periodontium.

Although most research on the relationship between diabetes and periodontal disease has focused on how diabetes may affect periodontal status, a growing body of evidence also has examined the converse relationship; namely, how periodontal diseases affect the metabolic state. For example, a two-year longitudinal trial demonstrated a sixfold increased risk of worsening glycemic control in patients with type 2 diabetes who had severe periodontitis compared with that in subjects with type 2 diabetes who did not have periodontitis.[19] Intervention trials during the past 15 years have resulted in varied metabolic responses in patients with diabetes. These trials often examined the effects of scaling and root planing on glycemic control, either alone or in combination with adjunctive systemic tetracycline therapy. Tetracyclines usually are the antibiotic of choice because they decrease the production of matrix metalloproteinases such as collagenase, which often are elevated in patients with diabetes.[20]

Some studies have shown that the combination of scaling and root planing with systemic doxycycline therapy is associated with an improvement in periodontal status that is accompanied by significant improvement in glycemic control, as measured by the glycated hemoglobin assay (HbA1c).[21-23] The HbA1c test provides an estimate of glycemic control over a period of approximately two to three months before the test, and the normal value is less than 6 percent.[3]

Conversely, a recent study of subjects with type 2 diabetes who underwent scaling and root planing and received adjunctive doxycycline therapy demonstrated significant improvement in periodontal health but only a nonsignificant reduction in HbA1c values.[24] When researchers performed scaling and root planing but did not administer adjunctive antibiotic therapy, the study results were similarly equivocal.[25-28] Some studies showed significant improvement in glycemic control after treatment,[25,26] while others showed no significant improvement in glycemic control despite improvements in patients' periodontal health.[27,28]

These conflicting study results make it difficult for practitioners to determine the clinical applicability of the data. We must remember that each study population was different, and medical treatment regimens used by these patients were not standardized across the studies. Thus, changes in glycemic control, or lack thereof, may be related to factors other than changes in periodontal inflammation. Conclusions from the above studies are based on mean data; however, closer examination reveals significant variations between individual subjects with regard to changes in glycemic control after periodontal therapy. Some patients experienced no change in glycemic control after periodontal intervention, while others demonstrated marked improvement in glycemic control after the same treatment regimens.[25]

A recent meta-analysis of 10 intervention trials that included more than 450 patients found an average decrease in absolute HbA1c values of about 0.4 percent after scaling and root planing.[29] This value was not statistically significant in the

analysis. The addition of adjunctive systemic antibiotic therapy to the scaling and root planing regimen resulted in a mean absolute reduction of 0.7 percent in posttreatment HbA1c values, which also is not statistically significant. I should note, however, that absolute reductions in HbA1c of 0.7 percent often are considered to be clinically significant in the practice of medicine.[3] Likewise, while the overall mean changes in periodontal parameters in the studies described above revealed improved periodontal health, not all subjects experienced similar responses. Further research is required to determine how variations in clinical responses after periodontal therapy might be reflected in changes, or a lack of changes, in glycemic control.

Variability among patients. The variation among patients with diabetes in their responses to periodontal therapy seen in these studies may be mirrored in any given dental practice. Periodontal treatment may be associated with minimal glycemic impact in some patients, while others may have quite striking responses.

For example, Kiran and colleagues[26] recently conducted a study of patients with well-controlled type 2 diabetes who had only gingivitis or mild periodontitis. They examined the effect of prophylaxis and localized scaling and root planing without systemic antibiotic therapy on periodontal health and glycemic control. A control group of subjects with diabetes whose periodontal status was similar received no treatment.

The treated subjects experienced a 50 percent reduction in the prevalence of gingival bleeding three months after treatment. This was accompanied by a statistically significant improvement in glycemic control, with a reduction in the mean HbA1c value of 0.8 percent (from 7.3 percent at baseline to 6.5 percent at the three-month posttreatment follow-up assessment). As expected, the untreated control group experienced no change in gingival bleeding or glycemic control. In this study, some patients experienced little change in glycemic control, while others experienced major improvement. Dentists treating patients with diabetes for periodontal diseases should expect this variability in responses.

MECHANISMS OF INTERACTION BETWEEN DIABETES AND PERIODONTAL DISEASES

Years of research have established a number of mechanisms by which diabetes can influence the periodontium. Many of these mechanisms share common characteristics with those involved in the classic complications of diabetes, such as retinopathy, nephropathy, neuropathy, macrovascular diseases and altered wound healing. Because periodontal diseases are infectious diseases, research initially focused on possible differences in the subgingival microbial flora of patients with and without diabetes. Although some early studies reported higher proportions of certain bacteria in the periodontal pockets of patients with diabetes, later studies involving cultures generally revealed few differences in periodontally diseased sites of subjects with diabetes and those of subjects who did not have diabetes.[30] Because the pathogens associated with periodontitis do not appear to differ greatly in people with and without diabetes, researchers have focused attention on potential differences in the immunoinflammatory response to bacteria between people with diabetes and those without diabetes.

Function of cells. The function of cells involved in this response, including neutrophils, monocytes and macrophages, is altered in many people with diabetes. The adherence, chemotaxis and phagocytosis of neutrophils often are impaired.[31] These cells are the first line of host defense, and inhibition of their function may prevent destruction of bacteria in the periodontal pocket, thereby increasing periodontal destruction.

Other immunoinflammatory responses are upregulated in people with diabetes. For example, macrophages and monocytes often exhibit elevated production of proinflammatory cytokines and mediators such as tumor necrosis factor α (TNF-α) in response to periodontal pathogens, which may increase host tissue destruction.[32,33] Elevated TNF-α levels are found in the blood and gingival crevicular fluid, suggesting both a local and systemic hyperresponsiveness of this immune cell line. Glycemic control may be an important determinant of this response. In a study of subjects with diabetes and periodontitis, Engebretson and colleagues[34] found that crevicular fluid levels of interleukin 1 β (IL-1β) were almost twice as high in subjects with HbA1c levels greater than 8 percent compared with subjects whose HbA1c levels were less than or equal to 8 percent.

Altered wound healing. Altered wound healing is a common problem in people with diabetes. The primary reparative cell in the periodontium, the fibroblast, does not function prop-

erly in high-glucose environments.[35] Furthermore, the collagen that is produced by these fibroblasts is susceptible to rapid degradation by matrix metalloproteinase enzymes, the production of which is elevated in diabetes.[20] Thus, periodontal wound healing responses to chronic microbial insult may be altered in those with sustained hyperglycemia, resulting in increased bone loss and attachment loss.

One of the major characteristics of diabetic complications is a change in microvascular integrity, which underlies end-organ damage, such as that responsible for retinopathy and nephropathy.[36] People with diabetes, especially those with poor glycemic control, accumulate high levels of irreversibly glycated proteins called advanced glycation end products (AGEs) in the tissues, including the periodontium.[37,38] AGEs are a primary link between numerous diabetic complications, because they induce marked changes in cells and extracellular matrix components. These changes, including abnormal endothelial cell function, capillary growth and vessel proliferation, also occur in the periodontium of some people with diabetes.[36,39]

The accumulation of AGEs in patients with diabetes also increases the intensity of the immunoinflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs.[37] Interactions between AGEs and their receptors on inflammatory cells result in the increased production of proinflammatory cytokines such as IL-1β and TNF-α.[40] This interaction may be the cause of the marked elevation in gingival crevicular fluid levels of IL-1β and TNF-α seen in subjects with diabetes compared with those without diabetes, and it may contribute to the increased prevalence and severity of periodontal diseases found in numerous studies of populations of people with diabetes.[32]

Mechanisms. The mechanisms by which periodontal diseases may affect the diabetic state have been elucidated only recently. Both periodontal diseases and diabetes, especially type 2 diabetes, have major inflammatory components. Systemic bacterial and viral infections such as the common cold or influenza result in increased systemic inflammation, which increases insulin resistance and makes it difficult for patients to control blood glucose levels.[41] Chronic periodontal diseases also have the potential to exacerbate insulin resistance and worsen glycemic control, while periodontal treatment that decreases inflammation may help diminish insulin resistance.[42]

Proinflammatory cytokines. Patients with inflammatory periodontal diseases often have elevated serum levels of proinflammatory cytokines.[43] In patients with diabetes, hyperinflammatory immune cells can exacerbate the elevated production of proinflammatory cytokines. This has the potential to increase insulin resistance and make it more difficult for the patient to control his or her diabetes.[42] It also may explain the research showing a greater risk of poor glycemic control in patients with diabetes who have periodontitis compared with that in patients with diabetes who do not have periodontitis, as well as the research showing improvement in glycemic control after periodontal therapy in some patients with diabetes.

In a recent study of subjects with type 2 diabetes and periodontitis, Iwamoto and colleagues[44] found that periodontal treatment resulted in a significant reduction in serum levels of TNF-α that was accompanied by a significant reduction in mean HbA1c values (from 8.0 to 7.1 percent). The improvement in HbA1c values was correlated strongly with the reduction in serum TNF-α levels across the patient population. This suggests that a reduction in periodontal inflammation may help decrease inflammatory mediators in the serum that are associated with insulin resistance, thereby improving glycemic control.

CONCLUSION

Dentists should discuss with their patients the relationships between diabetes and periodontal health, using the evidence as a basis for discussion. Diabetes is associated with an increased risk of developing inflammatory periodontal diseases, and glycemic control is an important determinant in this relationship. Research reveals numerous biologically plausible mechanisms through which these interactions occur. Less clear is the impact of inflammatory periodontal diseases on the diabetic state.

While some evidence suggests that patients with diabetes who have periodontitis are at greater risk of developing poor glycemic control and that periodontal treatment aimed at reducing oral inflammation also may improve glycemic control, the evidence is not undisputed. Large, randomized, controlled intervention trials are needed to extend the evidence base. Inflammation is a

common link between periodontal diseases and diabetes. Further research is needed to clarify how inflammatory periodontal diseases may affect insulin resistance, glycemic control and the risk of developing other diabetic complications. ■

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