Periodontal Disease and Diabetes Mellitus

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Infections of the tissue surrounding the teeth (periodontitis) are usually caused by anaerobic gram-negative microorganisms. This infection causes destruction of the supporting alveolar bone and can lead to tooth loss. Removal of these microorganisms can slow or arrest the progression of periodontitis. Diabetes patients are at greater risk of developing periodontitis, may not respond as well to periodontal therapy as nondiabetic patients, and may require more aggressive treatment to manage periodontitis. Microorganisms that cause periodontitis and the host response to these may increase insulin resistance in diabetic patients. Treatment of periodontitis could improve glycemic control. A model is presented in which periodontal pathogens may cause increases in proinflammatory cytokines that mediate increases in insulin resistance, resulting in an increase in blood glucose. Following periodontal therapy, this process may be reversed.

Introduction

Research has established a strong relationship between periodontal disease and type 1 and 2 diabetes. This relationship can be seen clinically, and more recently on the molecular level. Periodontal disease has been described as a sixth complication of diabetes mellitus [1,2]. Evidence is mounting that poorly controlled diabetic patients are believed to have an increased risk for periodontal disease, and periodontal disease has the potential to affect glycemic control. The potential exists to influence the course and management of diabetes mellitus through periodontal therapy. Conversely, a poor healing response to periodontal therapy in diabetic patients may indicate poor glycemic control and warrant a medical consultation to rule out systemic influences on the periodontium.

Periodontal Disease

Collectively, the tissues anchoring the teeth in the mandible and maxilla are called the periodontium. The periodontal attachment apparatus consists of cementum, a layer of calcified interfibrillar matrix and collagen fibrils on the root surface of the tooth, the periodontal ligament, and alveolar bone. The periodontal ligament is principally collagen fibers anchoring the tooth to alveolar bone and provides shock absorption for the tooth. The dentogingival unit consists of gingival connective tissue fibers and the junctional epithelium. The gingival attachment creates a protective barrier preventing foreign material access to the connective tissue, alveolar bone, and root surfaces of the teeth, braces the gingiva against the tooth, and provides support necessary to withstand the forces of mastication.

There are a group of inflammatory diseases that affect the periodontal attachment apparatus, collectively known as periodontal diseases. These can be classified into six categories: 1) gingival diseases; 2) chronic periodontitis; 3) aggressive periodontitis; 4) periodontitis as a manifestation of systemic disease; 5) necrotizing periodontal diseases; and 6) abscesses of the periodontium [3]. Of these, two disease states, gingivitis and chronic periodontitis, account for the majority of these diseases seen in clinical practice. Gingivitis affects approximately 50% of adults in the United States [4]. This inflammatory process is usually due to local factors and is often self-limited. However, under certain conditions it may develop into chronic periodontitis. Chronic periodontitis is estimated to affect approximately 35% of the adult population, whereas the moderate to advanced forms of the disease is estimated to affect 13% to 15% of adults [5,6]. The following discussion pertains to chronic periodontitis, because other than gingivitis it is the most prevalent form of the disease seen most frequently by clinicians and it causes irreversible tissue destruction.

Currently chronic periodontitis, an inflammatory disease of the supporting structures of the dentition, is believed to be multifactorial with specific microorganisms or groups of microorganisms being the primary etiologic factor. Colonization of bacteria continuously occurs on the surfaces of the teeth. If allowed to accumulate, a subgingival biofilm develops consisting of an accumulation of bacteria enclosed in a polymetric matrix. The bacteria of the biofilm are associated with gingival inflammation. The biofilm is resistant to host defenses and antibiotic treatment. Among the 200 bacterial taxa that can inhabit the oral cavity, three specific gram-negative pathogens have been implicated as etiologic agents for chronic periodontitis: *Actinobacillus actinomycetemcomitans*, *Bacteroides*

forsythus, and *Porphyromonas gingivalis* [7]. Additionally, research suggests several other bacteria such as *Prevotella intermedia*, *Treponema denticola*, and *Eikenella corrodens* or various complexes of oral bacteria have a role in initiating or perpetuating periodontitis [8,9].

As dental plaque is allowed to accumulate, an inflammatory reaction occurs within the gingiva. As this plaque continues to adhere to the teeth and mature, in a susceptible individual the resulting inflammatory process may lead to clinical attachment loss, migration of the attachment apically on the root surface, gingival enlargement or recession, loss of alveolar bone, and periodontal pocket formation, or bleeding gums. With more advanced disease abscess formation, mobility of affected teeth or tooth loss can occur. Early in the inflammatory process up to 70% of the collagen in the gingival connective tissue is destroyed [10]. As the disease progresses the epithelial lining of the periodontal pocket loses its integrity resulting in ulceration of the periodontal pocket, allowing bacteria and bacterial products access to the underlying periodontal tissue. It has been estimated that in the patient with generalized advanced periodontitis the combined surface area of these ulcerations is approximately 72 cm^2 [11]. Studies have demonstrated that recurrent transient bacteremias occur in patients with daily activities such as tooth brushing and chewing [12].

Clinicians generally use the following methods to assess destruction of the attachment apparatus due to periodontitis: 1) visual examination for the clinical signs of tissue destruction; 2) radiographic examination for the evaluation of loss of alveolar bone surrounding the teeth; and 3) measurement of clinical attachment levels of the gingival tissue to the teeth with a periodontal probe [13]. The clinical diagnosis of periodontitis is usually made using a combination of these methods.

Microbial dental plaque is the primary etiologic agent of periodontal disease. The pathogenesis and progression of periodontitis can be influenced by numerous risk factors. These factors may include aging, cigarette smoking, stress, diabetes mellitus, genetic factors such as interleukin (IL)-1β polymorphism, specific systemic conditions or medications, and certain dental anatomic features [14].

Microbes suspected of being the etiology of periodontal disease possess features that contribute to the initiation and progression of disease. Virulence factors include the ability to colonize, evade the antibacterial host defenses, and produce substances that can directly initiate tissue inflammation and destruction. Certain strains of bacterial pathogens such as *P. gingivalis* and *A. actinomycetemcomitans* possess virulence factors that allow them to invade the tissue [8]. In addition, they are capable of producing proteolytic enzymes or leukotoxins, which allows them to evade the host response [15]. The suspected periodontopathic bacteria express antigens, lipopolysaccharide, and products that can affect the immune response and cell growth. *A. actinomycetemcomitans* and *P. gingivalis* produce proteases and metabolic byproducts that can degrade surrounding tissue [16]. Additionally, bone resorption can be induced by bacterial lipopolysaccharide [17].

The pathogenic organisms associated with periodontal disease induce an inflammatory cascade within the periodontium that may lead to host-mediated tissue destruction. It is generally believed the majority of periodontal destruction results from host-derived proteinases or matrix metalloproteinases. Although bacteria produce lytic enzymes, the tissue destruction seen in periodontitis occurs from the activation of the host response rather than direct bacterial challenge and is dependent on the host-parasite equilibrium [18]. Bacterial endotoxin, toxins, and cell membrane products challenge the host, activating an inflammatory cascade with the synthesis and secretion of IL-1β, tumor necrosis factor (TNF)-α, and IL–6, which induce and enhance the production of prostaglandin E_2 and matrix metalloproteinases. The upregulation of cytokines is a major factor in the connective tissue destruction and alveolar bone resorption seen in periodontal disease [19,20]. Cytokine levels are elevated in sites demonstrating periodontal disease. Specifically, IL-1β, TNF-α, and IL–6 levels increase during periods of tissue and bone destruction, whereas levels decrease after periodontal therapy [21,22].

Chronic periodontal disease is a relatively slowly progressing insidious disease that can remain undetected by the patient for years. Often, the first presenting symptoms may be a painful loose tooth, drifting teeth, or a painful abscess. Frequently, tissue destruction is of such a magnitude that it requires extraction of teeth. For this reason it is particularly important for persons with diabetes to have regular and systematic evaluation of the periodontal tissues by a health care professional to determine the need for periodontal treatment.

Being a chronic infection, treatment of periodontitis generally differs from treatment for acute infections. Treatment attempts to reduce the number of pathogenic organisms and produce a periodontium that is conducive for health. Mechanical therapy remains the treatment of choice for periodontitis. Traditional therapy includes the nonsurgical treatment of scaling and root planning along with various surgical modalities to improve access for débridement, reduction of periodontal pockets, and the regeneration of destroyed periodontal tissue where possible. The goal of mechanical therapy is to disrupt the biofilm, thus reducing bacterial virulence factors and allowing the host to re-establish periodontal health. Adjunctive antibiotics may be used when deemed necessary, but are generally used after mechanical disruption of the bacterial biofilm. Upon successful completion of periodontal treatment, patients are placed on maintenance therapy. In this phase of therapy patients are seen as frequently as every second or third month to disrupt the reformation of bacterial biofilm and prevent recurrence of the disease through the use of mechanical débridement.

Diabetes and Periodontal Disease

Studies have suggested that patients with poor glycemic control are at a greater risk for the development of infections than nondiabetic patients and that these infections occur with increased severity in diabetic patients [23,24]. Many of these infections are caused by gram-negative anaerobes.

It has been postulated that the subgingival microflora may be altered in diabetic periodontal patients as compared to nondiabetic patients, thus leading to more severe disease. Laboratory data from in vivo studies suggest that the microflora of type 1 and type 2 diabetic patients is not specific or unique to these periodontal patients when compared to nondiabetic patients [25,26].

The development of these infections correlates with the level of glycemic control in these patients [27]. The exact mechanism, which predisposes these individuals to infections, is not known, but several aspects of immunity may play a role. Reduced polymorphonuclear leukocyte (PMN) chemotaxis, phagocytosis, and an impaired antioxidant killing of bacteria have been implicated [28,29]. Thickening of the vascular basement membranes may reduce tissue nutrition and inhibit the migration of PMNs.

One team of investigators has hypothesized that increased accumulation of advanced glycation end products (AGEs) and their interaction with the receptor for advanced glycation end products (RAGE) in the gingiva of diabetic patients increases vascular permeability, loss of tissue integrity, and barrier function. The increase in AGEs in the tissue may also attract and immobilize monocytes with the release of proinflammatory cytokines and matrix metalloproteinases. Additional cells such as fibroblasts affected by AGEs may lead to an increase in matrix metalloproteinases and a decrease in collagen production. This cascade of events may contribute to an exaggerated response to periodontal pathogens, with accelerated connective tissue and bone destruction seen in patients with diabetes [30]. It has been suggested that AGE monocytes and RAGE interaction results in chronic monocyte generation of proinflammatory mediators such as IL-1β, TNF-α, and IL–6, whose ultimate effects may result in activation of osteoclasts and collagenases/matrix metalloproteinases, thereby leading to bone and connective tissue destruction [31].

Wound healing appears to be compromised in diabetic patients and the exact mechanism is not known. Possible mechanisms include altered cellular activities and failure of PMNs to migrate toward the area of wound healing. As previously mentioned, collagen synthesis is affected in diabetic patients with a decrease in the production of collagen. Increased cross-linking and glycosylation of collagen renders it less soluble and possibly increases remodeling time. Increased collagenase production may degrade newly formed collagen.

Extensive supporting evidence indicates that a relationship between poor glycemic control and periodontal disease exists. Investigators have determined that type 1 diabetic patients have an increased risk of developing periodontal disease with age, and the severity of periodontal disease increases with duration of diabetes than in nondiabetic patients [32,33]. Significantly more periodontal attachment loss and alveolar bone is lost in type 1 diabetic patients who have poor glycemic control than those who are well controlled or nondiabetic patients.

Multiple studies on the Pima Indian population in Arizona who have an unusually high prevalence of type 2 diabetes indicate that diabetic patients have a higher prevalence of periodontal disease [34,35]. Additionally, the persons in the group with poorly controlled diabetes have more severe periodontal disease with an increased risk of progressive bone loss [36]. These findings have been corroborated in other populations. Turkish patients with non–insulin-dependent diabetes mellitus had more severe periodontal disease than nondiabetic patients [37].

Diabetic patients with severe periodontitis may also have an increased risk of diabetic complications. A case-controlled study at baseline found these patients to have a greater prevalence of proteinuria, stroke, transient ischemic attack, angina, myocardial infarction, and heart failure than in diabetic patients with mild periodontal disease [38].

Two recent investigations provided evidence that treatment for periodontitis in type 2 diabetic patients resulted in an improvement in glycemic control. Both used glycated hemoglobin A_{1c} (HbA_{1c}) as a measure of glycemic control. The first study provided mechanical therapy to the test group and no periodontal therapy to the control group [39]. After 3 months, the reduction in HbA_{1c} was significantly greater for the test group than the control group, with a 21% versus 9% reduction.

A second investigation combined ultrasonic scaling with systemic doxycycline or irrigation with water, chlorhexidine, or povidone-iodine [40]. At 3 months the test groups receiving doxycycline had significantly greater reductions in HbA_{1c} that approached 10%. Those groups not receiving doxycycline had smaller and nonsignificant reductions in HbA_{1c}. The authors suggested the use of doxycycline was beneficial in two ways: first in part to its antimicrobial effects, and second due to the ability of the drug to modify the host response. Doxycycline, a modified tetracycline, may alter the host response by suppressing collagenolytic activity, increase protein synthesis and secretion, inhibit matrix metalloproteinases, inhibit nonenzymatic glycation, and block protein kinase C activity, a step in the secretion of IL-1β and TNF-α [40].

The effect of improved metabolic control of diabetes on periodontitis without periodontal therapy over a period of 8 months resulted in no significant improvement in the periodontal status of these patients [41]. There appears to be no conclusive evidence suggesting strict metabolic control will improve periodontal status without periodontal treatment. However, a cause and effect relationship has not been established. What has been well documented is that diabetic patients with good glycemic control will respond to periodontal treatment as well as nondiabetic patients

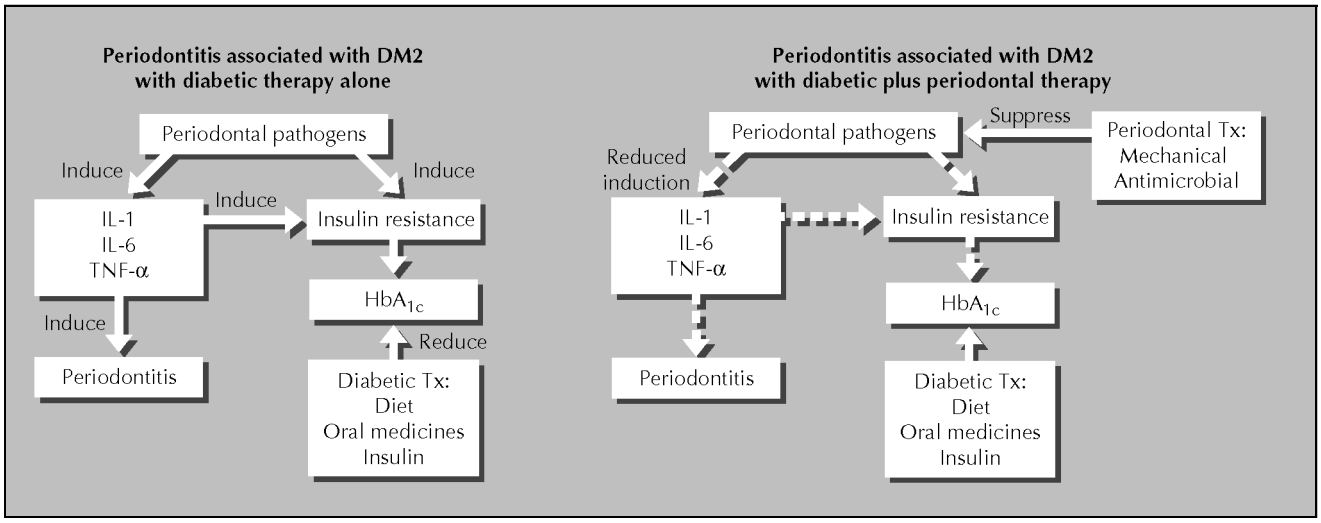

Figure 1. Hypothetical model of the association between periodontitis and type 2 diabetes mellitus (DM2). The *left side* shows that periodontal pathogens can induce proinflammatory cytokine release leading to periodontal tissue destruction. These cytokines may also induce insulin resistance and elevated hemoglobin A_{1c} (HbA_{1c}). The *right side* shows that when periodontal pathogens are suppressed by mechanical and antimicrobial therapy, reduced periodontal pathogens will be detected, leading to reduced proinflammatory cytokine release, improved insulin resistance, and reduced HbA_{1c}. IL—interleukin; TNF-α—tumor necrosis factor-α; Tx—treatment. (*From* Stewart *et al.*, Unpublished data.)

[42–44]. Poorly controlled patients may show an improvement in their periodontal status after therapy, but with less favorable results and recurrence of periodontitis over the long term [45]. Other studies have found that periodontal therapy did not have a statistically or clinically significant change in HbA_{1c} [42,43]. Two reviews of the literature suggest the current available research is insufficient to ascertain if periodontal therapy can contribute to the metabolic control of either type 1 or 2 diabetes [46•,47].

The systemic consequences of elevated proinflammatory cytokines in response to periodontal pathogens have not been fully investigated until recently. Insulin resistance occurs in both diabetic and nondiabetic patients during acute infections and during the recovery period, with an increase of 33% and 28%, respectively [48,49]. One suggested mechanism for the increase in insulin resistance is the release of cytokines, such as IL-1β and TNF-α, in response to bacteroides infections. It remains to be seen if chronic periodontal infections can result in increased insulin resistance.

Based on these data, we as well as others have developed a model to address the relationship between diabetes and periodontal disease. As can be seen in Figure 1, an increase in periodontopathic microorganisms causes levels of IL-β and TNF-α to rise, leading to increased insulin resistance with a concomitant rise in blood glucose. With removal of these pathogens, the pathways are reversed leading to a decrease in blood glucose. One hypothesis proposes "that periodontal infection-mediated cytokine synthesis and secretion may amplify the magnitude of the AGE-mediated cytokine response and vice versa. The relationship between diabetes and periodontal disease becomes a two-way relationship" [50•].

Conclusions

Additional research is needed to answer the following question: Will the treatment of periodontitis result in improved glycemic control? It will be important to determine if improved insulin resistance accompanies a decrease in the concentration of cytokines after periodontal therapy.

There is strong evidence that there is a connection between periodontal disease and diabetes on a molecular level. Poorly controlled patients with diabetes have an increased risk for periodontal disease, and periodontal disease has the potential to affect glycemic control. We have proposed such a model mediated by proinflammatory cytokines and insulin resistance. The potential exists to influence the course and management of systemic disease and health through periodontal therapy. A poor healing response to periodontal therapy may indicate systemic disease influencing healing and warrant a medical consultation to determine glycemic control in these patients.

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