Diabetes and Periodontal Infection: Making the Connection

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The oral cavity provides a continuous source of infectious agents, and its condition often reflects progression of systemic pathologies. Historically, oral infections were thought to be localized to the oral cavity except in the case of some associated syndromes and untreated odontogenic abcesses. A change in paradigm has dispelled this notion, and a whole new concept of the status of the oral cavity and its impact on systemic health and disease has evolved.

Diabetes affects > 18 million individuals in the United States and > 171 million individuals worldwide and has reached epidemic status.[1] The disease is characterized by an increased susceptibility to infection, poor wound healing, and increased morbidity and mortality associated with disease progression. Diabetes is also recognized as an important risk factor for more severe and progressive periodontitis, infection or lesions resulting in the destruction of tissues and supporting bone that form the attachment around the tooth.

Both diseases are thought to share a common pathogenesis that involves an enhanced inflammatory response that can be observed at the local and systemic level.[2–6] The inflammatory response is mainly caused by the chronic effects of hyperglycemia and specifically the formation of biologically active glycated proteins and lipids that promote inflammatory responses.[7,8]

Although there are undoubtedly underlying genetic contributions to diabetes and periodontitis, the focus of research in this area has targeted the bacterial and host contributions to expression of disease.[9–11] Both population-based and mechanistic studies have examined the potentiating effects of periodontal infection in the presence of hyperglycemia and have demonstrated increased innate immune responses and periodontal tissue destruction related to an altered inflammatory response.[12–15] Collectively these studies have provided insight into molecular mechanisms that support observed epidemiological associations between periodontal diseases and diabetes. The purpose of this review is to make the connection between periodontal disease and diabetes based on information in the literature and to discuss proper management and referral of patients who have signs and symptoms of periodontal disease and other oral complications.

PERIODONTAL DISEASE AND BACTERIAL INFECTION

Periodontal infection represents a complication that may be involved in altering systemic physiology in diabetic patients. Since periodontitis can be more than just a localized oral infection, the effects have been hypothesized to be far-reaching.[16,17] Severe chronic forms of this disease can result in systemic response to the bacteria and bacterial products that are disseminated due to breakdown of the periodontal apparatus (the ligament attachment around the tooth that includes the gingival tissues and bone). The interrelationships between diabetes and periodontal disease provide an example of systemic disease predisposing to oral infection, and once that infection is established, the oral infection exacerbates the progression of systemic disease.

In addition, it is also possible for oral infection to serve as a metabolic stressor that may exacerbate systemic disease. In order to understand cellular and molecular mechanisms responsible for such a cyclical association, one must identify common physiological changes associated with diabetes and periodontitis that produce a cooperative effect when the conditions coexist. Accumulation of advanced glycation end products (AGEs) as a result of the chronic hyperglycemic state or diabetes, coupled with the presence of infection and an exaggerated host response, may provide a viable explanation for the clinical outcomes observed in diabetic patients with periodontal disease.

Bacterial products such as endotoxin or lipopolysaccharide (LPS) also play a role in propagating an inflammatory response in the host through the Toll-like protein receptors (TLRs) and thus can induce an inflammatory cascade.[18] These receptors play an important role in the innate immune response, particularly in the initial interaction between the infecting microorganisms, such as *Porphy-*

IN BRIEF

This review focuses on the relationship between diabetes and periodontal infection and potential mechanisms involved in local and systemic disease progression. In addition, various oral complications of diabetes are discussed, along with recommendations for management, treatment, and proper referral.

romonas gingivalis, and phagocytic cells of the monocyte lineage.[19] Genetic and biochemical studies have shown that the toll protein family members play a critical role in the immediate response to infection.[20,21] Although LPS monocyte interactions provide one of the best-studied models of innate immunity using gram-negative bacteria and the bacterial endotoxin, the mechanisms behind periodontal disease and the regulation of TLR protein expression are still not well understood.

PERIODONTAL DISEASE AND DIABETES

Chronic hyperglycemia has been closely associated with an inflammatory response that has been linked to complications observed in diabetes. The presence of periodontal disease represents a unique opportunity for oral pathogens and their products to gain access to the systemic circulation. Bacterial toxins are known to elicit immune responses that can disrupt homeostasis of the system and in some instances can result in lethal outcomes to the individual.

Diabetes and periodontal disease are common chronic diseases observed in the U.S. population. These diseases are thought to be associated biologically, and a number of reviews and studies have proposed mechanisms to explain the relationship, including *1)* microvascular disease, *2)* changes in components of gingival crevicular fluid, *3)* changes in collagen metabolism, *4)* an altered host response, *5)* altered subgingival flora, *6)* genetic predisposition, and *7)* nonenzymatic glycation.[22–28]

In addition, in vitro studies of monocytes from people with diabetes have shown a hyperresponsive phenotype with overexpression of pro-inflammatory mediators such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and prostaglandin E_2.[3,29] In similar in vivo studies, patients with periodontitis and diabetes were found to have significantly higher levels of local inflammatory mediators compared to systemically healthy individuals with periodontal disease.[13,30]

Advances in the molecular biology of insulin resistance and β-cell dysfunction increasingly support a role for inflammatory mediators, particularly cytokines, and elements of the innate immune system in the pathogenesis of type 2 diabetes.[31] Cytokine production as a consequence of an infectious challenge could potentially contribute to insulin resistance in a number of ways, including *1)* modification of insulin receptor substrate-1 by serine phosphorylation,[32] *2)* alteration of adipocyte function with increased production of free fatty acids,[33,34] and *3)* diminution of endothelial nitric oxide production.[35,36] The process may also alter pancreatic β-cell function, either acting directly[37,38] or through stimulation of free fatty acid production.[39,40] In fact, cytokine-induced mechanisms have been suggested to participate in the β-cell damage or "burnout" seen in animal obesity models of type 2 diabetes that may be mediated through a c-Jun NH_2-terminal kinase–induced insulin resistance model.[41–43]

Fasting insulin is considered a marker, though imperfect, of insulin resistance. Increased resistance to skeletal muscle glucose uptake is part of the physiological adjustment to the catabolic milieu seen in inflammation.[44–47] As cytokines or inflammatory mediators decrease insulin sensitivity, insulin resistance may be part of a causal pathway linking inflammatory mediators to incident diabetes. Adipocytes produce large quantities of cytokines, such as TNF-α and IL-1β, in the presence of inflammation.[34] Infections have been investigated with regard to the development of coronary heart disease, with mechanisms similar to those discussed here being proposed to mediate their effects.[48–50] Diabetes and infections have long been known to contribute to metabolic dysregulation.[51–53] This fact allows us to speculate that repeated or chronic infections such as periodontitis, or some susceptibility to them, may represent an additional causal element for type 2 disease, a hypothesis that deserves further study.

ADVANCED GLYCATION

Evidence has accumulated supporting a role for AGEs in exacerbating diabetic systemic complications and periodontal disease severity associated with a chronic and intense inflammatory response. Moreover, AGEs have been associated with enhanced oxidant stress[54,55] and subsequent expression of endothelial expression of vascular cell adhesion molecule 1[56]; altered structure and function of basement membrane in vitro,[57] which are detected in situ in tissues from diabetic animals and humans;[56–58] upregulation of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6; and growth factors such as platelet-derived growth factor.[59–62]

The irreversible nature of AGEs and the interaction with their receptors[63] provides an environment in which tissues and cells are constantly exposed to these products, thereby creating a state of heightened cellular activity. The severity and progression of periodontal disease in diabetes often does not correlate with the classical presentation in a non–systemically challenged patient. The amount of tissue destruction found in patients with diabetes may not correspond to the etiological burden (i.e., bacterial plaque) observed clinically.

The host response during an infectious challenge involves a number of cytokines and hormones of the immune system. These effector molecules serve to modulate the interactions between various cells types involved in the inflammatory process. Inflammation is a complex set of events and involves release of mediators by resident and infiltrating cells. Chronic hyperglycemia with accumulation of AGEs is associated with increased expression of various genes regulated by the transcription factor nuclear factor-κB (NF-κB).[64] Strong evidence has accumulated to indicate that chronic dysregulation of NF-κB activation may contribute to

many inflammatory diseases, such as periodontal disease.[65–68] AGEs and LPS-induced NF-κB activation could be responsible for promoting the aberrant transcriptional gene regulation observed in diabetic patients with periodontitis that may be directly related to the accumulation of AGEs intra- and extracellularly.

PERIODONTITIS AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH DIABETES

Diabetes is a systemic disease with a number of major complications that may adversely affect quality and length of life, particularly as it relates to cardiovascular events and sudden death. Studies to date have reported conflicting associations between oral infection, coronary heart disease, and incident coronary heart disease.[69–71] However, there is evidence that dental infection is associated with coronary atherosclerosis and that bacterial DNA has been identified in atherosclerotic plaques,[65,66] and other studies have related dental infection to the incidence of coronary events.[65,66]

The Dental Atherosclerosis Risks in Communities Study is one of the studies providing evidence of a relationship between periodontal infection and presence of subclinical atherosclerosis.[67] Also, data available from the Insulin Resistance Atherosclerosis Study has shown that chronic hyperglycemia was positively associated with increased intimal-medial wall thickness (IMT). This study demonstrated an independent association between fasting glucose and individuals with established diabetes and IMT.[68]

Although studies have reported separately on associations of periodontitis and diabetes and periodontitis and coronary heart disease, the impact of periodontitis on progression of cardiovascular disease in individuals with diabetes has not been extensively investigated. It is believed that infection-mediated upregulation of cytokines and other inflammatory mediators play a central role in this pathological process. The high prevalence of cardiovascular disease and periodontitis in individuals with diabetes may be attributed to an increased inflammatory response leading to atherosclerosis that is usually more extensive and that develops at an earlier age compared to those without diabetes.

ORAL COMPLICATIONS OF DIABETES

Periodontal disease has been reported as the sixth complication of diabetes, along with neuropathy, nephropathy, retinopathy, and micro- and macrovascular diseases.[72] Many studies have been published describing the bidirectional interrelationship exhibited by diabetes and periodontal disease. Studies have provided evidence that control of periodontal infection has an impact on improvement of glycemic control evidenced by a decrease in demand for insulin and decreased hemoglobin A_{1c} levels.[73–75]

In addition to periodontal infection and gingival inflammation, a number of other oral complications have often been reported in patients with diabetes. These include xerostomia, dental caries, candida infection, burning mouth syndrome, lichen planus, and poor wound healing. Proper management of these complications requires that they first must be properly diagnosed. Many of the problems can be properly identified by provision of a comprehensive oral examination at each medical or dental visit.

Periodontal Disease and Gingivitis

The classic presentation of periodontal disease is associated with accumulation of plaque and calculus that harbors bacteria and potent virulence factors, which lead to destruction of periodontal tissues and resorption of alveolar bone around the teeth. Periodontitis is often preceded by various stages of gingival inflammation referred to as gingivitis. Gingivitis is an inflammation of the gums and is the initial and most easily treatable stage of gum disease.

The direct cause of gingivitis is plaque, the soft, sticky, colorless film of bacteria that forms constantly on the teeth and gums. Classic signs and symptoms of gingivitis include red, swollen, tender gums that may bleed upon toothbrushing. If gingivitis is not treated, it can and often will progress to periodontal disease. The infection then leads to formation of pockets between the teeth and gums signaling breakdown of the periodontal apparatus and bone. Some patients may experience recurring halitosis (bad breath) or a bad taste in the mouth, even if the disease is not advanced. The gum tissue around teeth may also have receded along the root surface, exposing the roots and giving teeth an elongated appearance.

Therapeutic goals for management of periodontal disease and gingivitis in patients with diabetes must involve elimination of infection by removal of plaque and calculus, a decrease in the inflammation response, and maintenance of glycemic control. Management should be accomplished by regular dental cleaning every 6 months by a licensed dental care provider and routine oral self-care (tooth-brushing and flossing) by patients.

Studies have compared the efficacy of different types of toothbrushes (manual, oscillating, or sonic) and have found that the mode of tooth-brushing may affect the amount of plaque retained interproximally.[76,77] Several studies have found the oscillating or sonic brushes most effective. The American Dental Association recommends brushing at least twice a day and daily flossing.[78,79] Generally, morning and night are convenient brushing times for most people. Toothbrushes should be replaced every 3–4 months. Children's toothbrushes may need to be replaced more often.

In addition, there are a number of over-the-counter and prescription oral antibacterial rinses that can decrease bacterial load to allow for tissue healing and repair. Listerine and chlorhexidine gluconate (Peridex) have the acceptance and seal of the American Dental Association's Council on Dental Therapeutics. Listerine involves bacterial cell wall

destruction, bacterial enzymatic inhibition, and extraction of bacterial LPS. Chlorhexidine has the ability to bind to hard and soft tissue with slow release.[80] Other products that have been shown to have promising antimicrobial effects are mouth rinses and dentifrices containing triclosan.[81,82]

Based on the amount of progression of periodontal disease, more aggressive therapeutic interventions may be indicated. Therapy may involve surgery, antimicrobials (local or systemic), or a combination of both.

Acute episodes of oral infection in diabetic patients should be addressed immediately. Appropriate antibiotics and pain management should be provided, along with referral to a dentist as soon as possible. The most common antibiotic used for treatment of acute dental infection is amoxicillin; for individuals who are allergic to penicillin, clindamycin is the drug of choice. Because of concerns within the medical and dental communities about the development of antibiotic resistant organisms, the minimum effective dose should be given. The dosage for amoxicillin is 250 mg, three times a day for 7 days, or clindamycin, 300 mg four times a day for 7 days. For patients with uncontrolled diabetes, the dosages may need to be higher and prescribed for longer periods of time to address defective immune and healing responses. Chronic periodontal disease should also be identified, and patients having it should be referred to a dental practitioner for evaluation and treatment.

Xerostomia and Dental Caries

Diabetes can lead to marked dysfunction of the secretory capacity of the salivary glands.[83] This process is often associated with salivary gland dysfunction. Xerostomia is qualitative or quantitative reduction or absence of saliva in the mouth. It is a common complication of head and neck radiation, systemic diseases, and medications.

Normal salivary function is mediated by the muscarinic M3 receptor.[84–86] Efferent nerve signals mediated by

acetylcholine also stimulate salivary glandular epithelial cells and increase salivary secretions.[87] Individuals with xerostomia often complain of problems with eating, speaking, swallowing, and wearing dentures. Dry, crumbly foods, such as cereals and crackers, may be particularly difficult to chew and swallow. Denture wearers may have problems with denture retention, denture sores, and the tongue sticking to the palate. Patients with xerostomia often complain of taste disorders (dysgeusia), a painful tongue (glossodynia), and an increased need to drink water, especially at night.

Xerostomia can lead to markedly increased dental caries, parotid gland enlargement, inflammation and fissuring of the lips (cheilitis), inflammation or ulcers of the tongue and buccal mucosa, oral candidiasis, salivary gland infection (sialadenitis), halitosis, and cracking and fissuring of the oral mucosa.[88,89] In patients with xerostomia, development of dental caries can be rampant and severe and, if left untreated, can result in infection of the dental pulp and tooth abcess.

The onset of caries requires *Streptococci mutans* bacteria. These bacteria adhere well to the tooth surface and produce higher amounts of acid from sugars than other bacteria in the mouth. When the proportion of *S. mutans* in plaque is high (in the range of 2–10%) a patient is at high risk for caries.[90–101] The combination of bacteria in the presence of a dry mouth and a source of sugar intake may lead to a high dental caries risk.

Etiology of xerostomia is associated with a noninflammatory, nonneoplastic enlargement of the parotid gland believed to occur in 25% of patients with moderate to severe diabetes and especially in patients with type 1 diabetes and poor metabolic control.[102]

Diagnosis of xerostomia and caries may be based on evidence obtained from patients' history or an examination of the oral cavity. Xerostomia would be suspected if a tongue depressor sticks to the buccal mucosa or, in women, if lipstick adheres to the front teeth. The oral

mucosa will also be dry and sticky or appear erythematous, which could be the result of an overgrowth of *Candida albicans*. These can be red or white patches or both, often found on the hard or soft palate or dorsal surface of the tongue. Occasionally, pseudomembranous candidiasis will be present, appearing as removable white plaque on any mucosal surface. There may be little or no pooled saliva in the floor of the mouth, and the tongue may appear dry with decreased numbers of papillae. The saliva may appear stringy, ropy, or foamy. Dental caries may be found at the cervical margin or neck of the teeth (the area where the tooth meets the gum) or the incisal margins (the edges or biting surfaces of teeth). Dry mouth is often exacerbated by activities such as hyperventilation, breathing through the mouth, smoking, or drinking alcohol.

Palliative interventions include saliva substitutes and stimulants. Many products can be purchased directly from the local pharmacy (xerolube, biotene products), while others will require prescription (pilocarpine, cevimeline).

Candidiasis

Oral candida is an infection of the yeast fungus *C. albicans*. The infection can occur as a side effect of taking medications such as antibiotics, antihistamines, or chemotherapy drugs. Other disorders associated with development of xerostomia include diabetes, drug abuse, malnutrition, immune deficiencies, and old age. Candida is present in the oral cavity of almost half of the population and has been shown be prevalent in people with diabetes as well. Studies have shown a higher prevalence candida in diabetic versus nondiabetic individuals.[103] In addition, Geerling et al.[104] reported a significantly higher prevalence of candida infection in people with diabetes.

The manifestation of candida can occur in many different forms and include median rhomboid glossitis, atrophic glossitis, denture stomatitis, and angular cheilitis. Candida does not generally become a problem until there is a

change in the chemistry of the oral cavity that favors candida over the other micro-organisms present. Contributing factors to infection are salivary dysfunction, a compromised immune system, and salivary hyperglycemia.[105,106]

Candida infection is also found commonly in denture wearers.[107] In the case of infection, the denture should be treated as well as the patient. The denture should be cleaned thoroughly and can be soaked or lined with anti-fungal medication or chlorhexidine. Further, ill-fitting dentures can cause breaks in the mucosal membranes at the corners of the mouth that can act as a nidus for candidal growth.

Treatment of candida infection is fairly straightforward and involves prescribing a therapeutic regimen of antifungals that can be applied locally. Common antifungals used are nystatin, clotrimazole, and fluconazole. Dosage for these medications will depend on the manifestation and extent of the infection and use of pastilles, lozenges, or troches to provide a local as well as systemic effect.

Lichen Planus

Oral lichen planus is a chronic inflammatory disease that causes bilateral white striations, papules, or plaques on the buccal mucosa, tongue, and gingivae. Erythema, erosions, and blisters may or may not be present. The pathogenesis of the disorder is unknown. Studies suggest that lichen planus is a T-cell–mediated autoimmune disease in which cytotoxic CD8+ T-cells trigger apoptosis of the oral epithelial cells.[108,109] Microscopically, a lymphocytic infiltrate is described that is composed of T-cells almost exclusively, and many of the T-cells in the epithelium adjacent to the damaged basal keratinocytes are activated CD8+ lymphocytes.

Lichen planus may predispose individuals to cancer and oral *C. albicans* superinfection.[110,111] Fewer than 5% of these patients will develop oral squamous cell carcinoma (SCC).[112] Atrophic, erosive, and plaque lesions may pose a

greater risk of malignant change, although SCC may arise in the unaffected oral mucosa as well.

The aim of treatment is to eliminate mucosal erythema, ulceration, pain, and sensitivity. This may involve topical or systemic steroid management. The use of steroids in individuals with diabetes may present additional complications, such as antagonism of insulin and subsequent hyperglycemia. Therefore, therapy by the dentist should be done in close consultation with the physician to avoid adverse reactions and drug interactions.

Burning Mouth Syndrome

A combination of factors appears to play a role in this process. Burning mouth syndrome is a chronic, oral pain condition associated with burning sensations of the tongue, lips, and mucosal regions of the mouth. The pathophysiology is mainly idiopathic but can be associated with uncontrolled diabetes, hormone therapy, psychological disorder, neuropathy, xerostomia, and candidiasis.[113,114] Generally, there are no detectable lesions associated with the syndrome, which is based solely on patient report of discomfort.

Treatment is targeted at the symptoms and requires attention to glycemic control, which will result in reduction of other complications involved in the process. Medications often used for this condition, benzodiazepines, tricyclic antidepressants, and anticonvulsants, have been shown to be effective therapies. Care must taken prescribing these medications to patients with diabetes because of associated xerostomic effects.

CONCLUSIONS

Maintenance of a healthy dentition for the purpose of asthetics, dietary intake and nutrition, quality of life, and overall general health is the ultimate goal of dental health care. In addition to public awareness and education efforts, much of dental care is focused on effective and efficient preventive and therapeutic management of two major clinical dis-

eases: dental caries and periodontitis.[115] While the prevalence of dental caries has declined in many but not all segments of the population, the prevalence of periodontal diseases in individuals with poorly controlled diabetes has been documented.[15,116]

Many studies conducted during the past decade have focused on a change in approach to studying periodontal infection and its relationship to systemic health and disease. Periodontal diseases are recognized as infectious processes that require bacterial presence and a host response. Risk factors in conjunction with bacteria and the host response can affect the severity of disease, patterns of destruction, and response to therapy.

Many medical conditions, particularly diabetes, predispose patients to development of more severe and progressive forms of periodontal disease.[117–119] In an effort to focus attention on the need for better oral health outcomes for patients with diabetes and periodontitis or other oral complications, providers should take several action steps, including:

1. Ask individuals with diabetes about their oral health, specifically if they have noticed any signs of infection, bad breath, or a bad taste in their mouth or if they have any other symptoms.
2. Inquire about the last dental and oral health examination.
3. Remind individuals with diabetes that they need periodic dental and periodontal examinations (every 6 months or more frequently) as recommended by the American Dental Association.
4. Encourage contact with patients' dental care provider if they notice signs of infection such as sore, swollen, or bleeding gums; loose teeth; mouth ulcers; or pain.
5. Perform an oral examination.
6. Refer all diabetic patients without a dental provider, regardless of oral findings or complaints, to a dentist for preventive care.

Although glycemic control is probably the single most important component in

maintenance of good oral health in individuals with diabetes, attention to these action steps will be very helpful toward achieving improved overall oral and systemic health. All of these measures play an important role in maintaining oral health, particularly in diabetic patients.

Many studies have emerged that focus on periodontal infection and systemic disease.[120–122] The information from these studies suggests that measures to combat complications of diabetes, especially periodontitis and gingivitis, may be important in reducing additional systemic inflammatory burden, thus potentially preventing diabetes, cardiovascular disease, and other systemic morbidities.

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