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Diabetes mellitus a risk to periodontium

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ABSTRACT

Diabetes mellitus (DM) is a complex disease with varying degrees of systemic and oral complications. The periodontium is also a target for diabetic damage. In recent years, a link between periodontitis and diabetes mellitus has been postulated. The oral cavity serves as a continuous source of infectious agents that could further worsen the diabetic status of the patient and serve as an important risk factor deterioration of diabetes mellitus. The present review highlights the relationship between diabetes mellitus and periodontitis. The potential mechanisms involved in the deterioration of diabetic status and periodontal disease are also discussed.

1. Introduction

The oral cavity is home to a vivid milieu of infectious agents, and its condition more often reflects the progression of systemic pathologies. There has been recently a shift in the paradigm from a traditional "oral cavity only" thought process to a systemic connection between the oral cavity and the internal milieu.[1]

Periodontitis is a chronic inflammatory disease characterized by the destruction of supporting structures of the teeth (periodontal ligament and alveolar bone).[2] Severe periodontitis has a prevalence of 10%–15% in the general population and has been shown to increase the risk of a first myocardial infarction as well as subclinical atherosclerotic heart disease.[1,3,4] It has been associated with the future cognitive decline, with poor control of hypertension, and with chronic obstructive pulmonary disease.[5–7] Periapical periodontitis has been shown to affect insulin sensitivity and exacerbate non-alcoholic steatohepatitis.[8,9]

Diabetes affects more than 415 million people worldwide and 69 million people in India.[10,11] It has reached an epidemic status and is predicted to affect 592 million people by 2035.[12] The prevalence of diabetes is likely to increase more in India compared to other countries.[12] An upsurge In diabetes has also led to an increase in various complications due to longer disease duration; neuropathy being the most common, followed by cardiovascular, renal, ocular, and foot complications.[13–15] Furthermore, Indians are more prone to earlier development of diabetic complications (20–40 years) than Caucasians (>50 years) which means diabetes must be carefully screened in the Indian population.[16]

Complications of diabetes pose a severe problem and cause the majority of morbidity and mortality in this population. Diabetes is associated with an increased susceptibility to infections, poor wound healing, and is hailed as a major risk factor for more severe and progressive periodontitis, leading to the destruction of tissues and supporting bone that forms the attachment around the tooth.[4]

In this brief review, we are going to discuss the interrelationship between these two closely linked diseases based on available literature.

2. Gingivitis

An overall assessment of the available data strongly suggests that diabetes is a risk factor for gingivitis and periodontitis.[17,18] In a classic study of diabetes and

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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.[19] Ervasti and colleagues[20] 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.[21] 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.[22]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 hyper inflammatory gingival response in people with diabetes.[23]

3. 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 five -fold increased prevalence of periodontitis in teenagers.[19] A recent case-control study confirmed that attachment loss is more prevalent and extensive in children with diabetes than in children without diabetes.[24] In addition, epidemiologic research supports an increased prevalence and severity of attachment loss and bone loss in adults with diabetes.[25,26] 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.[25,26] In a meta-analysis of studies conducted before 1996 that included more than 3,500 adults with diabetes, Papapanou[17] 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 II diabetes compared with that in adults who did not have diabetes.[27] 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.[28] 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.[27–29] However, other studies have shown only a marginal or insignificant relationship between glycemic control and periodontal status.[30,31] 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 the 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 six fold 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 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.[32] 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).[33–35] 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 non-significant reduction in HbA1c values.[36] When researchers performed scaling and root planning but did not administer adjunctive antibiotic therapy, the study results were similarly equivocal.[37–39] Some studies showed significant improvement in glycemic control after treatment,[37,38] while others showed no significant improvement in glycemic control despite improvements in patients' periodontal health.[39,40] 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.[41] This value was not statistically significant in the analysis. The addition of adjunctive systemic antibiotic therapy to the scaling and root planning regimen resulted in a mean absolute reduction of 0.7 percent in post treatment 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. 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 changes, in glycemic control.

4. 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[38] 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 planning 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 post treatment 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.

5. Mechanism of Interaction Between Diabetes & Periodontium

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, macro vascular diseases and altered wound healing. Because periodontal diseases are infectious diseases, research initially focused on possible differences in the sub gingival 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.[42] 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 immune inflammatory response to bacteria between people with diabetes and those without diabetes.

5.1. 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.[43] 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 immune inflammatory responses are up regulated in people with diabetes. For example, macrophages and monocytes often exhibit elevated production of pro inflammatory cytokines and mediators such as tumor necrosis factor α(TNF-α) in response to periodontal pathogens, which may increase host tissue destruction.[44,45] Elevated TNF-α levels are found in the blood and gingival crevicular fluid, suggesting both a local and systemic hyper responsiveness 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[46] found that crevicular fluid levels of interleukin 1 (IL-1) 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.

5.1.1. 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 properly in high glucose environments.[45] 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.[33] Thus, periodontal wound healing responses to chronic microbial insult may be altered in those with sustained hyperglycemia, result 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.[46] 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.[47,48] 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.[49–51] The accumulation of AGEs in patients with diabetes also increases the intensity of the immune inflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs.[47] Interactions between AGEs and their receptors on inflammatory cells result in the increased production of pro inflammatory cytokines such as IL-1 and TNF-.[49] This interaction may be the cause of the marked elevation in gingival crevicular fluid levels of IL-1 and TNF- 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.[45]

5.2. 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.[52] 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.[53]

5.2.1. Proinflammatory cytokines

Patients with inflammatory periodontal diseases often have elevated serum levels of proinflammatory cytokines.[54] In patients with diabetes, hyperinflammatory immune cells can exacerbate the elevated production of pro inflammatory cytokines. This has the potential to increase insulin resistance and make it more difficult for the patient to control his or her diabetes.[55] 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[56] 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.

6. 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.[57] 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 A1c levels.[58–60] 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.

7. Periodontal Diseases and Gingivitis

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.[61,62] 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.[63,64] 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.[65] Other products that have been shown to have promising antimicrobial effects are mouth rinses and dentifrices containing triclosan.[66,67] 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.

8. Xerostomia and Dental Caries

Diabetes can lead to marked dysfunction of the secretory capacity of the salivary glands.[68] 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.[69–71] Efferent nerve signals mediated by acetylcholine also stimulate salivary glandular epithelial cells and increase salivary secretions.[72] 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.

9. 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.[73] In addition, Geerling et al.[74] 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.[75,76]

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.

10. 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 Tcell–mediated autoimmune disease in which cytotoxic CD8+ T-cells trigger apoptosis of the oral epithelial cells.[77,78] Microscopically, a lymphocytic infiltrate is described that is composed of T-cells almost exclusively, and many of the Tcells in the epithelium adjacent to the damaged basal keratinocytes are activated

CD8+ lymphocytes.

11. 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.[79,80] 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.

12. 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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None.

14. Conflicts of Interest

All contributing authors declare no conflict of interest.

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