

White Papers

ORAL INFLAMMATION

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Oral Inflammation and Diabetes

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Diabetes mellitus is a chronic metabolic disorder affecting carbohydrate, fat, and protein metabolism. It is characterized by hyperglycemia (*i.e.*, elevation of blood glucose concentration) caused by the defective secretion of insulin (type I), or impaired insulin action due to tissue resistance (type II). While there is no known cure for diabetes, appropriate measures can be taken to control blood glucose levels and prevent both acute and chronic complications. Poor glycemic control in diabetic patients has several repercussions, including some on oral health. Patients with diabetes are prone to develop oral complications such as gingivitis and periodontal disease, fungal infections (oral candidiasis, lichen planus), dental caries, tooth loss, enlarged parotid glands, xerostomia, taste dysfunction, and burning mouth syndrome.^{1,2}

The most prominent oral symptom associated with diabetes is the increased prevalence and severity of periodontitis; it is recognized as one of the major complications of diabetes.^{3,5} Persistent poor glycemic control has been associated with an increased incidence and more rapid progression of gingivitis and periodontitis with associated alveolar bone loss.² The degree of metabolic control and the duration of diabetes are closely associated with the severity of periodontal disease.⁶

The pathogenesis of periodontal disease involves two components: bacterial infection and the host response. Bacteria present in periodontal pockets initiate an oral inflammatory response that can lead to the deterioration of the supporting periodontal tissues. When the host response is comprised of an excess of pro-inflammatory mediators known as cytokines, prostanooids, and enzymes, the destruction of periodontal tissues occurs. This results in increased pocket depths, loss of clinical attachment, and radiographic evidence of bone loss.⁷ In patients with poorly controlled diabetes, periodontal destruction is exacerbated due to hyperglycemia.⁶

Hyperglycemia and Oral Health

The effects of hyperglycemia on oral health are two-fold. First, it causes an increase in the concentration of glucose in the saliva and the gingival crevicular fluid of the periodontal pocket,

contributing to bacterial proliferation and oral inflammation. Second, hyperglycemia increases the formation of advanced glycation end-products (AGEs); the overexposure of proteins (such as collagen) or lipids to aldose sugars induces non-enzymatic glycation and oxidation.⁶ These glycosylated products can create complex molecular arrangements, reducing collagen solubility and increasing levels of pro-inflammatory mediators responsible for the degradation of connective tissues throughout the body of the diabetic, including the

Factors Accentuating Periodontal Disease in Diabetic Patients

- Duration of diabetes
- Degree of metabolic control
- Co-occurrence of complications
 - Angiopathy (heart disease and stroke)
 - Delayed wound healing
 - Nephropathy (kidney disease)
 - Neuropathy
 - Retinopathy (eye disease)
- Concurrent risk factors
- Hormonal variations (*e.g.*, adolescence, pregnancy, menopause)
- Medications
- Plaque
- Smoking
- Stress

From Ryan *et al.*, 2003⁸

oral cavity. Changes to collagen metabolism result in accelerated degradation of both non-mineralized connective tissue and mineralized bone.⁶ Research has demonstrated the presence of elevated levels of pro-inflammatory mediators in the gingival crevicular fluid of periodontal pockets of poorly controlled diabetics, compared to non-diabetics or well-controlled diabetics, resulting in significant periodontal destruction with an equivalent bacterial challenge.^{3,6,8} For clinicians and diabetic patients, this means that the oral hygiene of the diabetic must be optimized to prevent further stimulation of an already primed and heightened host response.

The interaction of AGEs with target cells, such as macrophages, via cell-surface polypeptide receptors stimulates the production of cytokines and matrix

metalloproteinases, including collagenases and other connective tissue-degrading enzymes.³ This exacerbation of the pro-inflammatory response in diabetics can lead to delayed wound repair and amplify damage to connective tissues.⁶ This is important to consider when evaluating the response of poorly controlled diabetic patients to periodontal therapy. The pro-inflammatory response may be further heightened by the chemotactic properties of AGEs for human monocytes which differentiate into the chronic inflammatory macrophage cells.⁶

Degradation of newly synthesized collagen in connective tissues and alterations in the immune response can both contribute to predisposition to periodontal disease and impaired wound healing. The degree of metabolic control and the presence of other complications (e.g., retinopathy and nephropathy) can be predictive of the periodontal status. Concurrent risk factors (plaque, smoking, stress, medications, pregnancy, hormonal variations) are cumulative and should be considered in the assessment of the periodontal status of a patient.⁶

The presence of AGEs has also been linked to thickening of the basement membrane and altered vasculature. These changes may be associated with enlargement of the parotid glands and decreased salivary flow seen in diabetics, which facilitates plaque accumulation and increases the risk for caries, gingivitis, periodontitis, and candidiasis. Degenerative vascular changes may interfere with nutrient and leukocyte migration to gingival tissue, decreasing oxygen diffusion and elimination of metabolic waste, thereby increasing the severity of periodontitis by decreasing dental healing capacity.⁶ Collectively, diabetes creates specific conditions leading to enhanced oral inflammation associated with overproduction of inflammatory mediators and degradation enzymes, all of which participate in worsening periodontal disease.

Oral-Systemic Interactions

While a systemic condition like diabetes can affect oral health, there is growing evidence that oral infections can also have systemic repercussions.⁹ This bi-directional relationship is especially important for the metabolic control of diabetes. Studies of active inflammatory connective tissue disease have shown that inflammation can trigger insulin resistance.¹⁰ Cytokines, such as tumor necrosis factor (TNF)- α , have been reported to interfere with lipid metabolism and to cause insulin resistance, while interleukins (IL)-1b and IL-6 antagonize insulin action.¹⁰ The host-mediated inflammatory response can thus hinder glycemic control in diabetic patients, in turn creating a vicious cycle of events that compromises diabetes control and

further stimulates periodontal disease. Poor metabolic control of diabetes can also increase the risk for other complications of diabetes, such as angiopathy, nephropathy, retinopathy, neuropathy, and delayed wound healing. Prevention and control of oral infection and inflammation, i.e., periodontal disease, is essential for appropriate prevention and optimal management of diabetic complications.¹¹

It is also thought that elevations of AGEs in gingival tissue increase vascular permeability.¹¹ An inflamed periodontium is highly vascular and may serve as a portal to the systemic circulation for bacterial products (bacteremias) and host-produced local inflammatory mediators.¹⁰ Other connections between a poor periodontal status and systemic health sequelae have been studied; adverse pregnancy outcomes and cardiovascular disease are both known complications in diabetics. Recent research has shown that pregnant women with severe periodontitis have a higher risk of giving birth to preterm low-birth-weight babies. Other studies have shown that the risk of major cardiovascular events, such as heart attack and stroke, is significantly higher in those with severe periodontal disease.⁷ It has become apparent that prevention and treatment of periodontitis are essential to optimal systemic health, particularly in the diabetic patient.

Management of Diabetes and Oral Inflammation

Control of blood glucose is the fundamental aspect of diabetes management to minimize related complications. Adequate glycemic control will not only reduce glucose concentration in serum, gingival crevicular fluid, and saliva, but also reduces AGE formation and limits inflammation.¹¹ Prevention and control of periodontal disease must be considered an integral aspect of diabetes management, since improved oral health can lead to improvements in the overall health of diabetic patients.¹¹

Given the increased susceptibility of diabetic patients for oral inflammation, emphasis should be placed on reduction of bacterial infection and gingivitis. An optimal prevention plan should include twice-daily brushing and flossing to remove bacterial plaque from teeth.¹² A dentifrice containing triclosan/copolymer (Colgate Total[®] Toothpaste) has been shown to be very effective in controlling bacterial infection, reducing plaque and gingival inflammation, and preventing or slowing the progression of periodontitis.¹³ Restriction of oral infection and inflammation as manifested in periodontitis contributes to the maintenance of normal blood glucose levels, which aids in the overall management of diabetic patients.

For the treatment of periodontitis, a two-step process aimed at the two components of the disease offers the most favorable outcome.¹² The

first step is reduction and control of bacteria, both supragingival and subgingival, in the tooth pockets and spaces around teeth. Scaling and root planing helps remove bacterial plaque and associated toxins from the tooth and root surfaces, and can help to prevent the bacterial accumulation that is common on rough surfaces. The second step is inhibition of the enzymes that destroy periodontal tissue so that connective tissue degradation is minimized (host modulation therapy). Clinical trials have demonstrated the efficacy of some tetracycline analogs to inhibit a series of host-derived, tissue-destructive enzymes and inflammatory mediators,^{5,8} thereby reducing the connective tissue damage associated with periodontitis.

Conclusion

Diabetes is a complex disease with a wide range of potential complications, including effects on oral health. Integrated strategies for the prevention and treatment of periodontal disease involving the removal of periodontal pathogens and host modulation therapy greatly reduce the risk for severe periodontitis, and can help in the overall management of the diabetic patient. A diabetic patient who maintains rigorous glycemic control and good oral health has the same risk of severe periodontitis as a non-diabetic patient, emphasizing the importance of diabetes and oral health management.

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