

# Oral Manifestations of Diabetes

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**D**iabetes is a clinically and genetically heterogeneous group of metabolic disorders manifested by abnormally high levels of glucose in the blood. This hyperglycemia results from either a deficiency of insulin secretion caused by pancreatic  $\beta$ -cell dysfunction or resistance to the action of insulin in liver and muscles, or both (1). Periodontal disease is one of the most common chronic inflammatory diseases and is characterized by gradual destruction of connective tissue surrounding the teeth, eventually leading to tooth loss. Periodontitis occurs primarily in adults, and its incidence increases with age (2). Type 2 diabetes and chronic periodontitis are both common in older age-groups. The relationship between both these diseases has been extensively studied.

## Epidemiological Considerations

The prevalence of type 2 diabetes is increasing rapidly. According to World Health Organization estimates, the number of adults with diabetes worldwide will increase from 171 million in 2000 to 366 million by 2030 (3). India has been called “the diabetes capital of the world” because of its high diabetes rates; ~41 million Indians have diabetes, accounting for one-fifth of all diabetes cases worldwide (4). The prevalence of periodontal disease in India is also alarming, with incidences of 296 million in 2000, 319 million in 2005, 341 million in 2010, and an estimated 363 million in 2015 (5). Both diabetes and periodontitis are

more severe and progress more rapidly when these conditions occur simultaneously.

Many studies have reported correlations between periodontal health and various diabetes-related factors such as A1C and duration of diabetes. In the U.S. Third National Health and Nutrition Examination Survey (2), adults with an A1C >9% had a significantly higher rate of severe periodontitis than those without diabetes. Periodontitis is considered a “sixth complication of diabetes” (6). A study by Williams and Mahan (7) involving 2,273 people with diabetes found a 60% prevalence of periodontal disease; the incidence of periodontitis was two- to fourfold higher.

## Oral Manifestations of Diabetes

The effects of diabetes on oral health have been studied extensively. Diminished salivary flow is a common oral feature of diabetes and may or may not include symptoms of a burning sensation in the mouth or tongue and concomitant enlargement of the parotid salivary glands (8). Table 1 shows the prevalence rates of these and other oral manifestations in controlled and uncontrolled diabetes (9). As the table clearly shows, these manifestations are more prevalent in individuals with uncontrolled diabetes (10).

## Effects of Diabetes on the Periodontium

Diabetes is a risk factor for gingivitis and periodontitis, and the degree

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DOI: 10.2337/diaclin.34.1.54

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**TABLE 1. Prevalence of Oral Manifestations in Controlled and Uncontrolled Diabetes (9)**

Oral Manifestation	Prevalence in Controlled Type 2 Diabetes (%)	Prevalence in Uncontrolled Type 2 Diabetes (%)
Hyposalivation	68	84
Halitosis	52	76
Periodontitis	32	48
Burning mouth sensation	32	24
Candidiasis	28	36
Taste alteration	28	44

of glycemic control appears to be an important determinant in this relationship (11). Individuals with type 1 diabetes and high blood glucose levels are more likely to have advanced periodontal diseases, and there are increases in the prevalence and severity of gingival inflammation and periodontal destruction in these patients (12). In people with poorly controlled type 2 diabetes, one study found an 11 times higher risk of alveolar bone loss over a 2-year period compared to control subjects without diabetes (13).

### Mechanisms of Diabetes' Effects on Periodontal Disease

#### Subgingival Microflora

Differences in the subgingival microflora of diabetic and nondiabetic patients with periodontitis have been reported (14), with a higher proportion of *Capnocytophaga* species in those with diabetes. However, an apparent lack of significant differences in potential pathogens suggests that alterations in the host immune inflammatory response may play a major role in the increased prevalence and severity of periodontal destruction in people with diabetes.

#### Host Immune Cells

The function of immune cells, including neutrophils, monocytes, and macrophages, is altered in diabetes. Neutrophil adherence, chemotaxis, and phagocytosis are often impaired, which may inhibit bacterial killing in the periodontal pocket and significantly increase periodontal destruction (15). Peripheral blood monocytes

from individuals with diabetes produce elevated levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in response to antigens from *Porphyromonas gingivalis* compared to monocytes from control subjects without diabetes (16). The effects of a hyperglycemic state include inhibition of osteoblastic cell proliferation and collagen production, which results in decreased bone formation and diminished mechanical properties of the newly formed bone (17).

#### Gingival Crevicular Fluid Glucose Levels

Increased plasma glucose levels are also reflected in elevated gingival crevicular fluid (GCF) glucose levels in individuals with diabetes (18). High GCF glucose levels directly hinder the wound-healing capacity of the fibroblasts in periodontium by inhibiting the attachment and spreading of these cells that is crucial for wound-healing and normal tissue turnover.

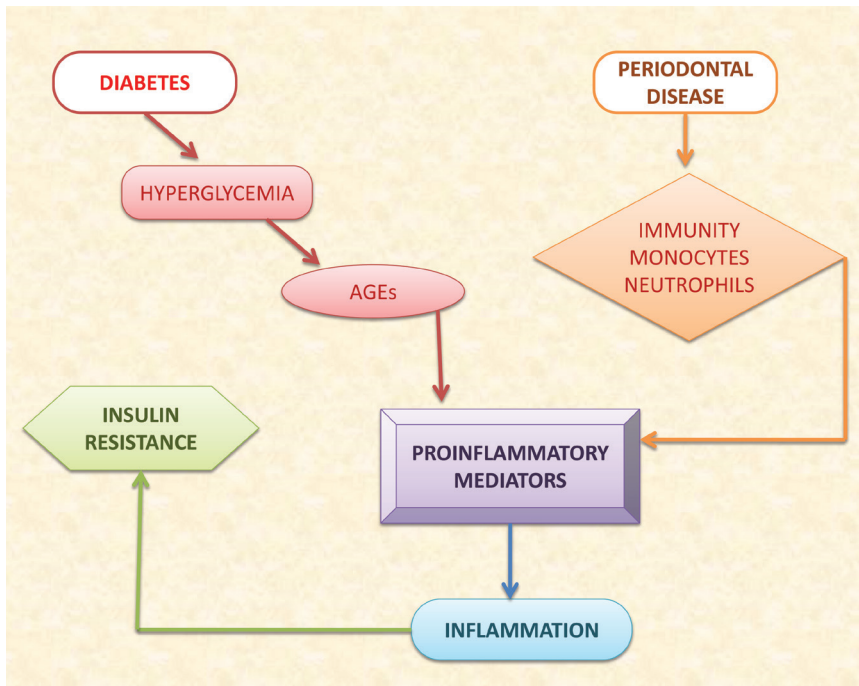
#### Advanced Glycation End Products

In conditions of sustained hyperglycemia, proteins combine with glucose molecules and undergo glycation to form advanced glycation end products (AGEs). These AGEs often form on collagen and increase collagen crosslinking, leading to formation of collagen macromolecules that sustain normal enzymatic degradation. Human gingival fibroblasts produce decreased amounts of collagen and glycosaminoglycans in the hyperglycemic state. The residual newly formed collagen is highly susceptible

to enzymatic degradation by collagenase, which is mostly present in active form in people with diabetes (19). All of these factors lead to altered collagen metabolism, which affects the normal wound-healing process. Collagen modified by AGEs accumulates on arterial walls, resulting in various macrovascular complications of diabetes. The basement membrane of endothelial cells also accumulates AGE-modified collagen, resulting in increased thickness in the microvasculature and altering normal homeostatic transport across the membrane. AGE-bone collagen may influence cellular, structural, and functional characteristics, leading to alterations in bone metabolism (20).

#### Receptors for AGEs

AGEs activate receptors for AGEs (RAGEs). These receptors are found on surfaces of smooth muscles, endothelial cells, neurons, and monocytes/macrophages and in the periodontium (21). A 50% increase in messenger RNA for RAGEs was identified in the gingival tissues of subjects with type 2 diabetes (22). Hyperglycemia results in increased expression of RAGEs and AGE-RAGE interaction on the endothelium, increasing vascular permeability. AGE-RAGE interaction on monocytes increases cellular oxidant stress and activates the transcription factor nuclear factor- $\kappa$ B, resulting in increased production of proinflammatory cytokines such as interleukin-1 $\beta$  and TNF- $\alpha$ . In a study of diabetic animal models (23), Lalla et al. found that blocking RAGEs decreases TNF- $\alpha$ , interleu-



**FIGURE 1.** A schematic presentation of the two-way relationship between diabetes and periodontitis.

kin-6, and matrix metalloproteinase levels in the GCF, diminishes accumulation of AGEs in periodontal tissues, and decreases alveolar bone loss in response to *P. gingivalis*.

### Mechanisms of Periodontitis' Effects on Diabetes

People with diabetes and periodontal infection have a greater risk of worsening glycemic control over time compared to people with diabetes who do not have periodontitis (24). Clinical trials in people with diabetes have reported improvement of glycemic control and decrease in insulin requirements after periodontal treatment, particularly when mechanical therapy was supplemented with the use of antibiotics (25–27).

### Role of Inflammatory Mediators

Because periodontitis leads to enhanced local production of proinflammatory mediators, the spilling of these mediators into the systemic circulation has been proposed as a mechanism whereby periodontal infection could amplify the cytokine dysregulation associated with diabetes (25). People with diabetes and peri-

odontitis have enhanced production of inflammatory mediators in the gingival tissues compared to people without diabetes who have periodontitis (28). These mediators can increase inflammation and worsen insulin resistance (Figure 1).

### Effects of Periodontal Therapy on Glycemic Control

Many studies have shown that periodontal therapy improves glycemic control in people with diabetes. Periodontal therapy in diabetic patients improved glycemic control by 17.1%, compared to 6.7% in diabetic patients who did not receive periodontal therapy (29). Effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a reduction in A1C. Control of periodontal infections thus should be an important part of the overall management of diabetes (25). In one study (30), A1C was reduced from a mean of 8.7% at baseline to a mean of 7.8% at follow-up after scaling and root planing (SRP) and the use of 0.2% chlorhexidine mouth wash. Janket et

al. (31) carried out a meta-analysis of 10 intervention studies to estimate the effect of periodontal treatment on A1C and found a weighted mean reduction of 0.66% in people with type 2 diabetes, although this change did not achieve statistical significance. A study by Singh et al. (32) showed that nonsurgical periodontal therapy was associated with improved glycemic control, and the use of systemic doxycycline resulted in a statistically significant improvement in A1C. Faria-Almeida et al. (33) evaluated the effect of SRP on the clinical parameters and glycemic control of people with and without diabetes. She found that those with diabetes showed improved metabolic control (i.e., lower A1C levels) 3 and 6 months after periodontal treatment. In another study, Dodwad et al. (34) observed significant reductions in A1C and C-reactive protein in a group receiving tetracycline plus SRP compared to a group receiving SRP alone. A study by Telgi et al. (35) concluded that nonsurgical periodontal therapy can effectively decrease A1C in people with type 2 diabetes who are on medication. In addition, Pradeep et al. (36) found that, in people with type 2 diabetes and chronic periodontitis, local delivery of 1% alendronate into periodontal pockets resulted in significantly greater reduction in probing depth, clinical attachment gains, and improved bone fill compared to placebo gel as an adjunct to SRP.

### Conclusion

Understanding the two-way relationship between diabetes and periodontitis is important for health care professionals who treat either condition. Medical management of patients of diabetes should include consideration of possible oral conditions. Similarly, treatment of oral diseases should include systemic evaluation of patients for diabetes. To achieve successful results, both diseases should be controlled and treated properly when they occur as comorbid conditions.



## Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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