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Impact of uncontrolled diabetes on oral disease progression and healing

Pooja Jha<sup>1</sup>, Dr. Vandana<sup>2</sup>, Farha Azmeen<sup>3</sup>, Dr. Kunal Kishor<sup>4</sup>

\*1,3 Research Scholar, Department of Microbiology, School of Allied Health Sciences, Sharda University, Greater Noida Uttar Pradesh, India

2 Assistant Professor, Department of Microbiology, School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India

4 Professor, Department of Microbiology, School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India

Corresponding author's mail: [vandana.singh@sharda.ac.in](mailto:vandana.singh@sharda.ac.in)

[Assistant Professor, Department of Microbiology, School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India](#)

<i>Article History</i>	<i>Abstract</i>
<p>Received: 03-July-2023 Revised: 28-July -2023 Accepted: 10-August-2023</p>	<p>The two most prominent chronic diseases affecting people today, diabetes mellitus and periodontal disease, astonishingly, have a lot in common. Periodontitis is more common in persons with uncontrolled diabetes, according to epidemiologic data. The term "periodontitis" refers to a set of conditions that affect the alveolar bone, gingiva, root cementum, and periodontal ligament, which together make up the tooth's supporting structure. Gingivitis and periodontitis, the two most prevalent types of periodontal disorders, are defined by a host response cascade that is triggered by the presence of bacteria and results in periodontal tissue damage. Several shared predisposing variables of a genetic, microbiological, and lifestyle origin as well as the production of advanced glycation end products as a result of hyperglycaemia are thought to be the mechanisms behind the connections between diabetes mellitus and periodontal disease. Uncontrolled diabetes and the accompanying hyperglycaemia are known to have a role in the development and progression of oral disorders. Diabetes also affects normal tissue reparative responses inside the oral cavity, which can hamper healing and result in clinical problems.</p>
<p>CC License CC-BY-NC-SA 4.0</p>	<p><b>Keywords:</b> <i>Diabetes, periodontal disease, hyperglycaemia, healing</i></p>

## Introduction

The oral microbiome may play an important role in diabetes etiology – although it is also possible that the varying glucose concentrations affect the types and abundance of microbes. Diabetes is a clinically and genetically heterogeneous group of metabolic disorders manifested by abnormally high levels of glucose in the blood. Diabetes can affect your mouth by changing your saliva—the fluid that keeps your mouth wet. Saliva helps prevent tooth decay by washing away pieces of food, preventing bacteria from growing, and fighting the acids produced by bacteria. Saliva also has minerals that help protect tissues in your mouth and fight tooth decay. Diabetes can also increase the amount of glucose in your saliva. Diabetes occurs when your blood glucose level, also called blood sugar, is too high. High levels of glucose in your blood can also cause glucose to build up in your saliva. This glucose can feed harmful bacteria that combine with food to form a soft, sticky film called plaque, which causes cavities. If you don't remove plaque, it can also build up on your teeth near your gum line and harden into a deposit called tartar, which can cause gum disease. This hyperglycaemia 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. 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. Diabetes is a risk factor for gingivitis and periodontitis, and the degree of glycaemic control appears to be an important determinant in this relationship. 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. 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. Peripheral blood monocytes from individuals with diabetes produce elevated levels of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) in response to antigens from *Porphyromonas gingivalis* compared to monocytes from control subjects without diabetes. The effects of a hyperglycaemic 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. 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 hyperglycaemic 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. All 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. People with diabetes and periodontal infection have a greater risk of worsening glycaemic control over time compared to people with diabetes who do not have periodontitis. 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. 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. Uncontrolled blood sugar lowers the healing response, which makes repairing gums and fighting off infection that much harder. “The mouth is the gateway to the body and is a perfect environment for bacteria to multiply.” Bacteria can then make its home in the gums. A healthy body finds it easier to fight off bacteria, but a body with disease (such as diabetes) or inflammation can't fight those bacteria as easily which can turn into a gum infection

Oral health problems are associated with diabetes

1. Dry mouth: Unmanaged diabetes can decrease saliva (spit) flow, resulting in dry mouth. Dry mouth can further lead to soreness, ulcers, infections, and tooth decay.
2. Gum inflammation (gingivitis) and periodontitis: Besides weakening white blood cells, another complication of diabetes is that it causes blood vessels to thicken. This slows the flow of nutrients to and waste products from body tissues, including the mouth. When this combination of events, the body loses its ability to fight infections. Since periodontal disease is a bacterial infection, people with unmanaged diabetes might experience more frequent and more severe gum disease.
3. Poor healing of oral tissues: People with unmanaged diabetes do not heal quickly after oral surgery or other dental procedures because blood flow to the treatment site can be damaged.
4. Thrush: People with diabetes who frequently take antibiotics to fight various infections are especially prone to developing a fungal infection of the mouth and tongue. The fungus thrives on the high glucose levels in the saliva of people with unmanaged diabetes. Wearing dentures (especially when they are worn constantly) can also lead to fungal infections.
5. Burning mouth and/or tongue: This condition is caused by the presence of thrush.

### Subgingival Microflora

Differences in the subgingival microflora of diabetic and nondiabetic patients with periodontitis have been reported (14), with a higher proportion of *Campylobacter* 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.

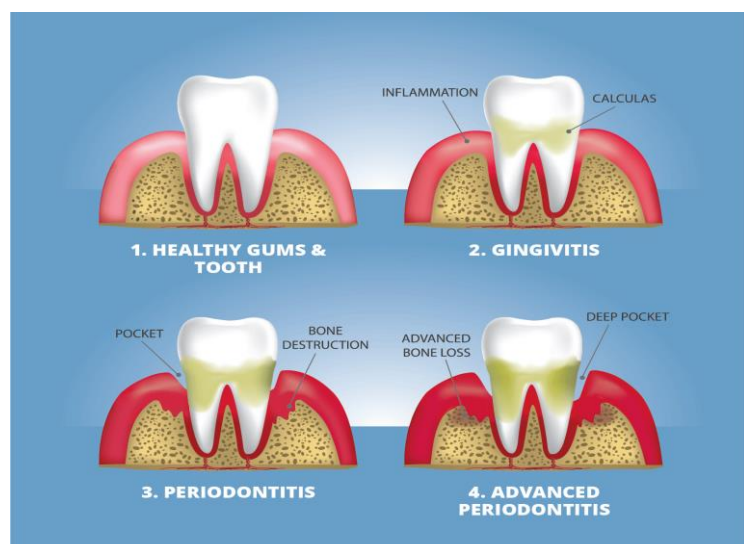
### Mechanisms of Diabetes' Effects on Periodontal Disease

#### Gingivitis, or inflamed gums

The first stage of gum disease is gingivitis, a mild inflammation of the soft tissues around your teeth. Gingivitis develops when plaque and tartar build up on your teeth near your gum line, irritating and inflaming your gums. As a result, your gums may become red and swollen, and may bleed easily.

#### Periodontitis

Untreated, gingivitis can progress to periodontitis, an infection of the gums and bone that hold your teeth in place. Your gums may pull away from your teeth, forming pockets that slowly become infected. The bacteria in your mouth and your body's response to the infection start to break down the bone and tissue that hold your teeth in place. If periodontitis is not treated, the teeth can become loose and may even need to be removed.

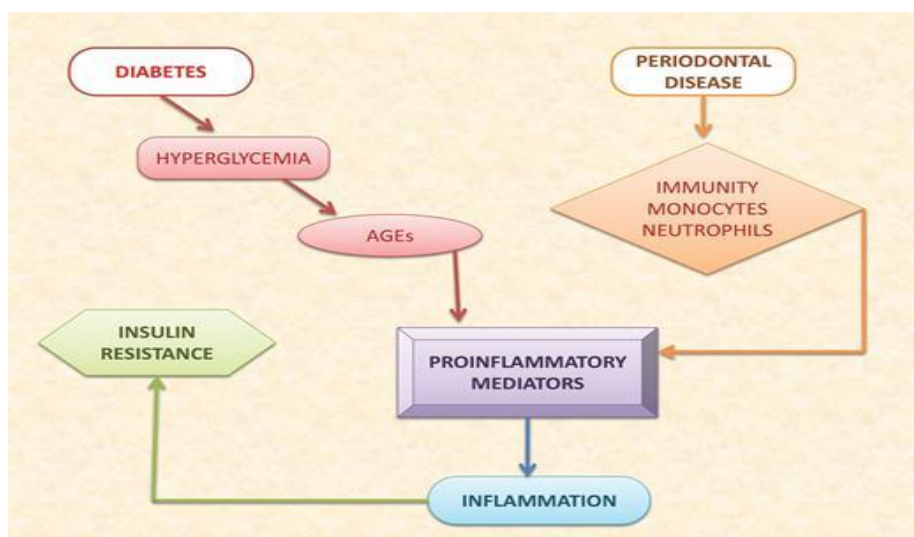


People with diabetes are more likely to have gum disease, cavities, and other problems with their teeth and gums and some of these mouth problems can make your diabetes worse. Taking good care of your teeth and gums, including getting regular cleanings and needed treatments, will help you prevent these problems or stop them from getting worse.

Bacteria in plaque, a sticky film, use sugar as food. Some of these bacteria can cause tooth decay, cavities, and gum disease. If the tooth is not treated, it can also lead to tooth loss. Gum disease can be more severe and take longer to heal if you have diabetes. If you have gum disease, your diabetes may be harder to manage.

#### Association between periodontitis and diabetes-pathophysiology

Type 2 DM is established as a major cause for periodontal disease with an estimated threefold increased manifestation in comparison to nondiabetics. Associated risk of tooth loss and subsequent edentulousness has raised concerns of undermined quality of life emphasizing the need for early diagnosis of this disease condition. DM has been indisputably substantiated as a paramount risk factor for periodontitis. Chronic periodontitis is ideally detected in the initial stages of the disease.



**Fig1.** Bidirectional between diabetes and periodontal disease

Increased plasma glucose levels are also reflected in elevated gingival crevicular fluid (GCF) glucose levels in individuals with diabetes. 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.

### Pathogenesis

The following two mechanisms explain the role of periodontal disease in systemic diseases:

- Direct mechanism: The endotoxins produced mainly by Gram-negative anaerobic bacteria in the oral cavity are known to directly contribute to systemic disease. The periodontal pathogens gain access into the blood circulation through the ulcers located in the soft tissue walls of the periodontal pockets resulting in collagen degradation, aggregation of platelets and thrombus formation [14,15,16];
- Indirect mechanism: This involves a possible trigger to periodontal pathogens producing inflammatory mediators in the body such as C-reactive protein (CRP), tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, prostaglandin E2 (PGE2) and matrix metalloproteinases (MMP) causing an autoimmune reaction.
- Periodontitis and Diabetes Mellitus: The Potential Mechanism of Bidirectionality

### Periodontitis and glycemic control in type 2 diabetics

Type 2 diabetics undergoing periodontal treatment have shown predictable improvements in glycemic control. Need of point-of-care testing eliminating the need to draw blood, reducing the total time involved by identifying at-risk groups more effectively increases the access to treatment, and improves the quality of care delivered by allowing treatment to begin immediately. Early detection of periodontitis is very important to track and monitor morbidity. Poor glycaemic control in type 2 diabetes is often cited as a risk factor for delayed wound healing. However, some studies report not finding such delay, for instance upon tooth extraction [55], [56], [57]. Importantly, the wound healing upon extraction of uninfected, erupted teeth was not disturbed by infections, hence antibiotics should not be prescribed only due to having type 2 diabetes nor due to the level of glycaemic control. A novel effect of hyperglycemia is deposit of iron elements in the dentin ("tooth bone") inside the tooth that is covered by the enamel on the crown, but not on the root. Such deposits can cause stain seen through the enamel and cause aesthetic issues. Such deposits might in the future be used for early indication of undiagnosed dysglycemia by dentists.

### Treatment and diagnosis of periodontitis and diabetes mellitus type 2

Antidiabetic drugs and lipid-lowering drugs reduce inflammation and C-reactive protein. It will reduce the symptoms of periodontitis but some of them may cause dry mouth which can lead to caries formation, oral candidiasis, and periodontitis. Magnolol is an antioxidant and has anti-inflammatory effects. In conditions of sustained hyperglycaemia, 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 hyperglycaemic 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. All 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.

### Future aspects

It is well known that poor oral hygiene can lead to the progression or development of many systemic diseases. This breakthrough association between oral and systemic health has led the search for biomarkers in the oral cavity that could assist in the detection of systemic illnesses. The advantages of using the oral cavity as a diagnostic tool are that it is easily accessible, comfortable and allows for non-invasive tests. Therefore, the oral cavity can be used for the early diagnosis and prevention of systemic diseases. The link between periodontitis and diabetes remains the subject of intense research and debate within dentistry. Although the association between periodontitis and diabetes is now better understood, especially with the development of “omics”-based markers for some diseases, the evidence for a causative role is still lacking. Most of the research in this area recommends ‘further studies are needed,’ but that should not prevent dental professionals taking a pragmatic approach in promoting a patient’s good oral health to benefit their overall health. It is acknowledged that the gaps in our knowledge remain large.

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