

**Periodontal Health and Diabetes: Current Understanding of the Bi-directional Relationship**

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**Introduction**

The abnormalities of any organ, organ system or any biological processes have profound effects in multiple body areas. The link between the oral cavity and general health is similar and it can be stated very correctly, “*The mouth is the window to your body’s health*” as it can show signs of illnesses, general infections and nutritional deficiencies<sup>1</sup>.

The periodontium is the specialized tissues that both surround and support the teeth, maintaining them in the maxillary and mandibular bones. It is composed of two soft tissues viz gingiva and periodontal ligament and two hard tissues namely cementum and alveolar bone. Inflammation of periodontium, i.e Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or group of specific microorganisms, resulting in progressive destruction of

the periodontal ligament and alveolar bone with pocket formation, recession or both.

Type 1 Diabetes Mellitus increases the risk of periodontitis, and all patients with diabetes (including children and young adults) should be considered to be at increased risk of periodontitis. The prevalence of chronic gingivitis and periodontitis is significantly higher in patients with type 1 diabetes than that in the healthy population and the difference appears at the time of adolescence<sup>4</sup>. An analysis of the National Health and Nutrition Examination Survey (NHANES) III data set confirms the significantly higher prevalence of periodontitis in diabetics than in non-diabetics (17.3% versus 9%). The analysis of the data also shows that the prevalence of diabetes in patients with periodontitis is almost double than that seen in non-periodontitis patients (12.5% versus 6.3%). A longer duration of diabetes has also been linked to greater severity of periodontitis<sup>5</sup>. Beck

et.al in a systematic review concluded that the majority of cross-sectional, case-control, and longitudinal studies reveal positive associations between poor periodontal status and diabetes metabolic control<sup>6</sup>.

Diabetes has become one of the most prevalent diseases in the world. The World Health Organization (WHO) predicts that the number of patients with diabetes will increase to almost 10% of adults by 2030<sup>2</sup>. Similarly, severe periodontitis leading to tooth loss affects 10-15% of the adults in most of the populations studied<sup>3</sup>.

The aim of the present review is to throw light on the current understanding of the bi-directional relationship between diabetes and periodontitis.

### **Influence of Periodontitis on Systemic Health**

Miller<sup>7</sup> proposed relationship between oral and systemic health way back in 1891 and came up with the theory “human mouth as a focus of infection”, and in 1900 William Hunter designated it with the term “Oral sepsis.”<sup>8</sup> The term Periodontal Medicine, as first suggested by Offenbacher (1996), can be viewed as a broad term that focusing on the wealth of new data establishing a strong relationship between periodontal health or disease and systemic health or disease<sup>9</sup>.

The Subgingival microbiota in patients with Periodontitis provides a significant and persistent gram negative bacterial challenge to the host. By genomic sequencing, researchers were able to identify hundreds of new microbial species. In 2006, Haffajee and Socransky estimated the subgingival biofilms to accommodate more than 700 microbial colonies<sup>10</sup>.

In advanced Periodontitis, there is an excessive local inflammatory response to the bacterial stimuli. The disease process involves the loss of epithelial integrity in the periodontal pocket that is, the sulcular epithelium which is frequently ulcerated and discontinuous. The local inflammatory response to the bacterial stimuli and the loss

of epithelial integrity in the periodontal pocket allows for penetration of bacteria and their products such as Lippolysaccharides into the inflamed tissues and into the systemic circulation<sup>11</sup>. Hence, Patients with untreated Periodontitis have an increased risk for transient bacteraemias. Bacteraemia and associated endotoxemia incite the overproduction of destructive proinflammatory mediators at distant sites in the periodontal patient.

Therefore, patients with Periodontitis may be at greater risk for developing a number of systemic conditions associated with a similar overactive host response to external stimuli, such as cardiovascular disease, adverse pregnancy outcomes and diabetic complications. Elevated levels of cytokines, prostanoids and enzymes are evident in all these conditions.

### **Influence of Periodontitis On Diabetes**

It is known that infections are often accompanied by tissue insulin resistance. Acute bacterial and viral infections have been shown to increase insulin resistance and aggravate glycemic control. Systemic infections increase tissue resistance to insulin, preventing glucose from entering target cells, causing elevated blood glucose levels, and requiring increased pancreatic insulin production to maintain normoglycemia.

It is suggested that chronic periodontal infections may also result in increased insulin resistance and poor glycemic control. Gram-negative organisms such as *P. gingivalis*, *T. Forsythensis*, *P. Intermedia* and their products stimulate cells present in periodontal tissue, such as fibroblasts, keratinocytes and macrophages. As a result there is a release of inflammatory cytokines such as TNF- $\alpha$ , PGE2, IL-1 $\beta$ , IL-6, IL-12, G-CSF and so on. Adipocytes produce large quantities of cytokines, such as TNF- and IL-1, in the presence of inflammation<sup>12</sup>.

In a study by Thorstensson et al., 82% of diabetic patients with periodontitis experienced one or more major

cardiovascular, cerebrovascular or peripheral vascular events during the study period of 1-11 years, compared to only 21% of diabetic people without Periodontitis<sup>13</sup>.

### **Influence of Diabetes On Periodontitis**

In diabetes, the same MMPs and cytokines involved in the development of well known complications of diabetes, such as nephropathy, neuropathy, angiopathy, retinopathy, and altered wound healing also play a role in the development of periodontitis as the sixth complication of diabetes<sup>14</sup>.

However, it should be noted that Diabetes mellitus does not cause these changes per se, but alters the response of the periodontal tissues to local factors, hastening bone loss and delaying and altering the response to periodontal treatment. In individuals with diabetes mellitus, the level of glucose is higher in gingival fluid thereby inducing changes in the flora that is conducive to the severity of periodontal disease. There is increase in incidence of *A. actinomycetemcomitans*, *P. intermedia* and black pigmented *Bacteroides*, all known periodontal pathogens<sup>15</sup>. In addition, the high concentration of blood-glucose and in body fluids encourages the growth of mycotic pathogens such as *Candida*.

Apart from the change in the bacterial flora, diabetic patients exhibit impaired immune defences: granulocytes have altered functionality with modifications in their movement towards the infection site and a deterioration in their microbicide activity, with greater predisposition to infection of the wound. This defect in chemotaxis, defective phagocytosis and impaired adherence of Polymorphonuclear Leukocytes contributes further to progression of Periodontitis<sup>16</sup>.

In vitro studies of monocytes from people with diabetes have shown a hyperresponsive phenotype with overexpression of pro-inflammatory mediators such as interleukin1 (IL-1), tumor necrosis factor- $\alpha$  (TNF-  $\alpha$ ), and

prostaglandin E2<sup>17</sup>. 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<sup>18,19</sup>.

The hypersecretion of TNF- $\alpha$  in diabetes, as observed both in GCF and by peripheral blood monocytic responses to LPS, has been proposed to be a contributing factor for increased severity of periodontal disease expression<sup>20</sup>.

Moreover, chronic hyperglycemia adversely affects synthesis, maturation and maintenance of collagen and extracellular matrix. Numerous proteins and matrix molecules undergoes a nonenzymatic glycosylation resulting in excess of accumulated glycation end products (AGEs). As a result, the collagen gets cross linked by AGE formation hence becoming less soluble and more difficult to be repaired or replaced. Cellular migration is impeded through cross-linked collagen. As a result collagen in tissues of diabetic patients is aged and more susceptible to breakdown. AGEs plays a key role in all classic complications of diabetes including diabetes. Poor glycemic control, with associated increase in AGEs renders the tissue more susceptible to breakdown<sup>21</sup>.

Excessive formation and accumulation of AGEs in tissues is the most common cause of diabetic complications. The binding of these molecules to neutrophils produces a hyper-inflammatory state that amplifies the response to cytokines. These previously activated neutrophils also show a heightened response on making contact with LPS of gram-negative bacteria in the subgingival biofilm, and the consequent triggering of the inflammatory cascade increases the destruction of periodontal connective tissue and the severity of diabetes<sup>22</sup>.

Chronic hyperglycemia with accumulation of AGEs is associated with increased expression of various genes

regulated by the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B)<sup>23</sup>.

The increased prevalence and severity of periodontitis in patients with diabetes, especially the ones with poor metabolic control, led to designation of periodontal disease as 6<sup>th</sup> complication of diabetes. In addition to five classic complications of diabetes, American diabetes Association has officially recognized that periodontal disease is common in patients with diabetes, and the Association's standards of care include taking a history of current or past dental infections as part of the physician's examination.

### Clinical Significance

A recent survey reports prevalence of caries and periodontitis among rural Indian adults to be as high as 65%. Moreover, India has the maximum number of adults with diabetes in the south-east Asian Region (72.9 million) with the numbers expected to rise to 134 million in 2045<sup>24</sup>.

Another recent study reported that eight out of ten participants in urban Delhi suffered from some form of oral disease and participants with diabetes had worse oral health<sup>25</sup>.

Given the widespread prevalence of adult periodontitis and diabetes, and the bi-directional association between the two, a treatment approach that addresses both the chronic disorders will prove to be of great value to the patients and the clinicians. Understanding this co-relation is a crucial step for both dental and medical professionals to contribute significantly to the overall health of the patient.

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