



Diabetes Mellitus and Periodontitis: Bidirectional Relationship

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Type 2 diabetes mellitus and chronic periodontitis hold a close relationship that has been the focus of many researches. Periodontitis is a common chronic inflammatory disease characterised by destruction of the supporting structures of the teeth. Evidences stated that diabetes is a major risk factor for periodontitis; susceptibility to periodontitis is increased by approximately threefold in people with diabetes. There is a clear relationship between degree of hyperglycaemia and severity of periodontitis. The mechanisms that underpin the links between these two conditions are not completely understood, but involve aspects of immune functioning, neutrophil activity, and cytokine biology. There is emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk for periodontitis, and periodontal inflammation negatively affecting glycaemic control. Oral and periodontal health should be promoted as integral components of diabetes management.

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1. INTRODUCTION

It is truly said that “oral cavity is the reflection of the whole body”. According to Hunter, microorganisms and their toxins enter the body through the mouth. Periodontitis is an inflammatory disease of oral cavity with multifactorial etiology. The initiation and progression of periodontitis is mainly governed by the microbial onslaught and the host response in the form of an inflammatory reaction that ensues to combat it [1]. Characterized by a breakdown of tooth -supporting tissues, periodontitis has been causally associated with several microorganisms, some definitively and some putatively. To deal with the microbial load, a gamut of mediators of the host response orchestrates the inflammatory reaction.

Diabetes mellitus has long been recognized as one of the leading cause of morbidity and mortality globally. it affects an estimated 20 million, about 35%-40 % of whom have not received diagnosis. There is an extensive literature suggesting a Two -Way relationship between diabetes and periodontitis. Numerous mechanisms have been elucidated to explain the impact of diabetes mellitus on periodontium while inflammation plays an obvious role in periodontal diseases, evidence in the medical literature also supports the role of inflammation in the pathogenesis of diabetes and its complications Periodontitis, being described as the sixth complication of diabetes mellitus has been directly correlated with the level of glycemic control [2]. Alterations in the microflora and neutrophil functioning as well as compromised wound healing make DM a risk factor for periodontal disease. At the same time, the effect of periodontal infections on the pathogenesis of certain systemic conditions has also been studied with equal fervor. A continuous low- grade infectious state is said to exist because of chronic periodontitis (CP) [3]. This has been attributed to both direct effects of disseminated periodontal pathogens and their toxins and the altered metabolic changes that they can bring about indirectly, e. g., increased insulin sensitivity.

Periodontal disease is a destructive inflammation of the tooth supporting tissues resulting from complex multifactorial disorder that involves various microorganisms in dental plaque biofilm and interaction of host cells. These plaque

bacteria and its products such as endotoxins elicits an host immunoinflammatory response. This immunoinflammatory response against the microbes in an attempt to wall off the infection results in the local tissue destruction by producing various inflammatory mediators such as prostaglandin E2, Tumor Necrosis Factor α (TNF α) and interleukins (IL-1, IL- 6) [4], adipokines (resistin, leptin, visfatin, chemerin, omentin etc). These proinflammatory mediators in addition to local tissue destruction also exerts certain systemic effects (⁰. Further more genetic predispositions, personal behavior such as oral hygiene, smoking and systemic diseases such as diabetes mellitus, play an important role in the etiopathogenesis of periodontitis which may lead to loss of attachment, destruction of alveolar bone and to periodontal pocket formation ultimately causing tooth loss.

Recent studies indicate that the co-morbid presence of periodontitis can in turn adversely affect diabetic status. Diabetes mellitus and periodontal disease are both multifactorial diseases with high prevalence worldwide. Periodontitis has been identified as the sixth complication of diabetes. Its prevalence in type 2 diabetes

Gumus P et al [5] elucidated the signs of a bidirectional relationship between diabetes and periodontitis. They said that Periodontitis was a multifactorial, irreversible and cumulative condition, initiated and propagated by bacteria and host factors. The multifactorial nature of periodontitis is related with the complex interactions between microorganisms in the microbial dental plaque and host response mechanisms, as well as environ mental factors. Progression of periodontal disease was very much dependent on host response. Diabetes mellitus (DM), a complex metabolic disorder characterised by prolonged hyperglycaemia, had long been recognised as one of the leading causes of morbidity and mortality globally. DM was a complex metabolic syndrome that affects both the quality and length of life with major complications. Periodontal disease and diabetes were highly prevalent chronic diseases and inflammation might play a critical role in their relationship.

Mesia R et al [6] through a case control study, quantified the immune responsiveness in individuals with type 2 diabetes (T2D) as

compared with patients without diabetes (NT2D) diagnosed with periodontitis.. Their results showed that T2D individuals demonstrated higher unstimulated levels of interleukin 6 (IL-6), IL- 1 β , tumor necrosis factor α , interferon γ , IL- 10, IL-8, macrophage inflammatory protein 1 α (MIP 1 α), and 1 β (MIP1 β), and higher stimulated levels of IL- 6, IL- 8, IL- 10 , MIP1 α and MIP 1 β , along with lower unstimulated and stimulated levels of Granulocyte -Macrophage Colony Stimulating Factor (GM-CSF) when compared with NT2D (p<0.05).

Suresh S et al [7] discussed that the hyperoxidative and a modified inflammatory state in obese individuals caused higher susceptibility to bacterial infection which influenced the initiation and progression of periodontal disease.

Numerous studies provide evidence for a bidirectional relationship and intense efforts have been devoted to elucidate the underlying mechanisms. Diabetes mellitus is a group of metabolic diseases that are characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [8].

The poorly controlled diabetes has a higher prevalence of periodontitis, to the extent that periodontitis has been called the sixth complication of diabetes. Conversely periodontitis has been recognized as a risk factor for systemic diseases where there is low grade inflammation like type 2 diabetes mellitus, cardiovascular diseases and cerebrovascular diseases [2].

2. PERIODONTITIS AND DIABETES- UNDERLYING PATHOPHYSIOLOGY

Comorbidities that contribute to systemic inflammation are likely to have an impact on diabetes control and on the development of diabetes complications, ultimately affecting diabetes - associated morbidity and mortality. Inflammatory periodontitis is one of the most common chronic inflammatory conditions worldwide. The oral cavity provides a nidus for bacterial dispersion into the blood stream. These oral bacteria can damage periodontal t issues through the action of matrix-degrading enzymes. The bacterial toxins may cause systemic effects as well as local cytotoxic effects at the periodontal tissues. The inflammatory response is characterized by secretion of host -derived mediators of inflammation and tissue

breakdown. Interleukin -1 β , Interleukin-6 , Prostaglandin E2 (PGE2), Tumor Necrosis Factor alpha (TNF- α), Receptor Activator of Nuclear Factor $\kappa\beta$ Ligand (RANKL), and Matrixmetalloproteinases (MMP -8, MMP-9, and MMP-13) are the most commonly implicated mediators of inflammation [9]. Tissue destruction occurs in periodontitis in the form of breakdown of the collagen fibers of the periodontal ligament, resulting in the formation of a periodontal pocket between the gingiva and the tooth. The pockets deepen as a result of the further destruction of fibers and the resorption of the alveolar bone also progresses with the progressing attachment loss.

Large bodies of evidence have focused on the role of periodontal infection and micro flora of the dental plaque in people with diabetes mellitus. Diabetes has many adverse effects on the periodontium, including decreased collagen turnover, impaired neutrophil function, and increased periodontal destruction. Neutrophil chemotaxis and phagocytic activities are compromised in diabetic patients, which can lead to reduced bacterial killing and enhanced periodontal destruction. Hyperglycemia increases the concentration of glucose in the saliva and the gingival crevicular fluid. These changes as well as basement membrane thickening and glycosylation of hemoglobin should promote a unique environment resulting in shifts of the microflora. This leads to proliferation of bacteria in the oral cavity. Hyperglycemia itself adds to the indirect adverse effect, stimulating the immune system" s cells to release inflammatory cytokines. Diabetic microangiopathy, impaired immune response and a lower resistance to infections contribute to the development of periodontitis in poorly controlled diabetics. The continuous exposure of collagen fibers in the supporting period on ligaments to aldose sugars induces their nonenzymatic glycation and oxidation. This glycation leads to changes in the physical properties of these molecules, reducing collagen solubility and increasing the degradation of connective tissues. This results in accelerated degradation of both connective tissue and bone. The vascular changes interfere with both delivery of nutrients and the migration of leukocyte to gingival tissues resulting in decreased oxygen diffusion and elimination of metabolic waste, contributing to an increased severity of periodontitis and decreased wound healing capacity.

Formation of AGEs, a critical link in many diabetic complications also occur in the periodontium and their deleterious effects on the other organ system may be reflected in periodontal tissues as well. The formation of AGEs occur when excess available glucose is in contact with structural and other proteins. This process is not driven enzymatically and once they are formed, AGEs bind to a specific cellular receptor known as the Receptor for AGE (RAGE). The binding of AGE and RAGE cause a series of pro inflammatory events that might be self sustaining because AGE -RAGE binding on the surface of endothelial cells induces the expression of vascular cell adhesion molecules-1 that attracts monocytes to luminal side of the endothelial cells thus perpetuating the inflammatory response.

Matrix metalloproteinases are critical components of tissue homeostasis and wound healing and are produced by all the major cell types in the periodontium. Matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases are produced by neutrophil granulocytes (especially matrix metalloproteinase - 8), fibroblasts, macrophages, plasma cells and many other cells . An imbalance of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases is a major factor leading to collagen breakdown in periodontal disease [10]. It was hypothesized that type 2 diabetes mellitus- related alterations in gingival crevicular fluid levels of matrix metalloproteinases and/ or their inhibitors may be part of the mechanism by which diabetes affects periodontal health [11].

The function of inflammatory cells, such as neutrophils, monocytes, and macrophages, is altered in diabetic patients. The circulating monocytes of diabetic patients are hyper responsive to LPS. Monocyte Chemo attractant Protein-1(MCP-1) acts as a major signal for the chemotaxis of mononuclear leukocytes. Monocytes play a significant part in periodontal tissue breakdown. These cells exhibit enhanced MCP - 1 expression in periodontal tissues [12]. Local and systemic hyper - responsiveness of these monocytes leads to increased TNF - α levels in gingival crevicular fluid (GCF).

The pentose phosphate pathway is contributory in the formation of Nicotinamide Adenine Dinucleotide Phosphatase (NADPH) and Ribose -5 -Phosphate for fatty acid, and nucleotide synthesis, respectively. NADPH is important for

NADPH oxidase activity and for the rejuvenation of glutathione in neutrophils and activation of NADPH oxidase results in a respiratory burst in neutrophils during the process of phagocytosis [13]. In diabetic patients, NADPH production is decreased, which leads, eventually, to compromised neutrophil function. Glucose 6 phosphate dehydrogenase (G6PDH) converts glucose 6 phosphate into 6 - phosphoglucono - α - lactone and is the rate limiting enzyme in the pentose phosphate pathway. G6PDH activity has been found to be considerably decreased in neutrophils, macrophages and lymphocytes and also the pentose phosphate pathway is down regulated in neutrophils.

3. ROLE OF ADVANCED GLYCATION END PRODUCTS

During hyperglycemia, increased accumulation of advanced glycation end - products in the gingiva of patients affected by chronic periodontitis was first demonstrated in 1996 by Schmidt AM et al [14]. Advanced glycation end-products are products of an irreversible nonenzymatic glycation and glycooxidation of proteins, including lipoproteins, intracellular proteins and plasma proteins [15].

3.1 Diabetes on Periodontal Pathogens

From evidences, it is reported that Insulin-dependent diabetic patients with periodontitis have been reported to have subgingival flora composed mainly of capnocytophaga, anaerobic vibrios, and *Actinomyces* species. *Porphyromonas gingivalis*, *Prevotella intermedia*, and *actinomycetemcomitans* present in non-diabetics are present in low numbers in diabetics. Increased glucose level in crevicular fluid in diabetics may favor the growth of some microbial species. Thorstensson et al. observed significantly greater numbers of *Porphyromonas gingivalis* in diabetics compared to controls, although no differences were seen with *Actinobacillus (Aggregatibacter) actinomycetemcomitans*, *Campylobacter rectus*, *Capnocytophaga* spp., *Eikenella corrodens*, *Fusobacterium nucleatum*, and *Prevotella intermedia* . Of the 17 species tested for, *Treponema denticola*, *Streptococcus sanguinis*, *Prevotella nigrescens*, *Staphylococcus intermedius*, and *Streptococcus oralis* levels were elevated in the supragingival plaque of diabetics compared with non-diabetics, although no significant differences were found in subgingival plaque samples [16].

3.2 Two Hit Model

Oral cavity and systemic diseases are two entities that can affect each other.

Golub et al [17] proposed a “two-hit” model for chronic periodontitis and systemic diseases like diabetes mellitus. They said that the periodontopathic bacteria provided one "hit", where as systemic inflammations elevating levels of proinflammatory biomarkers like CRP, IL- 6, TNF α etc in serum or plasma acted as a second “hit”. Similarly both Diabetes and periodontitis are both chronic inflammatory diseases where they have some commonalities of immune inflammatory response throughout the course of the disease. Diabetes mellitus is one of the risk factors that intensifies the extent and severity of periodontitis up to ten fold, frequently spurring rampant destruction of the periodontium. The periodontium in diabetes reflects increased crevicular glucose levels, increased vascular permeability and increase in levels of tissue MMPs, proinflammatory cytokines, adipokines etc [18,19]. Both diseases have a bi - directional relationship where, one disease affects the other as both periodontitis and diabetes are associated with exaggerated periodontal tissue destruction.

Since periodontal disease involves intricate interactions between the bacteria and the host immune cells, development of new diagnostic tests in the form of biomarkers would enhance the clinician’s role in improvising the diagnosis, disease activity and progression of periodontal disease, enabling the provision of need based care, rather than a stringent etiologic and maintenance phase of periodontal therapy.

4. CONCLUSION

Periodontitis is a common chronic inflammatory disease characterized by destruction of the supporting structures of the teeth. Epidemiological data confirm that diabetes is a major risk factor for periodontitis; susceptibility to periodontitis is increased by approximately threefold in people with diabetes. There is a clear relationship between degree of hyperglycaemia and severity of periodontitis. The mechanisms that underpin the links between these two conditions are not completely understood, but involve aspects of immune functioning, neutrophil activity, and cytokine biology. There is emerging evidence to support the existence of a two-way relationship between

diabetes and periodontitis, with diabetes increasing the risk for periodontitis, and periodontal inflammation negatively affecting glycaemic control. Controlling diabetes (i.e. improving glycaemic control) is likely to reduce the risk and severity of periodontitis. Furthermore, evidence suggests that resolution of periodontal inflammation can improve metabolic control are needed to further validate these findings.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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