Immune Dysfunction Linking Periodontitis And Diabetes

Harini Venkata Subbiah\textsuperscript{1}, Polani Ramesh Babu\textsuperscript{2}, Usha Subbiah\textsuperscript{1*}, Daniel Rajendran T\textsuperscript{3}, Vinod Kumar P\textsuperscript{3}

\textsuperscript{1}Human Genetics Research Centre, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India.
\textsuperscript{2}Department of Genetic Engineering, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India.
\textsuperscript{3}Department of Forensic Medicine, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India

Corresponding author: ushat75@yahoo.com.
ABSTRACT

Periodontitis is a polymicrobial initiated disease but the host inflammatory and immune responses also play a significant role in creating periodontal pockets and irreversible bone loss. The presence of periodontal pathogens and their toxins cause elevations of proinflammatory cytokines such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha). Host response is altered by the presence of various factors including diabetes. Periodontitis and diabetes are prevalent chronic diseases with many epidemiological studies implying a two-way or bidirectional relationship between the two diseases. In this review, we focus on how hyperglycemia relates periodontitis and diabetes mellitus.

Keywords: Immune dysfunction, Linking periodontitis, Diabetes, polymicrobial
INTRODUCTION

Periodontitis is an inflammatory disease of the gums destroying tooth supporting tissues characterized by periodontal pocket formation, alveolar bone resorption, and eventually tooth loss. Some of the bacteria involved in periodontitis are Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola but the presence of bacteria alone cannot determine the type or severity of periodontitis. Host immune responses against periodontal pathogens influence the course of periodontal disease (Silva et al., 2015). Periodontitis is a multifactorial disease with several factors responsible for its severity initiated by pathogenic bacteria, progressed by host immune response and inflammation against bacteria and modified by various environmental and genetic factors (Pietropaoli et al., 2010). Diabetes is considered a risk factor, and advanced chronic periodontitis often coexists with poorly controlled diabetes (Choi et al., 2010). Diabetes exacerbates periodontal condition by upregulation of cytokines from monocytes/polymorphonuclear leukocytes and predisposes to chronic inflammation leading to progressive tissue breakdown and reduced tissue repair capacity. It was found that the prevalence of severe attachment loss increased with decreasing control of diabetes (Ohlrich et al., 2010)

Hyperglycemia

Hyperglycemia can result in an increased glucose concentration in saliva and gingival crevicular fluid (GCF), leading to increased proliferation of bacteria in the oral cavity (Sharma et al., 2016). In diabetic patients with persistent hyperglycemia, there is an exaggerated immuno-inflammatory response against periodontal pathogenic bacteria, which results in a more rapid and severe periodontal tissue destruction (Taylor et al., 2008). In hyperglycemic patients, there is an increased deposition of advanced glycation end products (AGEs) in periodontal tissues, and interactions between AGEs and their receptor (RAGE) can lead to activation of local immune responses. Altered immune responses result in an increased secretion of cytokines, increased oxidative stress, and disruption of receptor activator of nuclear factor ligand RANKL/osteoprotegerin (OPG), and all of these factors result in resorption of alveolar bone and periodontal connective tissue damage (Preshaw, Bissett et al., 2019). Study conducted by Vieira Ribeiro et al., 2011 showed that RANKL, Interferon γ (IFNγ), Interleukin- 17 (IL-17), and IL-23 were elevated in type 2 diabetes patients with chronic periodontitis as compared to patients with chronic periodontitis only and a possible association was suggested. Some important factors that link periodontitis and diabetes are explained below and summarized in Figure 1.
Fig 1: Factors linking periodontitis and diabetes

Hyperglycemia induced destructive tissue mechanisms

Age/rage
The chemical transformation of amine-containing molecules such as proteins or nucleotides by reducing sugars results in AGEs or Maillard products (Vlassara et al., 2015). Diabetes especially when poorly controlled, increases the formation of AGEs (Lalla AMBROSIO et al., 2001). Interaction of AGE with its receptor RAGE in endothelial cells activates downstream signaling leading to hyperpermeability and enhanced expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1). This interaction induces chemotaxis and an increased generation of cytokines such as tumor necrosis factor (TNF), IL-1, or IL-6 resulting in increased susceptibility to tissue destruction. Several AGEs initiate a range of cellular responses, including stimulating monocyte chemotaxis, osteoclast-induced bone resorption, the proliferation of vascular smooth muscle cells, aggregation of platelets, stimulation of secretion of collagenase, and several growth factors (Rajeev et al., 2011).

Upregulated Cytokine Production
Periodontal pathogens and their endotoxins are recognized by toll-like receptors (TLRs) on the surface of immune cells, initiating an inflammatory response. Also, AGE produced due to elevated glucose levels in diabetic patients interacts with its monocytic receptors contributing to the hyperresponsive phenotype seen in periodontitis through activation of transcription...
factor NF-kB, increasing gene transcription for inflammatory cytokines (Iacopino et al., 2001). Various proinflammatory cytokines, including prostaglandin E2 (PGE2) and IL-1β decrease the collagen synthesis by fibroblasts and influence osteoclastic bone resorption, and these cytokines in crevicular fluid and gingival tissue in patients with chronic periodontitis increased proportionally to the severity of periodontal disease (Tawfig et al., 2016). The balance between stimulatory and inhibitory cytokines and their signaling cascades determines the level of periodontal tissue loss (Graves et al., 2008).

**Rankl/Opg**

Increased cytokines are secreted in GCF/saliva due to inflammation, and RANKL, a ligand belonging to TNF family, is expressed by osteoblasts, activated T and B cells, and fibroblasts in response to these cytokines. RANK receptor is expressed on the surface of preosteoclasts, and osteoclasts and the secreted RANKL ligand binds directly to its cognate RANK receptor resulting in differentiation and the activation of osteoclasts that mediate bone resorption (Ochanji et al., 2017). Under physiological conditions, the activities of osteoclasts and osteoblasts are highly regulated and play a significant role in bone remodeling with the resorption of bone by osteoclasts followed by new bone formation by osteoblasts (Tanaka et al., 2005). However, in pathological processes, the two processes are disrupted. Diabetes affects osteoclast and osteoblasts in the periodontium by increasing the expression of inflammatory mediators and RANKL/OPG ratios and by enhancing the levels of AGEs and reactive oxygen species (ROS) (Wu et al., 2015). OPG is considered a protective factor against bone loss as it functions as a decoy receptor for RANKL and prevents RANKL binding to RANK, thereby preventing bone loss, and RANKL/RANK/OPG system is a master regulator of bone resorption (Liu, Zhang et al., 2015). In a study by Mahamed et al. 2005, in type 1 diabetes, after A. actinomyctemcomitans inoculation, nonobese diabetic mice exhibited higher alveolar bone loss associated with significantly higher proliferation and expression of RANKL.

**Dysregulated Neutrophil Function**

Neutrophils are considered the first line of defense against periodontal pathogens, and defects in neutrophil function and recruitment have been observed in diabetic patients. In type 1 diabetics with severe periodontitis, it has been shown that the peripheral blood neutrophils have reduced chemotactic and phagocytic activity when compared with non-diabetics with periodontitis (Manouchehr-Pour et al., 1981). In contrast, hyperactivity of neutrophils has also been noted. Inflammatory cytokines increase vascular permeability and recruit neutrophils.
into the tissue, where they release lysosomal enzymes that contribute to tissue degradation. Neutrophils from diabetic patients with periodontitis produce abnormally high levels of superoxide radicals due to hyperglycemic state and periodontitis condition, which brings about significant tissue damage compared to healthy subjects with periodontitis alone (Shetty et al., 2008).

**Oxidative Stress**

Host immune cells like neutrophils release large amounts of reactive oxygen species (ROS) by NADPH oxidase complex at the site of infection that enables the immune system to cope with microorganisms by attacking the membranes of bacterial pathogens (Nguyen et al., 2017). Hyperglycemia in diabetic patients activates a particular metabolic route that involves diacylglycerol (DAG) - protein kinase C (PKC) - NADPH oxidase and culminates in the generation of ROS (Volpe et al., 2018). Oxidative stress occurs when there is a disturbance in the balance between the production of ROS and antioxidant defenses, which in turn lead to tissue injury in numerous inflammatory diseases, including periodontitis by causing damage to host biological macromolecules - lipids, proteins, nucleic acids, and carbohydrates (Betteridge et al., 2000). In a study, it has been reviewed that oxidative capacity in periodontitis patients is contradictory with some studies showing leukocytes from patients with periodontitis are exhausted and have a low oxidation activity, other studies pointing toward higher production of ROS by leukocytes from periodontitis patients (Celec et al., 2017).

**Hyperlipidemia**

Hyperlipidemia can arise from a high-fat diet, metabolic disorders such as type 2 diabetes, or can be produced in response to infectious processes (Fentoglu et al., 2008). Defects in insulin action and hyperglycemia could lead to changes in plasma lipoproteins and the lipoprotein abnormalities commonly present in type 2 diabetes, including hypertriglyceridemia and reduced plasma high-density lipoprotein (HDL) cholesterol (Goldberg et al., 2001). Cytokines such as TNF-α and IL-1β produced on exposure to periodontal pathogens/endotoxin result in elevated levels of free fatty acids, low-density lipoprotein (LDL), and triglyceride through enhanced hepatic lipogenesis, increased synthesis or reduced clearance of triglyceride, and reduced clearance of LDL due to reductions in lipoprotein lipase activity (Lutfioğlu et al., 2017). In addition, hyperlipidemia may be associated with the progressive periodontal disease through polymorphonuclear priming and hyperfunction, causing increased neutrophil respiratory bursts leading to oxidative stress. Lei et al., 2013 study found that hyperlipidemia may lead to more severe periodontal bone loss by impairing...
the immune response to *P. gingivalis* challenge by altering pattern recognition receptor (PRRs) expression in macrophages leading to an inhibited cytokine network response and decreased bacterial clearance. In a study conducted in 2014, it was found that LDL-cholesterol was increased in chronic periodontitis patients than in healthy subjects in contrast HDL-cholesterol levels were increased in healthy subjects than in subjects with chronic periodontitis(Akkaloori et al., 2014).

**Defective Collagen Synthesis**

Collagen is an important component of the periodontium and the synthesis, maturation, and homeostasis of collagen are affected by the glucose level(Surlin et al., 2014). Proteins become glycated in high glucose environment to form AGE which accumulates in the periodontium, causing changes in the cells and extracellular matrix (ECM) components. Collagen produced by fibroblasts under these conditions is susceptible to rapid degradation by matrix metalloproteinase (MMP) enzymes, such as collagenase, the production of which is significantly higher in diabetes condition 32. Elevated GCF collagenase degrades newly synthesized collagen fibers and decreases gingival fibroblast collagen synthesis(Ryan et al., 2003). Glycation of the collagen fibers also reduces its solubility, affecting remodeling and healing(Grover et al., 2013).

**Antimicrobial Peptides**

Antimicrobial peptides are part of innate immune responses and components of first line of defense against periodontal pathogens. A study conducted in 2019 showed that levels of cathelicidin and human neutrophil peptides (HNPs) 1-3 were increased in patients with chronic periodontitis and type 2 diabetes compared with controls(Zainab et al., 2019). Another study showed that beta-defensin 1 level in GCF was reduced in periodontitis with type 2 diabetes (Yilmaz et al., 2018). One of the reasons for reducing defensins could be explained by the inhibition of P38 mitogen-activated protein kinases (p38MAPK) signaling, resulting from increased AGE formation in diabetic patients(Lanet al., 2011).

**Conclusion**

Diabetes and periodontitis are two widespread chronic inflammatory conditions. In diabetic patients, hyperglycaemia stimulates the immune system's cells to release inflammatory cytokines. Elevated inflammatory mediators alter the activity of leukocytes and osteoblasts-osteoclasts, and the tissue remodeling process. Since diabetes and periodontitis are interlinked, it is imperative to keep diabetes under control while considering treatment for periodontitis.
Author contribution
Harini Venkata Subbiah, Polani Ramesh Babu conceived of the presented idea Usha Subbiah, Daniel Rajendran T, Vinod Kumar P encouraged and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Study significance
The study significance focuses on how hyperglycemia relates periodontitis and diabetes mellitus.

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