Immune Dysfunction Linking Hyperglycemia with Periodontitis in Diabetes Management

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Abstract

Background: Periodontitis is a progressive inflammatory disease affecting the gums and supporting tissues, often worsened by diabetes. Its pathogenesis involves pathogenic bacteria and the host's immune response. Hyperglycemia in diabetes elevates glucose in saliva and gingival crevicular fluid (GCF), fostering bacterial growth and periodontal tissue damage. This study investigates the mechanisms linking immune dysfunction, periodontitis, and diabetes, emphasizing advanced glycation end products (AGEs), cytokine production, and oxidative stress. Methods: We performed a comprehensive literature review to analyze the relationships among hyperglycemia, AGEs, inflammatory cytokines, oxidative stress, and periodontal damage. Data were sourced from studies examining diabetes' impact on periodontal health, focusing on AGEs and their receptor (RAGE), the RANKL/OPG system, neutrophil function, oxidative stress, hyperlipidemia, collagen synthesis, and antimicrobial peptides. Results: Persistent hyperglycemia leads to increased AGEs, which interact with RAGE to heighten inflammatory responses and oxidative stress. This interaction triggers cytokine release and disrupts the RANKL/OPG balance, enhancing osteoclast activity and bone resorption. Additionally, oxidative stress from elevated reactive oxygen species (ROS) and hyperlipidemia worsens periodontal damage. Neutrophil function in diabetic patients can be dysregulated, with either impaired or excessive activity contributing to tissue degradation. Changes in collagen synthesis and antimicrobial peptide levels further aggravate periodontal disease in diabetes. Conclusion: Hyperglycemia and periodontitis involve complex mechanisms, including AGE-induced inflammation, oxidative stress, and altered bone remodeling. Effective diabetes management is essential to mitigate its impact on periodontal health. Understanding these mechanisms can inform targeted interventions, improving treatment outcomes for patients with both conditions. Future research should focus on strategies addressing these interconnected factors for enhanced periodontal and diabetic care.

Keywords: Immune Dysfunction, Periodontitis, Diabetes Mellitus, Advanced Glycation End Products, Cytokine Production

Significance | This review discusses the mechanisms linking hyperglycemia with periodontitis highlights the need for comprehensive management of diabetes to improve periodontal health.

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Introduction

Periodontitis is a progressive inflammatory disease affecting the gums and supporting tissues of the teeth, characterized by the formation of periodontal pockets, resorption of alveolar bone, and eventual tooth loss. The pathogenesis of periodontitis involves a complex interplay between pathogenic bacteria and the host's immune response. Key bacterial species assotciated with periodontitis include *Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Porphyromonas gingivalis, Tannerella*

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forsythia, and *Treponema denticola*. However, the presence of these bacteria alone does not solely determine the type or severity of the disease; rather, it is the is the host's immune response that significantly influences the disease progression (Silva et al., 2015).

Periodontitis is recognized as a multifactorial disease, initiated by pathogenic bacteria, exacerbated by host inflammatory responses, and modified by environmental and genetic factors (Pietropaoli et al., 2010). One significant risk factor for periodontitis is diabetes, particularly when poorly controlled. The interplay between diabetes and periodontitis is well-documented, with diabetes exacerbating periodontal disease through mechanisms such as heightened inflammatory responses and impaired tissue repair capabilities (Choi et al., 2010). Persistent hyperglycemia, common in uncontrolled diabetes, increases glucose levels in saliva and gingival crevicular fluid (GCF), fostering bacterial proliferation and exacerbating periodontal tissue destruction (Sharma et al., 2016; Taylor et al., 2008).

Hyperglycemia in diabetic patients leads to the formation of advanced glycation end products (AGEs), which interact with their receptors (RAGE) on periodontal tissues. This interaction triggers local immune responses, increases cytokine secretion, and promotes oxidative stress, all contributing to alveolar bone resorption and connective tissue damage (Preshaw et al., 2019). Studies have highlighted elevated levels of inflammatory cytokines and markers like RANKL and IFNγ in diabetic patients with chronic periodontitis, suggesting a direct association with disease severity (Vieira Ribeiro et al., 2011).

The pathophysiology of diabetes-induced periodontal damage involves several interrelated mechanisms. One key factor is the interaction between advanced glycation end products (AGEs) and their receptor (RAGE). Hyperglycemia leads to the formation of AGEs, which, through receptor-mediated signaling, enhances the inflammatory response, causing tissue damage and increasing susceptibility to periodontal destruction (Vlassara et al., 2015; Rajeev et al., 2011). Additionally, periodontal pathogens and AGEs stimulate inflammatory pathways, resulting in elevated cytokine levels that promote tissue degradation and disrupt collagen synthesis (Iacopino et al., 2001; Tawfig et al., 2016).

Another significant mechanism is the imbalance in the RANKL/OPG system, which plays a critical role in bone remodeling. In diabetes, this system becomes disrupted, leading to increased osteoclast activity and subsequent bone resorption (Wu et al., 2015; Liu et al., 2015). Furthermore, neutrophils in diabetic patients often exhibit dysregulated function, either being impaired or hyperactive, which contributes to increased tissue damage through oxidative stress (Manouchehr-Pour et al., 1981; Shetty et al., 2008).

Oxidative stress is another important factor; elevated reactive oxygen species (ROS) production due to hyperglycemia exacerbates tissue damage and inflammatory responses (Nguyen et al., 2017; Betteridge et al., 2000). Hyperlipidemia, often associated with diabetes, further worsens periodontal disease by altering lipid profiles, which impacts immune responses and enhances tissue damage (Fentoglu et al., 2008; Akkaloori et al., 2014). Additionally, high glucose levels lead to collagen glycation, affecting collagen stability and accelerating tissue breakdown (Surlin et al., 2014; Ryan et al., 2003). Changes in antimicrobial peptide levels in the gingival crevicular fluid (GCF) of diabetic patients can also influence the severity of periodontal disease (Zainab et al., 2019; Yilmaz et al., 2018).

Diabetes and periodontitis are deeply interconnected chronic inflammatory conditions. Effective management of diabetes is essential for mitigating its detrimental effects on periodontal health and improving overall treatment outcomes for periodontitis.

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.

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-l (VCAM-I). 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.actinomycetemcomitans* 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,

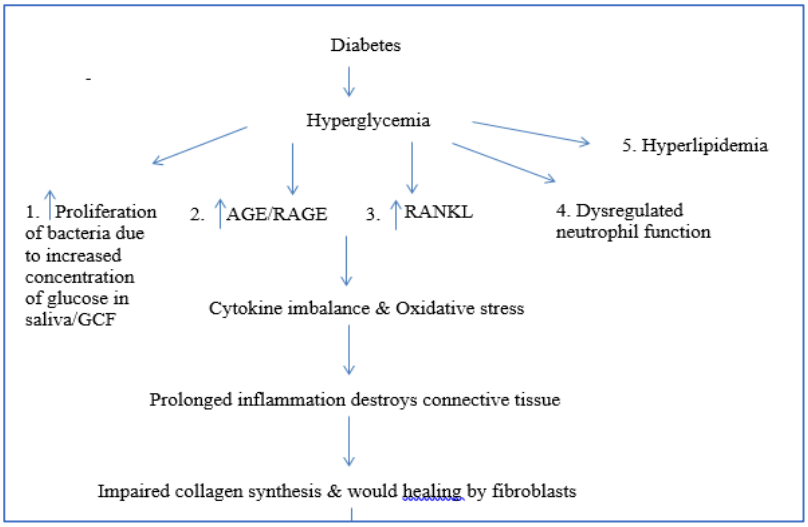

Figure 1. Factors linking periodontitis and diabetes

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 intimately connected chronic inflammatory conditions that exacerbate each other, leading to significant health complications. Hyperglycemia in diabetic patients enhances inflammatory responses, increases oxidative stress, and disrupts key cellular and molecular pathways involved in periodontal tissue homeostasis. Elevated levels of advanced glycation end products (AGEs) and altered receptor interactions amplify the inflammatory cascade, contributing to tissue damage and bone resorption. The disruption of the RANKL/OPG balance further accelerates bone loss, while dysregulated neutrophil function and heightened oxidative stress exacerbate periodontal destruction. Additionally, hyperlipidemia and defective collagen synthesis in diabetes worsen periodontal disease by impairing immune responses and compromising tissue integrity.

To effectively manage the interplay between diabetes and periodontitis, it is crucial to control blood glucose levels and address periodontal health comprehensively. Interdisciplinary approaches that integrate diabetes management with periodontal care can significantly improve patient outcomes. By optimizing glycemic control and employing targeted periodontal therapies, healthcare providers can mitigate the adverse effects of diabetes on periodontal health, thereby enhancing overall quality of life for affected individuals.

Author contributions

H.V.S. and P.R.B. conceived the initial idea for the study. U.S., D.R.T., and V.K.P. contributed to the research design and methodology. All authors were involved in the discussion of results and provided critical feedback throughout the research process. Each author contributed to the drafting and revision of the final manuscript, ensuring its accuracy and completeness.

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Competing financial interests

The authors have no conflict of interest.

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