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Review Article

Diabetes and periodontitis - a bidirectional relationship – A review of current literature

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ABSTRACT: Periodontal disease and diabetes mellitus are two most common diseases affecting millions of people globally. They share common pathobiologic mechanisms involving inflammatory pathways that further affect the severity and progression of the disease. An ensuing bidirectional relationship has been proven by various studies, signifying the importance of prompt treatment strategies to control the effect of both conditions on each other. This review highlights the current literature available and provides insights regarding the underlying mechanisms of pathogenesis.

Keywords: Diabetes mellitus, Periodontal disease, bidirectional relationship, advanced glycation end pproducts, insulin resistance.

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INTRODUCTION

Diabetes mellitus is one of the commonest chronic metabolic condition affecting millions of individuals worldwide. Similarly, periodontal disease is the chronic inflammatory disease with a huge global burden. Studies have proved a bidirectional relationship between diabetes mellitus and periodontal disease. It is supported by regulatory procedures that are reciprocal. The subgingival space's microbial ecosystem can be impacted by hyperglycemia, which can also

impair cellular processes and alter collagen metabolism. The extracellular matrix can be further altered by the creation of advanced glycation end-products (AGEs), and inflammation can be made worse by cellular receptor binding. Additionally, insulin resistance and hyperlipidemia are also brought on by periodontitis. This cyclical association is brought about by the overproduction of proinflammatory cytokines including tumour necrosis factor and interleukin [1]. Promising periodontitis therapies may involve systemic inhibition of proinflammatory cytokines or AGE receptors.

A shorter life expectancy, an increase in morbidity from microvascular complications brought on by diabetes, a higher risk of macrovascular consequences such ischemic heart disease, stroke, and peripheral vascular disease, as well as a lower quality of life are all associated with it. It affects adults most frequently and is closely associated with obesity [1,2,3]. A third category of hyperglycemia is that which is brought on by systemic illnesses or disorders, which includes gestational diabetes.

Localized infections in the mouth can cause periodontitis, which permanently damages the tooth attachment system [4]. Periodontal pockets, which allow for more bacterial colonisation and difficulty, develop as a clinical sign of periodontitis. Some other symptoms include dental hypermobility, redness, and gingival edema. One of the most frequent causes of tooth loss in adults nowadays is periodontitis [5,6]

Most studies characterize the relationship between diabetes and periodontitis according to the age and type of the disease, which were described in 1960 [7]. The older diabetics had more periodontal attachment and bone loss than the younger diabetics, according to studies comparing diabetic and non-diabetic Pima Indians [7,8]. The Third National Health and Nutrition Examination Survey (NHANES III) in the US found that patients with periodontal disease had a prevalence of diabetes that was about twice as high as diabetics without periodontal disease [7–9].

Studies have also discovered a connection between glucose intolerance, metabolic syndrome symptoms, and other diabetes-related side effects such as cardiovascular problems [10-12]. Periodontitis is therefore referred to as the sixth consequence of diabetes due to the almost universal occurrence of both conditions, and some data also points to a strong bidirectional link between periodontal disease and diabetes [13].

According to numerous studies, those with poorly controlled type I or type II diabetes have much lower periodontal health, including more attachment loss, than people with improved or well-controlled diabetes or healthy people. One frequent metric for evaluating periodontal health is attachment loss [8]. Because those studies also considered other markers like the bleeding and pocket depth, diabetes patients had inferior periodontal health [14,15,16,17].

Even though some studies found no statistically significant difference between diabetics and non-diabetics in probing depths or attachment loss, the majority of researchers believed that diabetic people experienced periodontal changes including increased gingivitis [18,19]. It's also important to note that the majority of this research used type

1 diabetes (IDDM) as a criterion for selection, indicating a tenuous connection between the two conditions. However, more thorough investigation is needed to support this assertion. A smaller sample size and test participants who were younger than average (adolescents) may also have tainted the research's findings [20]. The majority of previous studies on the subject showed a connection between diabetes and worsening periodontal health [21].

Additionally, research revealed that patients with proper metabolic control lost attachments more slowly than those with poor control. In contrast, research has demonstrated that periodontal therapy enhances glycemic control [22,23,24,25] and numerous recent meta-analyses have supported the importance of this finding [26,27]. In those studies, the effect of infection control in diabetes patients was examined. It was discovered that systemic antibiotics and mechanical debridement (scaling and root planing) together improved glucose control [28]. A tetracycline derivative called doxycycline, which shields the extracellular matrix from glycation, seems to be the most potent modulator of all antibiotics (ECM) [4].

However, several studies have found no substantial change in glycemic control following periodontal therapy [29]. A four-month investigation by Christgau and colleagues found that periodontal treatment decreased periopathogenic bacteria, enhanced clinical periodontal parameters, and decreased inflammatory cells' oxidative burst response [29,30]. However, there was no appreciable distinction between people with diabetes and those who had a healthy system. In a meta-analysis, Janket and colleagues discovered a trend in the HbA1c levels following weight loss, but not a substantial improvement [31]. A lengthy, extensive follow-up study conducted in Japan found no conclusive correlation between periodontal care and the incidence of diabetes, although periodontitis was associated with a higher risk of developing diabetes [32]. Dentists should treat a patient's periodontal condition in the mouth and manage the patient's diabetes condition, which is relevant clinically for us, in order to achieve the greatest results after periodontal therapy.

MECHANISMS PROPOSED FOR HOW DIABETES AFFECTS PERIODONTAL HEALTH: AGEs, which are adducts formed when proteins and lipids are glycated and oxidized, were thought to affect periodontal condition indirectly through advanced glycemia and directly through hyperglycemia, causing periodontal tissue changes and general wound healing impairment.

By increasing glucose levels and decreasing epidermal growth factor (EGF) levels in saliva and gingival crevicular fluid, early-stage diabetes modifies the microbial composition of periodontal pockets (GCF) [33,34]. Prevotella intermedia and Porphyromonas gingivalis, as well as gram-negative anaerobes like the periodontal pathogens Capnocytophaga spp., Actinomyces spp., and Campylobacter spp., showed enhanced growth in clinical trials [35,36]. However, in vitro research has shown that diabetes persons' periodontally diseased areas have the same bacterial microflora as non-diabetic subjects [36,37]. The little variability of the bacterial microflora suggests that changes in the human immune system may be more responsible for the greater prevalence and severity of

periodontal disease.

It has also been proposed that diabetes triggers a cytokine-induced acute-phase response by stimulating the innate immune system, which contributes to the pathophysiology of the illness and its side effects, such as dyslipidemia, atherosclerosis, and host inflammatory responses [38]. The stimulation of innate immunity, mostly by an increase in proinflammatory cytokines in the presence of gram-negative bacteria, is one of the processes causing periodontal disease, which may suggest that proinflammatory cytokines may control systemic periodontitis [39]. According to Salvi and colleagues, monocytic proinflammatory cytokines as interleukin (IL)-1,tumour necrosis factor (TNF), and prostaglandin (PG)E2 are hyperresponsive in diabetics with periodontal issues. [39,40].

Hyperglycemia causes a wide range of alterations in collagen. In one study, fibroblasts from diabetes patients and hyperglycemic culture conditions revealed lower collagen and glycosaminoglycan production [41]. In vivo research has demonstrated that people with diabetes have lower levels of osseous matrix and collagen synthesis [42]. Several animal investigations have shown increased collagenase and gelatinase activity in gingival tissues [43]. Changes in collagen metabolism, which are a major part of basement membranes and can negatively impact wound healing and turnover capacity, can also lead to microangiopathy [44]. The diffusion of growth factors, PMN chemotaxis, and the elimination of metabolic waste products can all be impeded by the basement membrane.

Last but not least, altered collagen metabolism, ECM glycation, ROS overproduction, and immunological dysfunction can all have an impact on the vascular system. When proteins and lipids are significantly glycated and ROS is produced as a byproduct of prolonged hyperglycemia, AGEs are produced. There have also been reports of AGE buildup in plasma and tissues in a number of pathophysiological conditions, such as metabolic failure, persistent inflammation, and neurodegenerative diseases [45]. AGEs can affect how cross-linking occurs in the matrix, lessen the effectiveness of growth hormones, and increase oxidative stress in diabetes individuals.

In investigations, it has been found that AGEs diminish the viability and differentiation capacity of MSCs and interrupt cell cycles in fibroblasts [45,46,47]. High AGE-cross-linked collagen levels modify ECM productivity and osteoblastic activity, which affects bone formation [48]. Freshly produced collagen degrades quickly due to this alteration in collagen metabolism [49]. The buildup of altered collagen molecules in tissues impairs the recovery of periodontal wounds and hastens the degeneration of mineralized bone and connective tissue.

Due to poor osteoblastic cell proliferation and collagen production, osteocytes produce less new bone, which has a lower strength [50,51]. As a result, AGEs hinder the healing of wounds and increase the amount of tissue damage.
High-affinity RAGEs are observed in monocytes, macrophages, endothelial, and epithelial cells. In a recent study, it was discovered that PDLCs and MSCs implanted on a glycated matrix had increased RAGE expression. The nuclear factor (NF)-B-regulated pathway is engaged, cytokines are produced, and inflammation is generated when AGEs bind to RAGEs. Increased expression of VCAM-1 and hyperpermeability brought on by RAGEs overexpression in

endothelial cells result in monocyte chemotaxis. RAGE thus has the capacity to convert short-term proinflammatory responses into long-term cellular dysfunction and immune system harm.

DIABETES AND PERIODONTAL TISSUE CHANGES: Tesseromatis and colleagues found that periodontal tissues showed morphological alterations in experimental diabetes [52]. 90 days following the onset of diabetes, their research revealed gingival epithelial hyperplasia, moderate-to-severe angiitis, and mild inflammation restricted to the lamina propria and perivascular area. Silva and colleagues noted thickening of the gingival epithelium, elongation of the dermal papilla, loose and disorganised collagen alignment in connective tissue, as well as more pronounced inflammatory cell infiltration in diabetic animals when plaque-retentive factors (such as the placement of subgingival ligatures) were present [53]. Our most recent research also showed that diabetes can delay mitogenesis and lengthen the periodontal disintegration process.

Liu and colleagues studied how diabetic mice' periodontal damage healed [54]. They discovered that diabetes can increase the amount of bone lost during the ligation procedure and may prevent the growth of new bone once the ligature is removed. Additionally, they found that diabetic rats had slower inflammation recovery, more apoptotic bone lining cells expressed, and fewer osteoblasts and periodontal ligament fibroblasts. They also examined the architecture of the alveolar bone following tooth extraction. They found that diabetic mice had severely necrotic alveolar bone, delayed epithelialization, mineralization, and tissue remodeling after extraction. They further hypothesised that increased apoptosis and decreased proliferation of fibroblasts may have contributed to the gingival lesions' slow recovery. Diabetes affects repair capacity, prolongs and intensifies periodontal damage, according to preclinical research.

PROPOSED MECHANISMS FOR PERIODONTITIS AFFECTING GLYCEMIC CONTROL: There is currently a paucity of knowledge regarding how periodontal illnesses affect diabetic states, despite the fact that It is becoming clearer how diabetes affects periodontal health. Periodontitis, an infection that mostly affects the mouth, is primarily brought on by gram-negative anaerobes. Pathogenesis in these bacteria is mediated by Endotoxins in the form of lipopolysaccharides are the main virulence factors for these microorganisms (LPSs) [55].

Through the direct release of cytokines from the GCF into the circulation or the indirect release of periodontal bacteria and their metabolites from periodontal biofilms, periodontitis can cause systemic diseases. Higher levels of serum proinflammatory cytokines have been linked in studies to attachment loss, suggesting that periodontitis is a systemic condition [56]. Additionally, periodontal therapy reduced systemic levels of IL-6, TNF alpha, and C-reactive protein (CRP), in addition to oral inflammation, showing that periodontal diseases also cause systemic changes in addition to local ones.

TNF alpha and IL-1 are expected to be key players in the emergence of systemic diseases because they were found to be elevated in the GCF and serum of people with periodontitis and diabetes. As periodontal disease damage and

the advancement of diabetes have been linked, it has been demonstrated that TNF alpha induces insulin resistance. There is proof that exposing the blood of people with periodontitis to the periodontal pathogen LPS increases triglycerides and decreases high-density lipoprotein (HDL) [57], indicating that local infections like periodontitis can alter the way that lipids are metabolized throughout the body. The cytokine cascade is assumed to have been activated as a result of the LPS. Elevated blood lipids may affect immune cell activity by enhancing pro-inflammatory cytokines, boosting superoxide generation by PMNs, changing monocyte surface antigens, and other processes.

A periodontitis-related overproduction of systemic proinflammatory cytokines including TNF alpha, IL-1, and IL-6 may also contribute to insulin resistance. By destroying pancreatic beta cells, blocking the effects of insulin, or modifying intracellular insulin signaling via NF-B and c-Jun N-terminal kinase, these cytokines improve insulin sensitivity (JNK).

CONCLUSION

The development of future therapeutic options for diabetics with periodontal disease depends critically on a complete knowledge of the possible mechanisms involving periodontal injury and periodontal repair that connect diabetes with periodontal disease.

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