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Review Article

Exploring the Reciprocal Link between Periodontitis and Diabetes Through Chronic Inflammation and Glucose Regulation

Sei Jin Chang[1], Eun-Sun Lee[2]*, Gahye Hong[3]

[1]Department of Biochemistry and Molecular Biology, School of Medicine, Kyung Hee University, Seoul 02447, Republic of Korea.
[2]Biomedical Science Institute, Kyung Hee University, Seoul 02447, Republic of Korea.
[3]Department of Biomedical Science, Graduate School, Kyung Hee University, Seoul 02447, Republic of Korea.

***E-mail** ✉ Eunsulee@yahoo.com

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ABSTRACT

Diabetes mellitus and periodontitis are two widespread long-term diseases that influence one another and have major consequences for global health. Periodontitis—an inflammatory gum disorder triggered by microbial imbalance—can make blood sugar regulation harder in diabetic patients, while poorly managed diabetes increases the severity of periodontal tissue destruction. This interaction forms a harmful loop, where immune disruption, infection, and inflammation constantly worsen both diseases and affect systemic health. The underlying biological links include persistent inflammation, immune irregularities, and microbial instability, creating an ongoing inflammatory process that extends beyond the mouth. Because of this connection, treating one disorder can positively affect the other. Evidence indicates that periodontal care can help improve glycemic balance in diabetic individuals, highlighting the value of joint management approaches. This review emphasizes the necessity of understanding the molecular and immune-based pathways behind this connection to create unified treatments that could substantially enhance patient well-being.

Keywords: Chronic periodontitis, Diabetes mellitus, Microbial imbalance, Inflammation, Hyperglycemia, Innate immune system

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Introduction

Among chronic disorders affecting humanity, periodontitis and diabetes mellitus stand out for their widespread occurrence and heavy burden on healthcare systems. The two diseases are closely linked through a mutual influence that complicates diagnosis and treatment. Periodontitis, second only to dental cavities as the most common oral condition [1], is a slow, progressive inflammatory disorder that damages the tooth-supporting structures—the gums, periodontal ligament, and alveolar bone [2]. Though related to several systemic conditions, its connection with diabetes mellitus (DM) is so well established that it is often described as the sixth complication of diabetes [3]. Diabetes mellitus refers to metabolic disorders marked by sustained hyperglycemia due to defects in insulin secretion, insulin action, or both [4]. Risk factors include obesity, aging, genetic predisposition, and ethnicity [5]. Both illnesses are alarmingly prevalent worldwide. The Global Burden of Disease Study (2021) estimated that nearly one billion individuals are affected by severe periodontitis [6–8], corresponding to a global standardized prevalence of 12.50% [6]. Meanwhile, diabetes mellitus affects about 10.5% of the world's population—over 536 million people, most of them with type 2 DM [9]. According to the World Health Organization (WHO), diabetes is

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expected to become the seventh leading cause of mortality by 2030 [10], mainly because of its association with cardiovascular, renal, and cerebrovascular complications.

Scientific studies reveal that the two conditions mutually intensify each other. Periodontitis can impair glycemic regulation in diabetic individuals, whereas uncontrolled diabetes accelerates gum and bone destruction [11]. The decline in glucose control seen in chronic periodontitis stems from systemic inflammation and cytokine production—particularly TNF-α and IL-6—that disrupt insulin signaling [12]. Increasing evidence for this bidirectional link has strong clinical relevance, suggesting that treating both diseases together leads to better outcomes [13]. Poorly regulated diabetes, especially Type 2 Diabetes (T2D), further aggravates periodontal damage by weakening immune defense, reducing neutrophil activity, and disturbing oral microbial balance, resulting in dysbiosis [14]. Research also highlights the contribution of advanced glycation end-products (AGEs) and their receptors (RAGEs) to sustained inflammation and delayed tissue repair, making diabetic patients more vulnerable to oral tissue breakdown [11]. These intertwined mechanisms stress the importance of multidisciplinary management focusing on reducing systemic inflammation, restoring immune function, and maintaining microbial stability. Therefore, this review aims to explain the biological and pathological links between these two disorders and discuss how this knowledge can improve diagnosis and therapy.

Periodontitis

Periodontitis is a chronic inflammatory disorder that affects the tissues supporting the teeth—including the gingiva, periodontal ligament, and alveolar bone—and is primarily driven by microbial infection, often leading to tooth and bone loss [15]. Gingival inflammation, referred to as gingivitis, typically precedes the onset of periodontitis [16]. As outlined by the most recent AAP/EFP classification, gingivitis is diagnosed when bleeding on probing (BoP) exceeds 10%. Periodontitis is confirmed when clinical attachment loss (CAL) is found at two or more interproximal sites that are not adjacent, or when interproximal CAL of ≥3 mm is observed on at least two teeth, excluding vestibular or lingual/palatal sites [17]. Moreover, this oral disease has been strongly linked to systemic conditions such as diabetes, respiratory infections, and cardiovascular disorders [14].

The accumulation of pathogenic dental biofilms, commonly known as plaque, initiates microbial imbalance that drives the progression of periodontitis [18]. This microbial dysbiosis—an alteration of the normal oral microbial community—is central to disease onset and persistence [19]. Continuous bacterial stimulation provokes an immune response which, when poorly regulated, leads to tissue degradation [20]. While microbial imbalance represents a critical factor, its presence alone is insufficient for disease manifestation; interactions with genetic predisposition, environmental factors, and habits like smoking determine disease severity [21].

The primary microbial contributors include Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia [22]. These organisms activate Toll-like receptors (TLRs), triggering inflammatory cascades that elevate pro-inflammatory cytokines and matrix metalloproteinases (MMPs), promoting tissue breakdown and bone loss [23]. Therefore, an in-depth understanding of microbial and immune dynamics is essential to comprehend periodontitis at the molecular level.

Pathophysiology of periodontitis

Microbial dysbiosis

The human oral cavity harbors over 700 microbial species [24]. While bacteria dominate, fungi, viruses, and archaea also inhabit this niche, forming intricate microbial networks of synergy and antagonism [25]. Among bacterial phyla, Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, and Proteobacteria are the most prevalent [26]. The composition of this microbiome varies by age, genetic makeup, diet, hygiene, and overall health [27]. Despite its diversity, only about 20–30 bacterial species are typically implicated in oral diseases such as caries and periodontitis, once the microbial equilibrium shifts toward dysbiosis [28].

Socransky (1998) classified these organisms into five microbial complexes, identifying P. gingivalis, T. denticola, and T. forsythia as members of the “red complex,” which exhibits strong pathogenic potential [29]. These species possess virulence mechanisms that enable them to destroy tissues, evade immunity, and perpetuate inflammation [30]. However, modern studies emphasize that the etiology of periodontitis extends beyond these red complex species [29]. Other pathogens, such as Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum—an anaerobic gram-negative bacillus—also significantly contribute to disease development [31]. A. actinomycetemcomitans is particularly linked to aggressive periodontitis due to its tissue invasiveness and ability to disrupt immune regulation [32]. Meanwhile, F. nucleatum functions as a bridging

organism, enabling coaggregation of other pathogens and stabilizing pathogenic biofilms [33].

Among these, Porphyromonas gingivalis remains the most studied and is considered a keystone pathogen in periodontal disease. This gram-negative, non-motile, asaccharolytic bacterium [34] expresses numerous virulence components—lipopolysaccharides (LPS), trypsin-like proteases known as gingipains, and fimbriae—that aid biofilm formation and interspecies adherence [35]. The asaccharolytic metabolism of P. gingivalis allows it to utilize amino acids and peptides as energy sources rather than sugars [36]. Gingipains enable the bacterium to produce fimbrial appendages attached to its outer membrane [37].

Two main types of fimbriae exist: long fimbriae composed of FimA protein, which interact with human glyceraldehyde 3-phosphate dehydrogenase (GAPDH) to induce cytokine release, and short fimbriae made of mfa1 subunits that attach to SspA and SspB proteins of other bacteria in biofilms. The FimA fimbriae play a major role in colonization and immune activation. These virulence components degrade extracellular matrix proteins, weaken epithelial barriers, and allow bacterial invasion of subepithelial tissues while breaking down iron-binding molecules [37, 38]. Gingipains cleave peptide bonds at lysine or arginine residues, forming lysine-gingipain and two arginine-specific gingipains (A and B) [39].

P. gingivalis, considered a late colonizer in biofilm maturation, cooperates with early colonizers such as Streptococcus oralis, S. mitis, S. gordonii, S. sanguis, and intermediate colonizers like F. nucleatum, which facilitate its adhesion and persistence through cooperative interactions, including with T. denticola [40]. While microbial imbalance initiates the disease, the host immune response drives much of the tissue destruction. Pathogenic bacteria trigger cytokine cascades, activating MMPs and osteoclasts responsible for alveolar bone resorption [41].

Host immune response

In periodontitis, the host's defense reaction is mainly dominated by inflammation [42]. Once bacterial pathogens are sensed, both branches of the immune system—innate and adaptive—are triggered [43]. At the onset of infection, the innate response plays a central role, relying on epithelial cells, phagocytes (notably neutrophils, macrophages, and dendritic cells), the complement network, pattern recognition receptors (PRRs), and the secretion of inflammatory messengers such as cytokines and chemokines. Together, these components form the first coordinated defense against microbial invasion.

Epithelial Cells and Barrier Defense

The oral epithelial lining forms the body's initial shield against microbial intrusion. When harmful microorganisms reach the gingival or oral mucosal surfaces, epithelial cells act as active participants in the immune process rather than passive barriers [44]. These cells contain pattern recognition receptors (PRRs) capable of detecting pathogen-associated molecular patterns (PAMPs) that are specific to microbes. PAMPs may include elements such as lipopolysaccharides (LPS) from Gram-negative bacteria like P. gingivalis, as well as peptidoglycan and flagellin [45]. Once PAMPs interact with PRRs—particularly Toll-like receptors (TLRs)—epithelial cells sense the microbial threat and begin signaling to the immune system **(Figure 1)**.

Following this recognition, epithelial cells release cytokines and chemokines that summon immune cells to the infection site [46]. Interleukin-8 (IL-8) acts as a strong attractant for neutrophils, which are the first immune cells to appear in periodontal inflammation [47]. Meanwhile, interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) intensify local inflammation and tissue destruction by enhancing the synthesis of matrix metalloproteinases (MMPs) and stimulating osteoclasts [48]. Chemokines such as CXCL1 and CXCL2 promote further migration of neutrophils and other leukocytes [49]. When chronic infection damages the epithelial barrier, permeability increases, allowing bacteria to penetrate deeper tissues and aggravate inflammation [50]. Some microorganisms—particularly P. gingivalis—can invade epithelial cells directly, manipulating immune pathways to create a survival advantage [51].

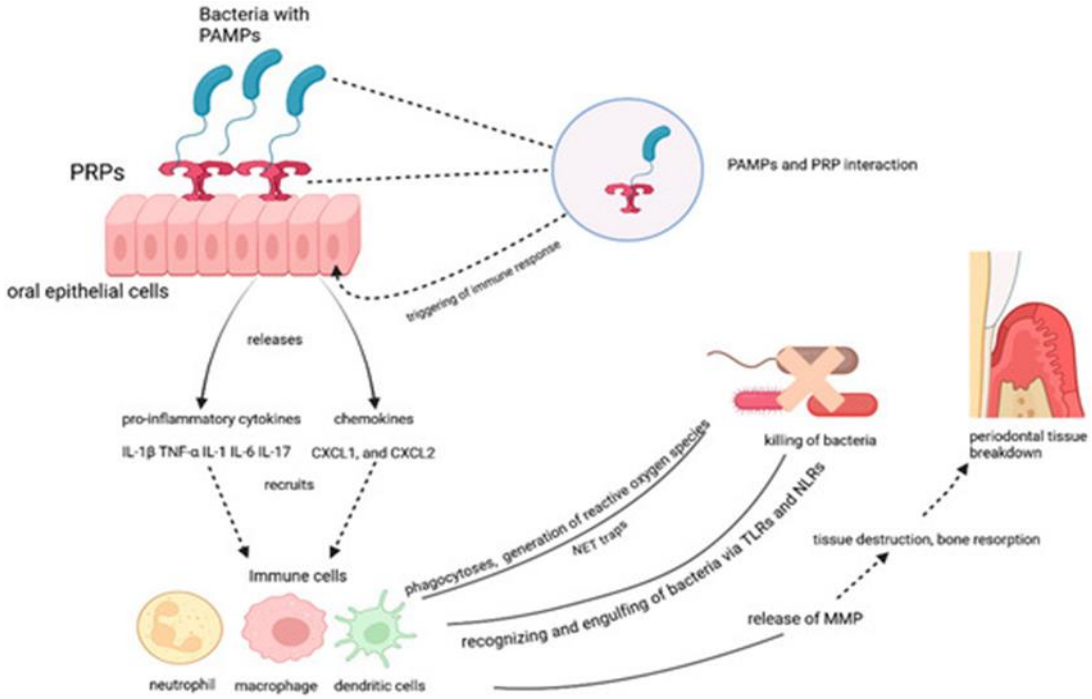


Figure 1. Interaction of oral epithelial cells and immune mechanisms contributing to periodontal tissue breakdown.

Phagocytic cells: neutrophils and macrophages

Cells with phagocytic capacity—mainly neutrophils, macrophages, and dendritic cells—are crucial in the body's defense strategy during periodontitis. Neutrophils serve as the earliest responders in the gingiva, where they contain bacterial proliferation and help preserve tissue integrity during early inflammation [52]. Their importance in maintaining periodontal balance has been confirmed in numerous investigations [53]. Neutrophils are drawn toward infection sites by chemotactic molecules such as IL-8 secreted by epithelial and resident immune cells.

These cells identify and ingest bacteria using their PRRs, including TLRs, through a process known as phagocytosis [54]. Inside the cell, pathogens are destroyed by reactive oxygen species (ROS) and antimicrobial molecules like defensins and cathelicidins [55]. Neutrophils can also extrude neutrophil extracellular traps (NETs)—web-like structures composed of DNA, histones, and enzymes—that immobilize microbes. While NETs are protective, excessive release can harm host tissues and intensify inflammation [56]. Additionally, neutrophils release MMPs, enzymes responsible for degrading extracellular matrix proteins, thereby contributing to connective tissue breakdown and alveolar bone loss [57]. Continuous neutrophil activation becomes destructive and leads to collateral tissue injury.

Macrophages, originating from monocytes that migrate from the bloodstream into inflamed periodontal areas, form another vital line of immune defense. These cells engage in phagocytosis, produce cytokines, and assist in tissue remodeling and repair [58]. Like neutrophils, macrophages recognize bacteria through PRRs such as TLRs and NOD-like receptors (NLRs). They are major sources of pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6, which maintain inflammation and recruit other immune cells [59]. They also secrete CCL2 (MCP-1) to attract more monocytes and lymphocytes into infected tissues. Furthermore, macrophages release MMPs, enzymes that participate in extracellular matrix turnover, but in periodontitis they exacerbate tissue and bone degradation [60].

The Complement System

The complement cascade represents a vital arm of innate immunity, responsible for detecting invading microbes, facilitating their elimination, and amplifying inflammatory reactions [61]. It consists of a sequence of proteolytic activations involving numerous plasma proteins that collectively produce a chain of immune responses [62]. These events lead to pathogen lysis, immune cell recruitment, and enhancement of phagocytic efficiency. In periodontitis, once antibodies recognize bacterial components and form immune complexes, the classical complement pathway becomes engaged through activation of the C1 complex, specifically the C1q subunit [62].

When the lectin pathway is initiated, mannose-binding lectins or ficolins attach to distinct carbohydrate or acetylated motifs present on bacterial cell walls [63], such as those characteristic of P. gingivalis. The alternative pathway, on the other hand, undergoes

continuous low-level activation, which is reinforced upon contact with microbial surfaces. This results in the deposition of complement fragments onto bacteria. During periodontal inflammation, C3b plays a major role in opsonization, tagging microbes for engulfment by neutrophils and macrophages [63].

The small complement fragment C5a functions as a powerful chemoattractant, guiding immune cells toward infection sites and intensifying inflammatory damage. In parallel, the membrane attack complex (MAC)—assembled from C5b through C9—can perforate bacterial membranes, leading to direct cell lysis. However, in periodontal lesions, this mechanism is less dominant due to the protective nature of the oral biofilm, which shields bacteria from complement-mediated killing.

Activation of pattern recognition receptors (PRRs) on epithelial cells by pathogen-associated molecular patterns (PAMPs) initiates a pro-inflammatory cascade. Engagement of PRRs results in secretion of cytokines such as IL-1β, TNF-α, IL-6, and IL-17, alongside chemokines including CXCL1 and CXCL2, which collectively attract neutrophils, macrophages, and dendritic cells. These recruited cells identify pathogens via Toll-like receptors (TLRs) and NOD-like receptors (NLRs), generate reactive oxygen species (ROS), and deploy neutrophil extracellular traps (NETs) to neutralize bacteria. Unfortunately, these same defense processes stimulate the release of matrix metalloproteinases (MMPs), leading to connective tissue degradation, alveolar bone loss, and progressive periodontal breakdown.

Inflammatory Mediators: Cytokines and Chemokines

Cytokines and chemokines orchestrate immune cell movement and activation during periodontal inflammation. Among the earliest mediators, interleukin-1β (IL-1β) is secreted rapidly after pathogen detection, promoting inflammation and inducing MMP synthesis, which accelerates tissue destruction [64]. Tumor necrosis factor-α (TNF-α) further stimulates immune activity and inflammatory signaling, playing a crucial part in alveolar bone resorption and connective tissue loss [43]. Interleukin-6 (IL-6), a central cytokine in acute-phase reactions, contributes to systemic inflammation and supports osteoclast differentiation, thereby facilitating bone degradation in periodontitis [65].

When innate immunity is insufficient to control microbial invasion, adaptive immune mechanisms—mediated by T and B lymphocytes—are activated. Unlike the rapid yet nonspecific innate response, adaptive immunity is slower but highly specific [66]. In periodontitis, this adaptive arm intensifies and sustains the immune reaction, but its prolonged activation can worsen tissue injury rather than promote healing.

T cells occupy a pivotal role in the adaptive immune phase of periodontitis. The Th1 and Th17 subsets are most influential in driving inflammation [67]. Th1 cells secrete interferon-γ (IFN-γ), which activates macrophages and heightens inflammatory signaling, while Th17 cells release interleukin-17 (IL-17) to attract neutrophils and amplify tissue inflammation. Overstimulation of Th17 pathways has been strongly linked to bone loss and tissue damage [68]. Cytotoxic T lymphocytes (CTLs) may aid in removing infected cells, though excessive activation can also intensify chronic tissue injury [69].

B cells produce pathogen-specific antibodies—mainly IgG—to neutralize bacterial toxins and facilitate microbial clearance [70]. Nevertheless, in periodontal disease, antibody activity often fails to completely remove pathogens and may inadvertently intensify tissue degradation by activating complement cascades and MMPs. Both T and B cells secrete a spectrum of cytokines that regulate immune dynamics; elevated levels of TNF-α, IL-1, IL-6, and IL-17 drive chronic inflammation, matrix destruction, and bone resorption [71]. These inflammatory mediators also interfere with insulin signaling by disrupting receptor activity and intracellular pathways, impairing glucose uptake and promoting insulin resistance, a hallmark of type 2 diabetes mellitus. Furthermore, oxidative stress induced by ROS compounds this dysfunction and contributes to metabolic and tissue injury.

Oxidative stress

Although microbial imbalance and host immune reactions are the central elements of periodontal disease, the contribution of oxidative stress has become increasingly evident. Elevated oxidative activity, particularly from hyperreactive polymorphonuclear neutrophils (PMNs), is strongly associated with disease progression [72]. Under stimulation from inflammatory cytokines, these neutrophils generate excessive reactive oxygen species (ROS) via the NADPH oxidase pathway [73]. The overproduction of ROS triggers further activation of immune cells and enhances osteoclast differentiation, leading ultimately to tissue degradation and alveolar bone resorption [74].

Diabetes mellitus

Diabetes mellitus is classified mainly into Type 1 (T1D) and Type 2 (T2D) variants. Type 1 diabetes, also known as autoimmune diabetes, arises from the destruction of pancreatic β-cells, resulting in an absolute lack of insulin and subsequent elevation of blood glucose levels [75]. In contrast, Type 2 diabetes,

which dominates in adults, represents the most common form of the disease [76]. It primarily develops because body tissues become insensitive to insulin, a condition known as insulin resistance, causing impaired glucose regulation [77]. The disorder stems from a multifaceted interaction of genetic predisposition and environmental conditions [78]. Around 90–95% of all diabetic patients suffer from T2D, while T1D forms only a minor subset. On a global scale, diabetes continues to pose a serious public health issue. Type 2 diabetes in particular results from defective β-cell function coupled with reduced insulin responsiveness in peripheral organs [79].

Pathophysiology of diabetes

Insulin resistance

Insulin, a peptide-based hormone secreted by β-cells within the islets of Langerhans, plays an essential role in enabling glucose transport into cells, thereby maintaining normoglycemia [80]. In diabetic individuals, this mechanism becomes disrupted, causing a persistent rise in blood glucose that affects multiple organs, including oral tissues. Insulin resistance, a defining feature of Type 2 diabetes, occurs when target cells fail to respond to insulin's metabolic effects under otherwise normal glucose conditions [81, 82].

This dysfunction is strongly linked with calorie-rich diets high in fats and sugars, which foster excess adipose accumulation—particularly in the visceral region. Such adiposity promotes the secretion of inflammatory cytokines including TNF-α, IL-6, and resistin [83]. These mediators impair insulin signaling and perpetuate low-grade systemic inflammation [84]. As the pancreas attempts to compensate by secreting more insulin, the overburdened β-cells progressively lose efficiency, producing relative insulin deficiency and persistent hyperglycemia.

Notably, early biochemical studies revealed that insulin and TNF-α may compete for the insulin receptor (INS-R) binding site, providing a molecular basis for insulin resistance. Experiments with rat liver membranes in the 1970s confirmed that insulin operates through surface receptor interactions [85]. The insulin receptor substrate (IRS) contains over 70 potential serine/threonine phosphorylation sites [86], many of which are targeted during inflammatory stress. In periodontal inflammation, the excess of TNF-α leads to serine phosphorylation of IRS-1 [87, 88], interrupting the insulin cascade and suppressing GLUT-4 expression [89, 90]. Consequently, TNF-α outcompetes insulin for receptor binding, blocking signal transmission and diminishing glucose uptake — a hallmark of insulin resistance.

Inflammatory response

Prolonged hyperglycemia induces widespread physiological harm. Elevated blood sugar promotes the creation of advanced glycation end-products (AGEs) through non-enzymatic interactions between glucose and proteins or lipids [91]. These AGEs accumulate in tissues and activate receptors for advanced glycation end-products (RAGEs), which stimulate the NF-κB signaling cascade, intensifying the production of pro-inflammatory cytokines [91]. This continuous inflammatory state contributes to vascular, neural, and organ impairment, while also weakening immune competence. As a result, diabetic individuals experience poor infection control and delayed tissue repair [92].

Effects of hyperglycemia

Elevated glucose levels also hinder normal immune performance. Neutrophil chemotaxis and bactericidal activity are reduced, and both macrophage and T-cell functions become dysregulated [93]. These impairments collectively increase vulnerability to infections such as periodontitis. Thus, diabetes not only damages systemic tissues but also disrupts oral immune homeostasis, establishing a two-way link between metabolic dysregulation and periodontal disease.

The bidirectional relationship

Diabetes mellitus—especially Type 2 diabetes—exerts a considerable influence on oral health, and its reciprocal link with periodontitis has long been documented in scientific research. Although diabetes itself does not directly trigger oral infections, the combination of impaired immune response and unstable blood glucose levels substantially promotes periodontal tissue breakdown in susceptible individuals [94].

In diabetic conditions, persistent hyperglycemia alters immune efficiency by disturbing neutrophil behavior, rendering diabetic patients more prone to microbial infections, including periodontal inflammation. Under elevated glucose levels, both neutrophil migration (chemotaxis) toward infected sites and phagocytosis, the engulfment and destruction of pathogens, are markedly reduced [95, 96]. As a result, the body's capacity to restrain bacterial proliferation within periodontal tissues weakens. Additionally, macrophage dysregulation under hyperglycemic stress heightens the release of pro-inflammatory cytokines, aggravating local tissue damage [97]. Diabetes also diminishes salivary secretion and disrupts the delivery of immune molecules in saliva, lowering the mouth's natural antimicrobial defense. The composition of

saliva changes as well, showing a decline in antimicrobial peptides, which further compromises infection control and tissue regeneration [98].

Chronic elevation of glucose also accelerates the generation of reactive oxygen species (ROS)—unstable free radicals that injure lipids, proteins, and DNA [99]. This oxidative stress interferes with fibroblast proliferation, collagen deposition, and extracellular matrix (ECM) organization, thereby delaying wound closure. The impaired healing process seen in diabetes predisposes patients to secondary oral infections, including those affecting gingiva and the periodontal ligament, thus intensifying disease progression and complicating treatment **(Figure 2)**. Elevated levels of chemokines such as IL-8, MCP-1, and CXCL-1 have also been observed in periodontal tissues among diabetic individuals [100].

Sustained hyperglycemia in diabetes promotes the Maillard reaction, in which glucose forms irreversible covalent adducts with proteins, lipids, and nucleic acids, yielding advanced glycation end-products (AGEs) [101]. Excessive AGE accumulation alters both the architecture and function of connective tissues [102]. Within the gums, AGEs bind to the extracellular matrix of the basement membrane in gingival tissues [103]. AGE-modified collagen thickens microvascular walls, reducing membrane permeability and restricting the passage of oxygen, nutrients, immune cells, and antibodies to affected regions [2, 104, 105]. Consequently, periodontal tissues become more fragile and inflamed, amplifying disease progression.

AGEs also interact with their specific receptors, RAGEs, located on macrophages, neutrophils, and endothelial cells, prompting a cascade that elevates pro-inflammatory cytokines and ROS generation, thereby intensifying periodontal inflammation [102]. Furthermore, AGEs cause cross-linking of collagen fibers in gingival and periodontal matrices, resulting in rigid, poorly remodelled tissue [106, 107]. This rigidity obstructs normal healing and accelerates degradation of the connective and osseous structures anchoring teeth. Studies indicate that AGEs also stimulate osteoclast activation, enhancing bone resorption [108]. In the context of periodontitis, this mechanism accelerates alveolar bone loss, leading to more severe clinical manifestations among diabetic patients.

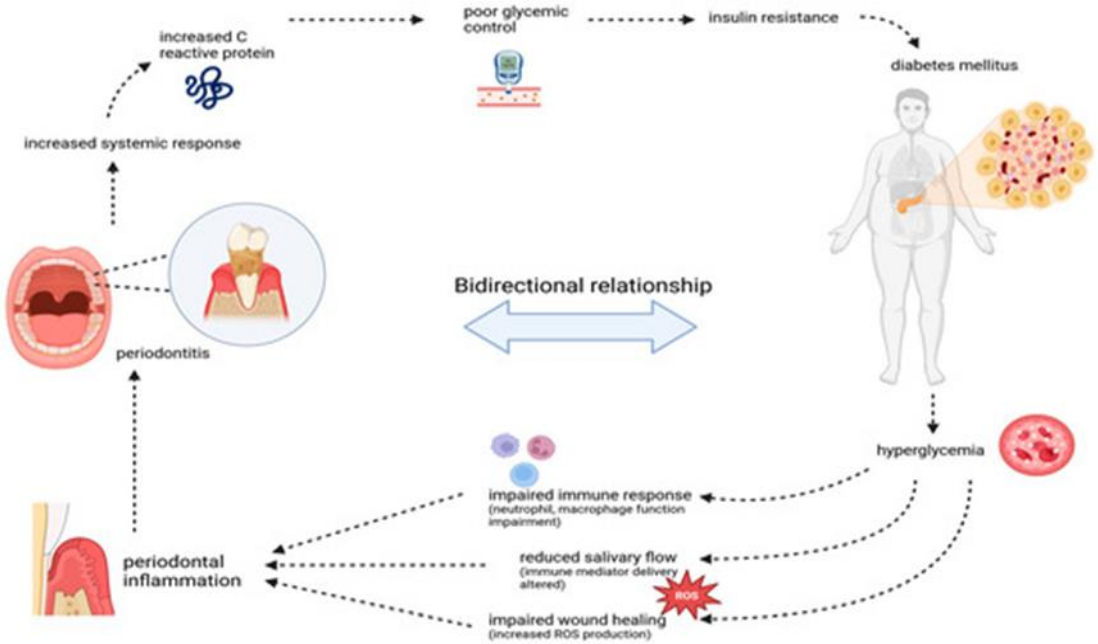


Figure 2. The interdependent relationship between periodontitis and diabetes mellitus forms a destructive feedback loop. Periodontal inflammation elevates systemic mediators such as C-reactive protein, which worsens insulin resistance and disrupts glucose metabolism, promoting diabetic progression. Conversely, diabetic hyperglycemia compromises immunity, delays wound repair, and raises oxidative stress, all of which aggravate periodontal inflammation and tissue destruction, sustaining this vicious cycle.

In periodontitis, the inflammatory mediators generated during the host immune response can extend beyond the oral cavity, producing systemic effects that worsen metabolic diseases such as diabetes mellitus. The principal systemic consequence of periodontal infection is an elevated inflammatory load, which interferes with metabolic regulation and exacerbates insulin resistance [109]. Persistent inflammation from periodontitis disrupts glycemic stability in diabetic patients through several intertwined mechanisms

[110]. Central to these mechanisms is the development of insulin resistance, which hinders the body's capacity to maintain proper glucose balance. Inflammation derived from periodontal tissue elevates cytokine levels, including TNF-α and IL-6, which interfere with insulin signaling cascades, blocking receptor activity and restricting cellular glucose uptake [111]. Continuous inflammatory stress further triggers the NF-κB pathway, enhancing cytokine expression that directly weakens insulin efficiency [112]. This creates a self-reinforcing loop: inadequate glycemic control accelerates periodontal breakdown, while periodontal inflammation further compromises insulin sensitivity. Elevated oxidative stress, commonly seen in periodontal tissues, adds to this cycle by damaging insulin receptors and molecules crucial for glucose metabolism [113] **(Figure 2)**.

Evidence of glycemic improvement following periodontal therapy

Multiple clinical trials demonstrate that periodontal treatment contributes to measurable improvements in glycemic control among individuals with Type 2 diabetes [114]. By diminishing systemic inflammation, periodontal therapy can enhance insulin responsiveness and optimize glucose utilization [115]. Research consistently shows that following periodontal procedures such as scaling and root planing (SRP) or surgical interventions, systemic inflammatory markers including CRP, IL-6, and TNF-α are significantly reduced [116]. This decline in cytokine activity correlates with improved metabolic function and insulin sensitivity [117].

A 2020 systematic review and meta-analysis found that SRP notably enhanced both metabolic regulation and decreased systemic inflammation in T2D patients [118]. Similarly, an umbrella review (2022) confirmed that non-surgical periodontal therapy significantly improved HbA1c levels at 3- and 6-month follow-ups in diabetic individuals [119]. Further investigations have reinforced that periodontal care enhances insulin sensitivity [120]. For example, in patients with T2D and periodontitis, SRP led to lower fasting glucose and improved HbA1c outcomes [121]. A 2024 study in the Journal of Clinical Periodontology reported that periodontal treatment markedly improved glycemic profiles, particularly in patients with HbA1c ≥ 7.0%, emphasizing the broader metabolic benefits of oral healthcare [122].

Molecular and microbiological interconnections

Beyond local tissue effects, the oral microbiome can affect systemic health via bacteremia, allowing bacteria or their components to enter the bloodstream [123]. During episodes of periodontal infection, microorganisms can reach distant organs such as the heart, liver, or pancreas, triggering systemic inflammation [124]. These circulating bacteria stimulate the production of C-reactive protein (CRP) and other pro-inflammatory mediators, perpetuating chronic low-grade inflammation, a hallmark of metabolic diseases including diabetes [125]. At a molecular level, diabetes and periodontitis share overlapping inflammatory signaling networks, particularly those that govern immune activation and metabolic dysfunction [126].

NF-κB (Nuclear Factor kappa B) Pathway

The NF-κB signaling cascade acts as a master regulator of immune and inflammatory gene expression [127]. It can be activated by diverse stimuli such as cytokines (TNF-α, IL-1β), bacterial lipopolysaccharides (LPS), oxidative stress, and advanced glycation end-products (AGEs) [112]. Once triggered, NF-κB migrates to the nucleus, promoting transcription of pro-inflammatory and survival genes [128].

Role in periodontitis and diabetes mellitus

In periodontitis, NF-κB governs the persistent inflammatory reaction against oral pathogens such as Porphyromonas gingivalis. Its LPS activates NF-κB in gingival tissues, driving overproduction of IL-1β, TNF-α, and IL-6 [129]. These mediators attract immune cells, stimulate osteoclast activity, and contribute to alveolar bone degradation while preventing effective tissue repair [130]. In diabetes, both hyperglycemia and excess AGE accumulation activate the NF-κB pathway, generating systemic inflammation and interrupting insulin signaling [131]. The overexpression of cytokines like TNF-α and IL-6 heightens insulin resistance and glucose intolerance [132]. Additionally, NF-κB activation in adipose tissue and endothelial cells increases ROS formation, contributing to vascular and metabolic complications [133]. In pancreatic β-cells, this pathway reduces insulin secretion and promotes apoptosis, worsening hyperglycemia [134]. Thus, NF-κB serves as a pivotal molecular link between diabetes and periodontitis, and its modulation may offer a therapeutic target for both diseases.

Oxidative stress and RAGE

Oxidative stress arises when reactive oxygen species (ROS) surpass the body's antioxidant capacity, resulting in cellular injury [135]. The receptor for advanced glycation end-products (RAGE) binds AGEs and other damage-associated molecular patterns (DAMPs), activating downstream inflammatory

signaling [136]. Engagement of RAGE enhances cytokine production and ROS generation, creating a feedback loop that sustains inflammation and tissue damage [137]. This dual mechanism accelerates the progression of both periodontal and metabolic disorders.

Therefore, it is vital for dental and medical professionals to understand this bidirectional interdependence between diabetes and periodontal diseases. Adopting integrated treatment strategies targeting both metabolic and inflammatory pathways can significantly enhance overall patient outcomes.

Conclusion

In summary, the complex two-way interaction between periodontitis and diabetes mellitus emphasizes the necessity for a coordinated management strategy for these chronic illnesses. The mutual influence of these conditions intensifies systemic inflammation and metabolic disturbances, leading to a significant decline in patients' overall health and daily functioning. Periodontitis aggravates glycemic control in diabetic patients via inflammatory pathways, immune dysregulation, and microbial imbalance, whereas diabetes increases both the risk and severity of periodontal disease.

Addressing oral dysbiosis through periodontal interventions—which are accessible and cost-effective—can disrupt this vicious cycle. By correcting microbial imbalance, complications that compromise quality of life, such as tooth loss and increased adiposity, may be mitigated. A multidisciplinary approach is crucial: dentists should consider recommending blood tests for diabetes when evaluating patients with periodontitis, while endocrinologists should advocate scaling and root planing (SRP) to reduce bacterial burden and improve metabolic outcomes. Coordinating with nutrition specialists to implement personalized dietary plans can further support the simultaneous management of both conditions.

Integrated therapies addressing both diseases can assist patients in navigating the challenges of dual management. Recent studies focusing on biomarkers such as advanced glycation end-products (AGEs) and their receptors (RAGEs), along with interventions targeting pro-inflammatory cytokines, provide promising directions for combined therapeutic strategies. By addressing shared inflammatory pathways, healthcare providers can enhance patient outcomes while reducing chronic systemic complications.

The public health significance of this topic is substantial, particularly for at-risk populations, due to the high prevalence and economic burden of concurrent diabetes and periodontitis. Implementing cohesive clinical protocols may improve patient care, prevent future disease progression, and reduce healthcare costs, promoting a more holistic and efficient approach to chronic disease management.

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