

Association Between Periodontal Disease and Glycemic Control in Diabetes Mellitus: A Review of Pathophysiology and Clinical Evidence

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ABSTRACT

Diabetes mellitus and periodontal disease are closely interrelated chronic conditions with a bidirectional relationship, wherein each can influence the onset, progression, and severity of the other. Diabetes increases susceptibility to periodontitis through mechanisms including hyperglycemia-induced immune dysfunction, oxidative stress, chronic inflammation, and advanced glycation end product (AGE)-RAGE signaling, which impair tissue repair and promote alveolar bone loss. Conversely, periodontal inflammation contributes to systemic inflammatory burden, elevates circulating cytokines such as TNF- α , IL-1 β , and IL-6, and exacerbates insulin resistance, thereby impairing glycemic control. This review synthesizes current evidence from recent clinical, epidemiological, and mechanistic studies (2020–2025) to elucidate the molecular and immunological pathways linking these two conditions. We discuss the role of periodontal pathogens, dysbiosis, and host immune responses in mediating tissue destruction and systemic metabolic effects, as well as emerging diagnostic biomarkers in saliva and gingival crevicular fluid for early detection and monitoring. Evidence demonstrates that non-surgical periodontal therapy, including scaling and root planning, with or without adjunctive host-modulatory interventions, can modestly but significantly improve glycemic control, reflected by reductions in HbA1c, and reduce systemic inflammatory mediators. The review also highlights limitations in current research, including heterogeneity in study designs, short follow-up periods, and variability in periodontal definitions, underscoring the need for standardized longitudinal studies. Integrating periodontal care into diabetes management, supported by lifestyle modifications and interdisciplinary collaboration, represents a promising strategy to improve both oral and systemic health outcomes. This review emphasizes the importance of recognizing periodontitis as a modifiable risk factor in diabetes and highlights potential therapeutic and diagnostic advancements that can inform clinical practice and future research.

Keywords: Diabetes Mellitus; Periodontitis; Glycemic Control; Inflammation; Biomarkers; Advanced Glycation End Products; Periodontal Therapy.

Introduction

Global Burden of Diabetes Mellitus

Online ISSN

3007-3197

Print ISSN

3007-3189

<http://amresearchreview.com/index.php/Journal/about>

Diabetes mellitus (DM) represents one of the most significant global public health challenges of the 21st century. It is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The disease is associated with substantial morbidity, mortality, and economic burden worldwide. According to the International Diabetes Federation (IDF) Diabetes Atlas (10th edition), approximately 537 million adults aged 20-79 years were living with diabetes globally in 2021, and this number is projected to increase to 643 million by 2030 and 783 million by 2045 if current trends persist (1). The rapid rise in diabetes prevalence is largely driven by population aging, urbanization, sedentary lifestyles, unhealthy dietary patterns, and the increasing prevalence of obesity (2).

The global distribution of diabetes demonstrates considerable regional variation, with the highest prevalence reported in low- and middle-income countries, where nearly 75% of individuals with diabetes reside (1). South Asia, the Middle East, and North Africa have experienced particularly rapid increases in diabetes incidence during the past decade. Countries such as Pakistan, India, and China have witnessed a substantial escalation in diabetes prevalence, largely reflecting demographic transitions, rapid urbanization, and lifestyle changes (3). Pakistan, in particular, has emerged as one of the countries with the highest diabetes burden globally, with recent epidemiological estimates indicating that over 33 million adults are currently living with diabetes, representing a major public health concern for the healthcare system (3,4).

Table 1: Global Prevalence and Burden of Diabetes and Periodontal Disease

Condition	Global Prevalence (%)	High-Risk Regions	Major Complications	Reference
Type 1 Diabetes	0.4	North America, Europe	Retinopathy, Nephropathy, Neuropathy	2,3
Type 2 Diabetes	9.3	Middle East, South Asia	Cardiovascular disease, Neuropathy, Kidney disease	2,5
Gestational Diabetes	2–10	Asia, Latin America	Type 2 diabetes later, macrosomia	37,39
Periodontitis (Moderate–Severe)	20–50	South America, South Asia	Tooth loss, systemic inflammation	19,20

The incidence of diabetes continues to rise globally, largely due to the growing prevalence of type 2 diabetes mellitus (T2DM), which accounts for approximately 90–95% of all diabetes cases (5). This increase is strongly associated with modifiable risk factors such as obesity, physical inactivity, and high-calorie diets. In addition, genetic predisposition, environmental influences, and metabolic abnormalities also contribute to disease development. Recent epidemiological studies have indicated that the prevalence of diabetes has nearly tripled over the past three decades, highlighting the

urgent need for effective prevention strategies and improved disease management approaches (2,6).

Poor glycemic control among individuals with diabetes significantly increases the risk of both microvascular and macrovascular complications, which contribute substantially to disease burden and healthcare expenditures. Chronic hyperglycemia can result in microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, all of which may lead to severe functional impairment and reduced quality of life (7). Furthermore, diabetes is a well-established risk factor for macrovascular complications including cardiovascular disease, stroke, and peripheral arterial disease, which remain leading causes of morbidity and mortality among diabetic patients worldwide (8).

In addition to these systemic complications, increasing evidence has demonstrated a strong association between diabetes and several oral health conditions, particularly periodontal disease, which is now recognized as one of the most prevalent complications of diabetes (9). Chronic hyperglycemia promotes the formation of advanced glycation end products (AGEs), oxidative stress, and the release of pro-inflammatory cytokines, all of which contribute to immune dysfunction and tissue damage (10). Consequently, individuals with poorly controlled diabetes exhibit an increased susceptibility to periodontal infection, more severe periodontal destruction, and impaired healing responses.

Given the rapidly increasing prevalence of diabetes and its wide range of systemic and oral complications, maintaining optimal glycemic control has become a critical component of diabetes management. Understanding the systemic consequences of chronic hyperglycemia, including its potential impact on periodontal health, is therefore essential for improving clinical outcomes and reducing the global burden of diabetes.

Overview of Periodontal Disease

Periodontal disease comprises a group of chronic inflammatory conditions that affect the supporting structures of the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone. Among these conditions, periodontitis represents the most severe form and is characterized by progressive destruction of periodontal tissues, ultimately leading to tooth mobility and tooth loss if left untreated (11). Periodontal diseases are primarily initiated by the accumulation of microbial biofilms, commonly referred to as dental plaque, which develop on the tooth surface and along the gingival margin. The interaction between pathogenic microorganisms within the biofilm and the host immune response plays a critical role in the initiation and progression of periodontal tissue destruction (12).

Online ISSN

3007-3197

Print ISSN

3007-3189

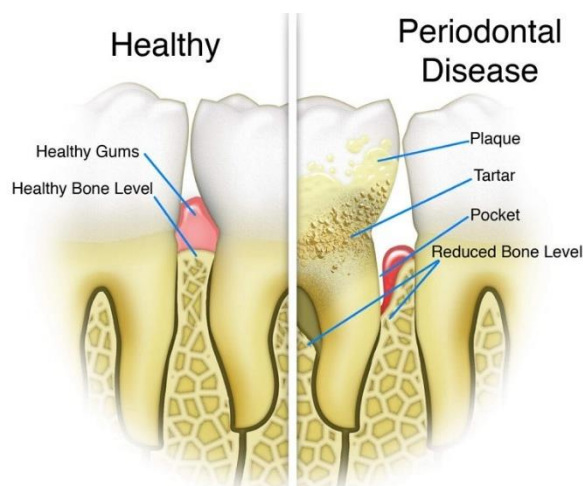
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Figure 1. Healthy VS Periodontal disease around the top of the tooth root

The pathogenesis of periodontal disease involves a complex interplay between subgingival microbial dysbiosis and the host inflammatory response. Key periodontal pathogens, including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, collectively known as the “red complex” bacteria, contribute significantly to disease progression by triggering host immune responses and inflammatory mediator release (13). These pathogens stimulate the production of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6), which promote connective tissue degradation and alveolar bone resorption (14). Additionally, the activation of matrix metalloproteinases (MMPs) and increased osteoclast activity further accelerate periodontal tissue destruction (15).

Clinically, periodontal disease progresses through several stages, beginning with gingivitis, a reversible inflammatory condition confined to the gingival tissues. Gingivitis is characterized by gingival redness, swelling, and bleeding upon probing, primarily caused by plaque accumulation (16). If gingivitis remains untreated, it may progress to periodontitis, a more advanced and irreversible condition involving the formation of periodontal pockets, clinical attachment loss, and alveolar bone destruction (17). Recent classifications proposed by the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions categorize periodontitis based on staging and grading systems, which consider disease severity, extent of tissue destruction, and risk of disease progression (18).

Periodontal disease is highly prevalent worldwide and represents one of the most common chronic inflammatory diseases affecting humans. According to recent global epidemiological estimates, severe periodontitis affects approximately 10–15% of the global adult population, making it a significant public health concern (19). Furthermore, moderate forms of periodontal disease are estimated to affect nearly 45–50% of adults globally, highlighting the extensive burden of this condition (20). The prevalence of periodontal disease increases with age and is influenced by several risk factors, including poor oral hygiene, tobacco use, diabetes mellitus, obesity, genetic susceptibility, and socioeconomic determinants (21). Given its high prevalence and potential systemic implications, periodontal disease has gained increasing attention as an important component of overall health.

Online ISSN

3007-3197

Print ISSN

3007-3189

<http://amresearchreview.com/index.php/Journal/about>

Importance of Oral-Systemic Health Connections

In recent decades, growing scientific evidence has highlighted the intricate relationship between oral health and systemic health, emphasizing the concept of oral–systemic interconnections. The oral cavity serves as a critical gateway to the human body and hosts a complex microbial ecosystem consisting of more than 700 bacterial species, many of which can influence systemic physiological processes (22). Disruptions in oral microbial balance and chronic periodontal inflammation can contribute to systemic inflammatory responses, thereby affecting overall health.

Periodontal disease has been increasingly recognized as a potential risk factor for several systemic conditions, including cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, respiratory diseases, and rheumatoid arthritis (23). The biological mechanisms underlying these associations are largely mediated by systemic dissemination of periodontal pathogens, inflammatory mediators, and bacterial endotoxins, which may enter the bloodstream through ulcerated periodontal pockets (24). This process can lead to chronic low-grade systemic inflammation, which is known to contribute to the pathogenesis of numerous metabolic and inflammatory disorders.

Among these systemic associations, the relationship between diabetes mellitus and periodontal disease has received considerable attention due to its bidirectional nature. Diabetes is recognized as a major risk factor for periodontal disease, while periodontal inflammation may adversely influence glycemic control and metabolic regulation (25). The interaction between these two chronic conditions is primarily driven by inflammatory pathways, immune dysfunction, and metabolic disturbances associated with persistent hyperglycemia. Consequently, periodontal disease is often referred to as the “sixth complication of diabetes”, highlighting its clinical relevance in diabetic patients (26).

Understanding the oral–systemic health connection is essential for developing integrated healthcare strategies that involve collaboration between dental professionals, endocrinologists, and primary healthcare providers. Such interdisciplinary approaches may improve disease prevention, enhance glycemic control, and reduce the risk of diabetes-related complications.

Rationale and Objective of the Review

Given the rapidly increasing global prevalence of diabetes mellitus and the high burden of periodontal disease, understanding the relationship between these two chronic conditions has become an important area of research. Numerous epidemiological, clinical, and mechanistic studies conducted in recent years have demonstrated a significant association between periodontal inflammation and impaired glycemic control in individuals with diabetes (27). Chronic periodontal infection may contribute to systemic inflammation, increased insulin resistance, and worsening metabolic control, thereby complicating diabetes management.

Despite the growing body of evidence, variations in study design, population characteristics, and diagnostic criteria have resulted in inconsistencies in the reported magnitude of this association. Furthermore, recent research has provided new insights into the molecular mechanisms, inflammatory pathways, and therapeutic interventions

linking periodontal disease with glycemic regulation. Therefore, a comprehensive evaluation of the current evidence is necessary to better understand the clinical implications of this relationship.

The primary objective of this review is to critically evaluate the contemporary evidence regarding the association between periodontal disease and glycemic control in patients with diabetes mellitus. Specifically, this review aims to examine the pathophysiological mechanisms linking these conditions, summarize recent epidemiological and clinical findings, and discuss the potential impact of periodontal therapy on glycemic outcomes. By synthesizing the latest research findings, this review seeks to highlight the importance of integrating periodontal care into the comprehensive management of diabetes and to identify potential directions for future research.

Pathophysiology of Diabetes Mellitus

Diabetes mellitus is a complex metabolic disorder characterized by persistent hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or both. The pathophysiology of diabetes involves intricate interactions between genetic susceptibility, environmental factors, metabolic dysregulation, and immune-mediated mechanisms. Chronic hyperglycemia leads to widespread metabolic disturbances affecting carbohydrate, lipid, and protein metabolism, which ultimately contribute to the development of long-term complications affecting multiple organ systems (28). Understanding the underlying pathophysiological mechanisms of diabetes is essential for improving disease management and identifying potential therapeutic targets.

The progression of diabetes is largely associated with impaired pancreatic β -cell function, insulin resistance, and dysregulation of glucose homeostasis. Persistent elevation of blood glucose levels triggers a cascade of biochemical alterations, including increased oxidative stress, activation of inflammatory pathways, and the formation of advanced glycation end products (AGEs), all of which contribute to cellular damage and tissue dysfunction (29).

Types of Diabetes

Diabetes mellitus is broadly classified into several types based on its underlying etiology and pathophysiological mechanisms. The most common forms include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (30).

Type 1 Diabetes Mellitus: Type 1 diabetes mellitus is an autoimmune disorder characterized by immune-mediated destruction of insulin-producing pancreatic β -cells located in the islets of Langerhans. This process results in an absolute deficiency of insulin, leading to chronic hyperglycemia (31). The disease is often diagnosed in childhood or adolescence, although it may occur at any age. Genetic susceptibility combined with environmental triggers, such as viral infections or immune dysregulation, is believed to initiate the autoimmune response against pancreatic β -cells (32). Patients with type 1 diabetes require lifelong insulin therapy to maintain normal glucose levels and prevent acute metabolic complications such as diabetic ketoacidosis (33).

Online ISSN

3007-3197

Print ISSN

3007-3189

<http://amresearchreview.com/index.php/Journal/about>

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus accounts for approximately 90–95% of all diabetes cases worldwide and represents the most prevalent form of the disease (34). It is primarily characterized by insulin resistance and progressive pancreatic β -cell dysfunction, resulting in inadequate insulin secretion relative to metabolic demand. Several risk factors contribute to the development of T2DM, including obesity, sedentary lifestyle, genetic predisposition, aging, and unhealthy dietary patterns (35). Insulin resistance in peripheral tissues such as skeletal muscle, liver, and adipose tissue leads to impaired glucose uptake and increased hepatic glucose production, thereby contributing to persistent hyperglycemia (36). Over time, chronic metabolic stress leads to β -cell exhaustion and decreased insulin secretion, further exacerbating glycemic dysregulation.

Gestational Diabetes Mellitus: Gestational diabetes mellitus is defined as glucose intolerance that develops or is first recognized during pregnancy (37). Hormonal changes during pregnancy, particularly increased levels of placental hormones such as human placental lactogen, cortisol, and progesterone, can induce insulin resistance, leading to elevated blood glucose levels (38). Although glucose metabolism typically returns to normal after delivery, women who develop gestational diabetes have a significantly higher risk of developing type 2 diabetes later in life (39). Furthermore, gestational diabetes is associated with adverse maternal and fetal outcomes, including macrosomia, preeclampsia, and neonatal metabolic complications.

Mechanisms of Hyperglycemia

Hyperglycemia in diabetes results from a combination of impaired insulin secretion, increased insulin resistance, and excessive hepatic glucose production (40). In healthy individuals, insulin plays a crucial role in regulating glucose homeostasis by facilitating glucose uptake into peripheral tissues and suppressing hepatic glucose output. However, in diabetic conditions, defects in insulin signaling pathways disrupt these regulatory mechanisms.

One of the central mechanisms contributing to hyperglycemia is insulin resistance, in which peripheral tissues such as skeletal muscle, liver, and adipose tissue exhibit a reduced biological response to insulin (41). As a result, glucose uptake by muscle cells decreases while hepatic gluconeogenesis increases, leading to elevated circulating glucose levels. In addition, progressive dysfunction of pancreatic β -cells reduces insulin secretion, further impairing glucose regulation (42).

Chronic hyperglycemia also promotes several metabolic pathways that contribute to tissue damage. These include the polyol pathway, protein kinase C activation, increased oxidative stress, and the formation of advanced glycation end products (AGEs) (43). AGEs accumulate in various tissues and interact with specific receptors known as receptors for advanced glycation end products (RAGE), triggering inflammatory responses and cellular dysfunction (44). These biochemical processes play a significant role in the development of diabetic complications and may also influence the progression of periodontal disease.

Chronic Complications of Diabetes

Persistent hyperglycemia is associated with a wide range of chronic complications that affect both microvascular and macrovascular systems. These complications are major contributors to the morbidity and mortality associated with diabetes.

Microvascular Complications: Microvascular complications arise from damage to small blood vessels caused by prolonged hyperglycemia. The most common microvascular complications include diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy (45). Diabetic retinopathy is one of the leading causes of preventable blindness worldwide and results from progressive damage to retinal microvasculature (46). Diabetic nephropathy, characterized by albuminuria and declining renal function, is a major cause of chronic kidney disease and end-stage renal failure (47). Diabetic neuropathy, which affects peripheral nerves, can lead to sensory loss, neuropathic pain, and increased risk of foot ulcers and amputations (48).

Macrovascular Complications: Macrovascular complications involve damage to large blood vessels and are primarily associated with atherosclerotic cardiovascular disease. Individuals with diabetes have a significantly higher risk of developing coronary artery disease, cerebrovascular disease, and peripheral arterial disease (49). These conditions contribute substantially to the increased cardiovascular mortality observed in diabetic populations. Hyperglycemia, dyslipidemia, endothelial dysfunction, and chronic inflammation collectively accelerate atherosclerotic plaque formation and vascular damage in diabetic patients (50).

Role of Chronic Inflammation in Diabetes

Chronic low-grade inflammation plays a pivotal role in the pathogenesis and progression of diabetes mellitus, particularly in type 2 diabetes. Increasing evidence suggests that metabolic abnormalities associated with obesity and insulin resistance lead to the activation of inflammatory pathways that impair insulin signaling (51). Adipose tissue in obese individuals produces a variety of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP), which contribute to systemic inflammation and metabolic dysregulation (52).

These inflammatory mediators interfere with insulin receptor signaling pathways, thereby promoting insulin resistance and worsening glycemic control. Furthermore, chronic inflammation contributes to endothelial dysfunction, oxidative stress, and vascular damage, which are key factors in the development of diabetic complications (53). Recent studies have also demonstrated that chronic inflammatory conditions, including periodontal disease, may further exacerbate systemic inflammation and negatively affect glycemic control (54). Periodontal infections can increase circulating levels of inflammatory cytokines and bacterial endotoxins, potentially worsening insulin resistance and metabolic imbalance. This interaction highlights the importance of understanding the link between periodontal inflammation and diabetes

pathophysiology.

Pathogenesis of Periodontal Disease

Periodontal disease is a chronic inflammatory condition affecting the supporting structures of the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone. The disease develops as a result of complex interactions between subgingival microbial biofilms and the host immune-inflammatory response. While bacterial infection initiates periodontal inflammation, the severity and progression of tissue destruction are largely determined by the host's immune response and environmental risk factors (11,12). Periodontitis represents the advanced stage of periodontal disease and is characterized by progressive loss of connective tissue attachment and alveolar bone, which can ultimately lead to tooth loss if untreated (17). The pathogenesis of periodontal disease is multifactorial and involves microbial dysbiosis, immune activation, inflammatory mediator release, and tissue degradation processes.

Periodontal Anatomy and Host Defense

The periodontium consists of specialized tissues that support and anchor teeth within the alveolar bone. These structures include the gingiva, periodontal ligament, cementum, and alveolar bone, which collectively maintain tooth stability and protect underlying tissues from microbial invasion (55). The gingiva acts as the first line of defense against bacterial colonization by forming a physical barrier between oral microorganisms and deeper periodontal tissues.

In addition to structural protection, the periodontium is equipped with multiple innate and adaptive immune defense mechanisms. Saliva, gingival crevicular fluid, antimicrobial peptides, and immune cells such as neutrophils, macrophages, and lymphocytes contribute to maintaining periodontal health by controlling microbial growth and preventing infection (56). Neutrophils, in particular, play a critical role in periodontal defense by migrating into the gingival sulcus and eliminating bacterial pathogens through phagocytosis and the release of antimicrobial enzymes. However, when the microbial burden becomes excessive or host immune responses become dysregulated, these protective mechanisms may fail, leading to persistent inflammation and periodontal tissue destruction (12).

Microbial Etiology of Periodontitis

The primary etiological factor in periodontal disease is the accumulation of dental plaque biofilm, which contains a complex community of microorganisms that colonize the tooth surface and subgingival environment. Periodontitis is associated with a shift from a symbiotic microbial community to a dysbiotic microbial ecosystem, characterized by the overgrowth of pathogenic bacteria (13).

Among the numerous bacterial species implicated in periodontal disease, three microorganisms collectively known as the “red complex” pathogens play a particularly important role in disease progression. These include *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (13). *Porphyromonas gingivalis* is

Online ISSN

3007-3197

Print ISSN

3007-3189

<http://amresearchreview.com/index.php/Journal/about>

considered a keystone pathogen due to its ability to disrupt host immune responses and alter the composition of the oral microbiota, thereby promoting periodontal dysbiosis (57). This bacterium produces several virulence factors, including gingipains, lipopolysaccharides, and proteolytic enzymes, which contribute to tissue destruction and immune modulation.

Tannerella forsythia is another important periodontal pathogen that contributes to epithelial cell damage and inflammatory responses within periodontal tissues. It produces surface proteins and enzymes that facilitate bacterial adhesion and invasion into host tissues (58). *Treponema denticola*, a highly motile spirochete bacterium, plays a significant role in periodontal disease through its ability to penetrate periodontal tissues and interact synergistically with other periodontal pathogens. The cooperative interactions among these microorganisms enhance their pathogenic potential and accelerate disease progression (13).

Host Immune Response

Although bacterial infection initiates periodontal disease, the host immune response plays a central role in determining disease severity and tissue destruction. The immune response to periodontal pathogens involves both innate and adaptive immune mechanisms that attempt to eliminate microbial infection while maintaining tissue homeostasis (56). Innate immune responses are triggered when periodontal pathogens activate pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), present on immune and epithelial cells. Activation of these receptors leads to the release of inflammatory mediators and recruitment of immune cells to the site of infection (59). Adaptive immune responses are mediated by lymphocytes, including T cells and B cells, which contribute to antigen-specific immune responses. These immune cells produce cytokines and antibodies that help control bacterial infection. However, excessive or prolonged immune activation can result in chronic inflammation and contribute to periodontal tissue destruction (14).

Inflammatory Mediators

The progression of periodontal disease is largely driven by the production of pro-inflammatory mediators that regulate immune responses and tissue remodeling. Periodontal pathogens stimulate host cells such as macrophages, fibroblasts, and epithelial cells to produce a variety of inflammatory cytokines and mediators (14). Among the most important cytokines involved in periodontal inflammation are interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6). These cytokines promote inflammatory cell recruitment, stimulate osteoclast activity, and enhance the production of tissue-degrading enzymes (60). Elevated levels of these cytokines have been consistently observed in periodontal tissues and gingival crevicular fluid of individuals with periodontitis.

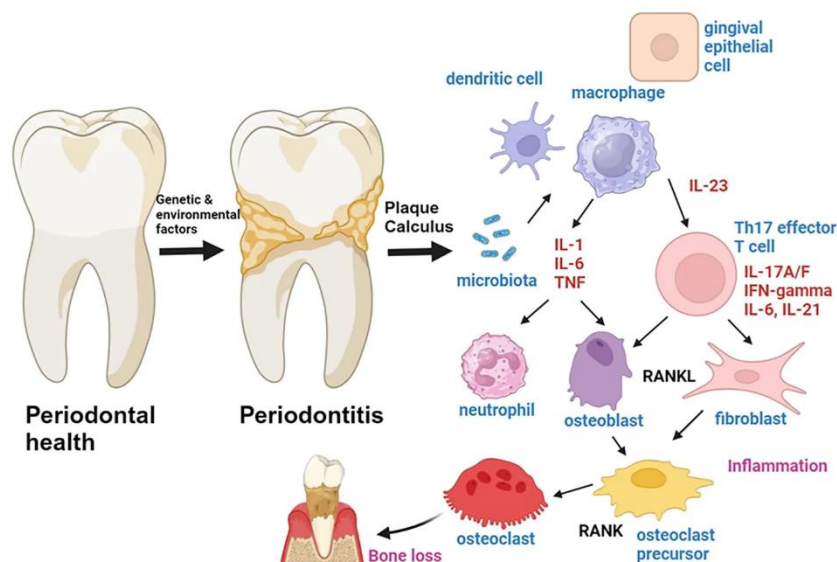


Figure 2. The role of cytokines in the pathogenesis of periodontitis is a topic of significant interest in the field of periodontal research

Another important mediator is prostaglandin E2 (PGE2), which is produced by inflammatory cells in response to bacterial infection. PGE2 plays a critical role in bone metabolism by stimulating osteoclast differentiation and promoting alveolar bone resorption (14). Increased levels of PGE2 have been associated with disease severity and periodontal tissue destruction.

Tissue Destruction Mechanisms

The hallmark of periodontitis is the progressive destruction of connective tissue attachment and alveolar bone surrounding the teeth. This tissue damage results from the combined effects of bacterial virulence factors and host-mediated inflammatory responses (15). One of the primary mechanisms responsible for connective tissue degradation is the activation of matrix metalloproteinases (MMPs), a group of enzymes capable of degrading extracellular matrix components such as collagen and elastin. These enzymes are produced by fibroblasts, neutrophils, and macrophages in response to inflammatory stimuli (15).

In addition to connective tissue breakdown, alveolar bone loss occurs through the activation of osteoclasts mediated by the RANK/RANKL/OPG signaling pathway, which regulates bone metabolism. Inflammatory cytokines such as IL-1 β and TNF- α stimulate the expression of receptor activator of nuclear factor- κ B ligand (RANKL), promoting osteoclast differentiation and bone resorption (60). The cumulative effects of connective tissue degradation, bone resorption, and chronic inflammation lead to the formation of periodontal pockets, clinical attachment loss, and eventual tooth loss, which are characteristic features of advanced periodontitis.

The Bidirectional Relationship Between Diabetes and Periodontal Disease

The relationship between diabetes mellitus and periodontal disease is widely recognized as bidirectional, meaning that each condition can influence the onset,

Online ISSN

3007-3197

Print ISSN

3007-3189

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progression, and severity of the other. Over the past two decades, substantial epidemiological, clinical, and mechanistic evidence has demonstrated that diabetes increases susceptibility to periodontal disease, while periodontal inflammation may adversely affect glycemic control (25,54). This reciprocal interaction is largely mediated through chronic inflammation, immune dysregulation, oxidative stress, and metabolic disturbances associated with hyperglycemia.

Patients with poorly controlled diabetes often exhibit increased prevalence and severity of periodontal disease compared to non-diabetic individuals. Conversely, severe periodontal inflammation may contribute to systemic inflammatory burden and insulin resistance, thereby complicating glycemic management in diabetic patients (61). These interactions highlight the importance of considering periodontal health as an integral component of diabetes care.

Diabetes as a Risk Factor for Periodontitis

Diabetes mellitus is considered one of the most significant systemic risk factors for periodontal disease. Numerous epidemiological studies have demonstrated that individuals with diabetes are more likely to develop severe periodontitis, increased clinical attachment loss, and alveolar bone destruction compared with non-diabetic individuals (25,62). The risk is particularly elevated in patients with poor glycemic control, as reflected by increased glycated hemoglobin (HbA1c) levels.

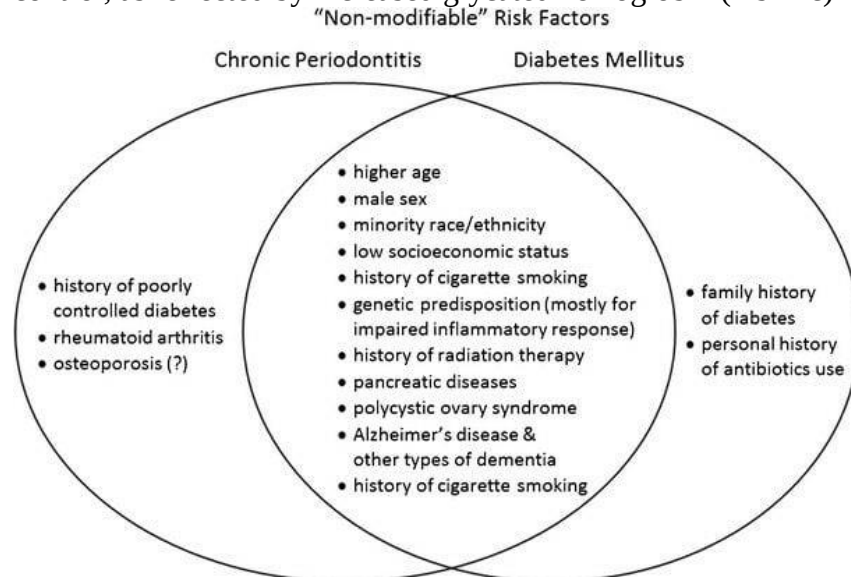


Figure 3. Non-modifiable risk factors for chronic periodontitis and diabetes mellitus are largely identical

Several biological mechanisms explain the increased susceptibility to periodontal disease among diabetic patients. Chronic hyperglycemia leads to impaired neutrophil function, altered collagen metabolism, reduced tissue repair capacity, and increased inflammatory responses, all of which contribute to periodontal tissue damage (54). Additionally, diabetes is associated with microvascular alterations that reduce blood supply to periodontal tissues, impairing nutrient delivery and immune defense mechanisms.

Online ISSN

3007-3197

Print ISSN

3007-3189

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The accumulation of advanced glycation end products (AGEs) in periodontal tissues further exacerbates inflammation and connective tissue degradation. These molecular changes create a hyperinflammatory environment that accelerates periodontal breakdown in diabetic individuals (63). As a result, periodontal disease is frequently more severe and progresses more rapidly in patients with uncontrolled diabetes.

Periodontal Disease Affecting Glycemic Control

In addition to diabetes increasing the risk of periodontal disease, growing evidence indicates that periodontal infection can also influence glycemic control in diabetic patients. Periodontal disease is characterized by chronic infection and inflammation of the periodontal tissues, which can contribute to systemic inflammatory responses. Periodontal pathogens and their endotoxins can enter the systemic circulation through ulcerated periodontal pockets, leading to increased levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 in the bloodstream (60). These inflammatory mediators interfere with insulin signaling pathways and contribute to insulin resistance, a key factor in the pathogenesis of type 2 diabetes (51).

Clinical studies have shown that individuals with severe periodontitis often exhibit higher HbA1c levels and poorer glycemic control compared to diabetic patients with healthy periodontal tissues (61). Furthermore, several interventional studies have demonstrated that periodontal therapy, including scaling and root planing, may lead to modest improvements in glycemic control, suggesting a direct relationship between periodontal inflammation and metabolic regulation (62). These findings support the concept that periodontal disease may act as a chronic inflammatory burden that exacerbates metabolic dysregulation in diabetes.

Role of Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are formed through non-enzymatic reactions between glucose and proteins, lipids, or nucleic acids during prolonged hyperglycemia. The accumulation of AGEs in tissues is a hallmark of diabetes and contributes significantly to the development of diabetic complications (43). In periodontal tissues, AGEs accumulate in collagen fibers and other extracellular matrix components, altering their structure and function. This process leads to reduced collagen turnover, impaired tissue repair, and increased susceptibility to periodontal destruction (63). Furthermore, AGEs can stimulate inflammatory responses by activating immune cells and promoting the release of cytokines and reactive oxygen species.

The presence of AGEs in periodontal tissues has also been associated with enhanced osteoclast activity and increased alveolar bone resorption, further contributing to periodontal tissue breakdown. These mechanisms explain why patients with poorly controlled diabetes often experience more severe periodontal disease progression.

RAGE Pathway Activation

The biological effects of AGEs are largely mediated through their interaction with specific cell surface receptors known as receptors for advanced glycation end products (RAGE). RAGE is expressed on various cell types, including endothelial cells, macrophages, fibroblasts, and epithelial cells within periodontal tissues (63).

Online ISSN

3007-3197

Print ISSN

3007-3189

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When AGEs bind to RAGE, they trigger intracellular signaling pathways that activate nuclear factor-kappa B (NF- κ B) and other transcription factors involved in inflammation. This activation leads to increased production of pro-inflammatory cytokines, adhesion molecules, and oxidative stress mediators (64). The AGE–RAGE interaction amplifies inflammatory responses and contributes to chronic tissue damage, impaired wound healing, and enhanced bone resorption in periodontal tissues. In diabetic patients, elevated levels of AGEs and increased RAGE expression create a persistent inflammatory environment that accelerates periodontal destruction.

These molecular mechanisms provide strong evidence supporting the bidirectional relationship between diabetes and periodontal disease, where metabolic dysregulation and chronic inflammation reinforce each other, leading to worsening outcomes for both conditions.

Impact of Periodontal Disease on Glycemic Control

Increasing clinical and epidemiological evidence suggests that periodontal disease can significantly influence glycemic control in individuals with diabetes mellitus. Periodontitis is a chronic inflammatory condition characterized by persistent bacterial infection and host-mediated inflammatory responses, which may contribute to systemic inflammation and metabolic dysregulation. The chronic inflammatory burden associated with periodontal infection has been shown to interfere with insulin signaling pathways and promote insulin resistance, thereby worsening glycemic control (60,61). The periodontal pocket epithelium in patients with periodontitis often becomes ulcerated, providing a pathway through which periodontal pathogens, endotoxins, and inflammatory mediators can enter the systemic circulation. This process can lead to elevated systemic levels of inflammatory cytokines, which are known to impair glucose metabolism and insulin sensitivity (51). Consequently, individuals with severe periodontal disease may experience greater difficulty maintaining optimal glycemic control compared to those with healthy periodontal tissues.

Evidence from Observational Studies

A growing number of observational studies have investigated the association between periodontal disease and glycemic control in diabetic populations. Cross-sectional and cohort studies conducted in different populations consistently demonstrate that individuals with diabetes who also suffer from periodontitis tend to exhibit higher levels of glycated hemoglobin (HbA1c) and poorer metabolic control (61,62).

Several recent epidemiological investigations have reported that the severity of periodontal disease correlates positively with glycemic status. Patients with advanced periodontitis often show significantly elevated HbA1c levels compared to diabetic patients without periodontal inflammation. These findings suggest that periodontal infection may act as a contributing factor to metabolic dysregulation in diabetic individuals (62). Furthermore, longitudinal cohort studies have indicated that individuals with severe periodontal disease may have an increased risk of developing worsening glycemic control over time. This relationship highlights the potential role of periodontal inflammation as a modifiable risk factor that may influence diabetes progression and management.

Online ISSN

3007-3197

Print ISSN

3007-3189

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Association with HbA1c Levels

Glycated hemoglobin (HbA1c) is widely recognized as the most reliable biomarker for assessing long-term glycemic control in patients with diabetes. Elevated HbA1c levels indicate prolonged exposure to hyperglycemia and are associated with an increased risk of diabetes-related complications (7). Multiple studies have demonstrated a significant association between periodontal disease severity and HbA1c levels. Patients with moderate to severe periodontitis frequently exhibit higher HbA1c values compared with individuals who maintain good periodontal health (61). This relationship is thought to be mediated by systemic inflammatory responses triggered by periodontal infection. Inflammatory cytokines produced in periodontal tissues can enter systemic circulation and interfere with insulin receptor signaling pathways, thereby reducing insulin sensitivity and contributing to hyperglycemia (51). As a result, persistent periodontal inflammation may lead to sustained elevations in HbA1c levels, complicating diabetes management.

Impact on Insulin Resistance

Insulin resistance is a central feature of type 2 diabetes and plays a crucial role in the development of chronic hyperglycemia. Increasing evidence suggests that periodontal disease may contribute to insulin resistance through inflammatory and metabolic pathways. Chronic periodontal infection stimulates the production of inflammatory mediators such as TNF- α , IL-6, and CRP, which are known to interfere with insulin signaling pathways (52). These cytokines inhibit insulin receptor activity and disrupt glucose transport mechanisms in peripheral tissues, ultimately leading to reduced glucose uptake by muscle and adipose cells.

Additionally, systemic dissemination of bacterial components such as lipopolysaccharides (LPS) from periodontal pathogens can activate immune responses that further exacerbate metabolic inflammation (60). This inflammatory state promotes insulin resistance and contributes to poor glycemic regulation in diabetic patients.

Effects on Diabetic Complications

Beyond influencing glycemic control, periodontal disease may also contribute to the development and progression of diabetes-related complications. Chronic inflammation associated with periodontal infection can exacerbate vascular dysfunction and promote oxidative stress, both of which are key mechanisms involved in diabetic complications (50). Several clinical studies have suggested that diabetic individuals with severe periodontitis may have a higher risk of developing complications such as cardiovascular disease, diabetic nephropathy, and retinopathy. The systemic inflammatory burden generated by periodontal infection may accelerate vascular damage and worsen metabolic control, thereby increasing the likelihood of complications (61).

Moreover, persistent periodontal inflammation may impair wound healing and immune responses, further complicating the management of diabetic patients. These findings underscore the importance of maintaining good periodontal health as part of a comprehensive strategy for diabetes management.

Online ISSN

3007-3197

Print ISSN

3007-3189

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Impact of Periodontal Therapy on Glycemic Control

Periodontal therapy aims to reduce microbial burden, control inflammation, and restore periodontal health. In recent years, research has increasingly focused on evaluating whether treating periodontal disease can improve glycemic control in patients with diabetes mellitus. Evidence suggests that effective periodontal therapy may reduce systemic inflammatory mediators and improve insulin sensitivity, thereby contributing to better metabolic regulation (62,64).

Non-Surgical Periodontal Treatment

Non-surgical periodontal therapy, particularly scaling and root planing (SRP), is the first-line treatment for periodontitis. SRP involves the mechanical removal of subgingival plaque and calculus, which reduces bacterial load and diminishes periodontal inflammation (14). Several clinical studies have demonstrated that SRP leads to significant reductions in periodontal pocket depth, bleeding on probing, and clinical attachment loss, resulting in improved periodontal health (62,65). For patients with diabetes, SRP not only addresses local periodontal inflammation but also appears to have systemic benefits. Reductions in circulating inflammatory cytokines following SRP may improve insulin signaling and glycemic control, highlighting the potential systemic impact of local periodontal therapy (51,61).

Effect on HbA1c Reduction

Multiple interventional studies and meta-analyses have assessed the impact of periodontal therapy on glycated hemoglobin (HbA1c) levels in diabetic patients. Evidence indicates that non-surgical periodontal therapy can lead to modest but clinically significant reductions in HbA1c, typically ranging from 0.3% to 0.5% over a 3–6 month follow-up period (62,66). For instance, a systematic review of randomized controlled trials reported that patients receiving SRP demonstrated a mean HbA1c reduction of approximately 0.36% compared to controls, indicating improved glycemic control following periodontal intervention (66). While the magnitude of HbA1c reduction may appear modest, it is comparable to the effect of some oral anti-diabetic medications and can meaningfully reduce the risk of diabetes-related complications (7).

Table 2: Clinical Evidence of Periodontal Therapy on Glycemic Control

Study	Study Design	Population	Intervention	Follow-up	HbA1c Change	Key Findings	Reference
D'Aiuto et al., 2020	RCT	264 type 2 DM patients	SRP ± systemic antibiotics	6 months	↓0.36%	Significant HbA1c reduction and improved periodontal parameter	66

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Engebretson et al., 2021	Multicenter RCT	200 type 2 DM	Intensive SRP	6 months	↓0.40 %	Reduction in systemic inflammation and HbA1c	69
Teeuw et al., 2020	Systematic Review & Meta-analysis	10 RCTs	Non-surgical therapy	3–6 months	↓0.3–0.5%	Modest but clinically relevant HbA1c improvement	62
Preshaw et al., 2020	Cohort	150 type 2 DM	SRP + host modulation	6 months	↓0.35 %	Combination therapy further improved periodontal outcomes	68

Adjunctive Therapies

In addition to mechanical debridement, adjunctive therapies such as local or systemic antibiotics, host-modulation therapy, and antiseptic rinses may be employed to enhance periodontal treatment outcomes. Systemic antibiotics, such as amoxicillin or metronidazole, may reduce bacterial load in patients with severe periodontitis or refractory disease (67). Host-modulation therapy, including the use of sub-antimicrobial dose doxycycline, targets inflammatory pathways and inhibits matrix metalloproteinases, thereby reducing tissue destruction (15,68). Several studies have reported that the combination of SRP with adjunctive therapies can further improve periodontal outcomes and may enhance glycemic control, although the additional effect on HbA1c is often small compared to SRP alone (62,67).

Evidence from Clinical Trials

Randomized controlled trials (RCTs) and prospective cohort studies provide the strongest evidence supporting the systemic benefits of periodontal therapy in diabetic patients. Most RCTs demonstrate that SRP, with or without adjunctive therapy, results in improvements in both periodontal parameters and glycemic control (62,66). For example, a 2021 multicenter RCT evaluated type 2 diabetic patients with moderate to severe periodontitis and reported that intensive periodontal therapy led to significant reductions in HbA1c (mean reduction 0.4%), along with improvements in probing depth and clinical attachment level over 6 months (69). These findings highlight the clinical relevance of integrating periodontal care into the comprehensive management

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of diabetes.

Mechanistically, the improvements in glycemic control following periodontal therapy are thought to be mediated by reductions in systemic inflammatory markers, including TNF- α , IL-6, and CRP, as well as decreased oxidative stress (51,60). This underscores the systemic impact of oral health interventions and reinforces the importance of oral-systemic health connections.

Molecular and Immunological Mechanisms Linking Periodontitis and Diabetes

The bidirectional relationship between diabetes mellitus and periodontitis is underpinned by complex molecular and immunological mechanisms. Both conditions are characterized by chronic inflammation, dysregulated immune responses, and oxidative stress, which together contribute to tissue damage and impaired metabolic control (51,54,60). Understanding these mechanisms is crucial to explain how periodontal therapy can impact glycemic outcomes and why diabetes predisposes patients to severe periodontal disease.

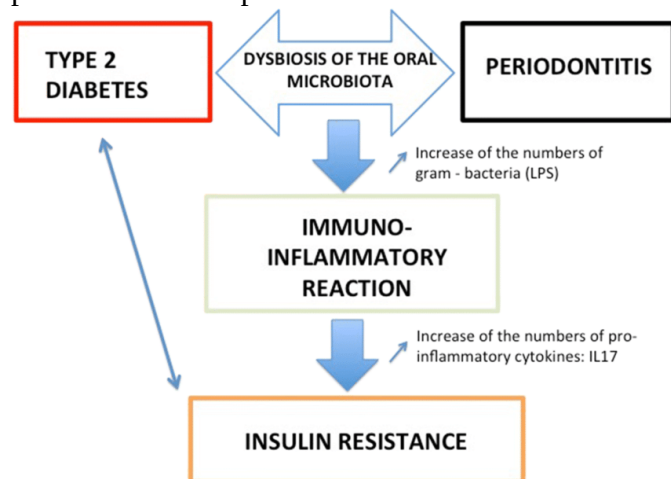


Figure 4. Bidirectional link explanation between Diabetes and Periodontitis

Cytokine Networks

Pro-inflammatory cytokines play a central role in linking periodontal disease and diabetes. Periodontal pathogens stimulate the host immune system to release cytokines such as interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6), which not only mediate local tissue destruction but also enter systemic circulation, contributing to chronic low-grade inflammation (60,62). In patients with diabetes, elevated systemic levels of these cytokines exacerbate insulin resistance by interfering with insulin receptor signaling pathways in skeletal muscle, liver, and adipose tissue (51). TNF- α , for instance, inhibits insulin receptor substrate (IRS) activity, reducing glucose uptake and promoting hyperglycemia (52). IL-6 and IL-1 β further enhance hepatic gluconeogenesis and impair pancreatic β -cell function, creating a vicious cycle where systemic inflammation worsens both periodontal disease and glycemic control.

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Table 3: Major Pathogens, Inflammatory Mediators, and Mechanisms in Periodontitis

Category	Key Factors	Function/Impact	Relevance to Diabetes	Reference
Microbial Pathogens	<i>Porphyromonas gingivalis</i> , <i>Tannerella forsythia</i> , <i>Treponema denticola</i>	Dysbiosis, tissue invasion	Trigger systemic inflammation, insulin resistance	13,57
Cytokines	IL-1 β , TNF- α	IL-6, Mediates local and systemic inflammation	Impairs insulin signaling, increases HbA1c	51,60
Prostaglandins	PGE2	Bone resorption, vasodilation	Contributes to tissue destruction	60
Matrix Metalloproteinases	MMP-8, MMP-9	Collagen degradation, tissue destruction	Exacerbates periodontal damage	15,72
AGE-RAGE	Advanced glycation end products, RAGE receptor	Chronic inflammation, oxidative stress	Accelerates tissue breakdown and insulin resistance	63,64

Oxidative Stress Pathways

Oxidative stress is another key mediator in the interplay between diabetes and periodontitis. Hyperglycemia increases the production of reactive oxygen species (ROS), which damage cellular components, activate inflammatory signaling, and exacerbate periodontal tissue destruction (43,51). In periodontal tissues, ROS contribute to collagen degradation, activation of matrix metalloproteinases (MMPs), and alveolar bone resorption (15,60). Systemically, oxidative stress impairs endothelial function, promotes atherogenesis, and aggravates insulin resistance, further linking periodontal infection to diabetic complications (50). Importantly, periodontal therapy has been shown to reduce oxidative stress markers, suggesting a mechanistic basis for its beneficial effects on glycemic control (66).

Dysbiosis of Oral Microbiota

Periodontitis is characterized by a shift from a symbiotic oral microbiome to a dysbiotic community, dominated by pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (13,57). Dysbiosis not only drives local periodontal

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3007-3197

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3007-3189

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inflammation but also contributes to systemic immune activation. *P. gingivalis*, in particular, produces virulence factors that modulate host immune responses, inhibit neutrophil function, and disrupt T cell activity, facilitating chronic inflammation (57). In diabetic patients, hyperglycemia exacerbates microbial dysbiosis by altering the subgingival environment, creating favorable conditions for pathogenic overgrowth and further enhancing inflammatory burden (54,61).

Systemic Inflammatory Spillover

The ulcerated epithelium of periodontal pockets allows periodontal pathogens and inflammatory mediators to enter systemic circulation, resulting in systemic inflammatory spillover (60,62). This phenomenon increases circulating levels of TNF- α , IL-6, IL-1 β , and CRP, all of which can impair insulin signaling, promote endothelial dysfunction, and exacerbate metabolic dysregulation (51,52). Systemic inflammation originating from periodontal tissues has been shown to contribute to insulin resistance, elevated HbA1c, and increased risk of diabetic complications, providing a molecular explanation for the clinical observations described in Section 5.

Endothelial Dysfunction

Endothelial dysfunction is a critical link between periodontal disease and diabetes-related vascular complications. Chronic systemic inflammation, oxidative stress, and AGE-RAGE signaling in diabetic patients reduce nitric oxide bioavailability and impair vascular homeostasis (44,50,63). Periodontal infection further amplifies endothelial activation, increasing the expression of adhesion molecules and pro-thrombotic factors, which can accelerate atherosclerosis (50). These vascular changes not only increase cardiovascular risk but may also exacerbate tissue perfusion deficits in periodontal tissues, creating a feed-forward loop of inflammation, vascular damage, and metabolic dysregulation (54).

Recent Advances in Diagnostic Biomarkers

The identification of reliable diagnostic and prognostic biomarkers for periodontal disease and diabetes has gained significant attention in recent years. Biomarkers can provide early detection of disease, assess severity, monitor treatment response, and elucidate the molecular links between systemic and oral health. Advances in molecular biology and proteomics have enabled the analysis of biomarkers in saliva, gingival crevicular fluid (GCF), and blood, offering non-invasive or minimally invasive diagnostic options (54,60).

Salivary Biomarkers

Saliva is an easily accessible biological fluid that reflects both local periodontal inflammation and systemic metabolic changes. Recent studies have demonstrated that salivary concentrations of pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β correlate with periodontal disease severity and glycemic status in diabetic patients (70,71). Additionally, matrix metalloproteinase-8 (MMP-8), a collagen-degrading enzyme produced by neutrophils and periodontal tissues, has emerged as a reliable marker of periodontal tissue destruction. Elevated salivary MMP-8 levels have been

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3007-3197

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3007-3189

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observed in patients with uncontrolled diabetes, highlighting its potential as a predictive marker for diabetes-related periodontal progression (72).

Other salivary biomarkers, including C-reactive protein (CRP) and oxidative stress markers, have also been shown to reflect systemic inflammation and correlate with HbA1c levels, providing a link between oral and systemic pathology (51,66).

Gingival Crevicular Fluid Biomarkers

Gingival crevicular fluid, a serum transudate or inflammatory exudate found in the sulcus around teeth, is a rich source of molecular biomarkers for periodontal disease. GCF analysis allows direct assessment of the local inflammatory environment and tissue degradation processes (60). Recent studies have reported elevated levels of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), prostaglandin E2 (PGE2), and MMPs in the GCF of diabetic patients with periodontitis (60,73). Importantly, the concentration of these biomarkers correlates with periodontal pocket depth, clinical attachment loss, and HbA1c, indicating their potential for diagnosis, prognosis, and monitoring treatment response (61).

The combination of GCF biomarkers with clinical periodontal indices enhances the predictive accuracy for disease progression, particularly in patients with diabetes who are at higher risk for severe periodontal destruction.

Microbiome-Based Diagnostics

Advances in high-throughput sequencing and metagenomic analysis have enabled detailed characterization of the subgingival microbiome in health and disease. Periodontitis is associated with microbial dysbiosis, characterized by an overrepresentation of pathogenic species such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (13,57).

Recent studies have utilized 16S rRNA sequencing and shotgun metagenomics to identify microbial signatures associated with both periodontal disease severity and poor glycemic control in diabetic patients (74,75). These microbiome-based diagnostics hold promise for early detection, risk stratification, and personalized treatment strategies, as they can identify shifts in microbial composition before clinical disease becomes evident. Furthermore, combining microbial analysis with inflammatory biomarkers from saliva or GCF may provide a comprehensive multi-parameter diagnostic approach, improving predictive accuracy for both periodontal disease progression and diabetes-related complications (70,74).

Therapeutic Implications and Future Directions

The bidirectional relationship between diabetes mellitus and periodontal disease has significant therapeutic implications. Recognizing periodontal disease as a modifiable risk factor in diabetes management emphasizes the need for integrated, interdisciplinary care. Advances in both clinical and molecular research provide opportunities to improve patient outcomes through targeted periodontal therapy, anti-inflammatory interventions, and lifestyle modifications (62,64).

Integration of Periodontal Care into Diabetes Management

Multiple clinical studies support the inclusion of periodontal screening and treatment

as a component of comprehensive diabetes management. Early detection and management of periodontal inflammation can reduce systemic inflammatory burden, improve insulin sensitivity, and contribute to better glycemic control (61,66). Interdisciplinary collaboration between dentists, endocrinologists, and primary care physicians is essential to ensure timely periodontal evaluation and intervention. Guidelines from professional organizations now recommend routine periodontal assessment in diabetic patients, with periodontal therapy incorporated as part of metabolic management strategies (62). Additionally, patient education regarding oral hygiene, regular dental visits, and self-care practices is critical for preventing periodontal disease progression and maintaining glycemic stability.

Adjunctive Anti-Inflammatory or Host-Modulatory Therapies

In addition to conventional mechanical periodontal therapy, adjunctive therapies targeting inflammation and tissue destruction are increasingly being investigated. Host-modulatory agents, such as sub-antimicrobial dose doxycycline, inhibit matrix metalloproteinase activity and reduce collagen breakdown, thereby improving periodontal outcomes in diabetic patients (15,68). Other emerging interventions include systemic anti-inflammatory agents, antioxidants, and biologics targeting cytokines such as TNF- α or IL-6. These therapies aim to modulate systemic and local inflammatory responses, potentially improving both periodontal health and glycemic control (51,60). Recent studies have also explored the potential of novel drug delivery systems, including nanoparticles and localized gels, to deliver anti-inflammatory or antimicrobial agents directly into periodontal pockets, enhancing efficacy while minimizing systemic exposure (75).

Lifestyle and Metabolic Interventions

Lifestyle modifications play a complementary role in managing the diabetes-periodontitis interface. Optimizing diet, increasing physical activity, and controlling obesity can improve insulin sensitivity, reduce systemic inflammation, and support periodontal healing (52,64). Nutritional interventions targeting anti-inflammatory and antioxidant pathways, such as increased intake of omega-3 fatty acids, polyphenols, and vitamins, may also support periodontal therapy and reduce systemic metabolic burden (70,74). Moreover, smoking cessation is critical, as tobacco use is a well-established risk factor for both periodontitis and poor glycemic control, and it negatively affects wound healing and therapeutic outcomes (21).

Future Research Directions

Despite substantial progress, several gaps remain in understanding and managing the diabetes-periodontitis relationship. Future research should focus on:

Longitudinal and large-scale clinical trials to determine the magnitude and duration of glycemic improvements following periodontal therapy (66,69).

Precision medicine approaches, including patient-specific microbial profiling and biomarker analysis, to develop personalized treatment strategies (74,75).

Mechanistic studies investigating molecular crosstalk between periodontal inflammation, systemic cytokine networks, and insulin resistance (51,63).

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3007-3197

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3007-3189

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Evaluation of novel host-modulatory and anti-inflammatory therapies in diabetic populations with periodontitis, particularly using minimally invasive delivery systems (68,75).

Integration of digital health technologies for remote monitoring of periodontal status and metabolic parameters, facilitating early intervention and patient adherence.

By addressing these research priorities, clinicians and researchers can develop targeted, evidence-based interventions that improve both oral and systemic health outcomes, ultimately reducing the burden of diabetes-related complications and severe periodontal disease.

Limitations of Current Evidence

Despite substantial advances in understanding the relationship between diabetes mellitus and periodontal disease, several limitations in the current evidence should be acknowledged. Most studies examining this bidirectional association exhibit considerable heterogeneity in study design, population characteristics, and diagnostic criteria for periodontal disease, which makes cross-study comparisons challenging (61,62). Many clinical trials have short follow-up periods, typically ranging from 3–6 months, limiting the assessment of the long-term impact of periodontal therapy on glycemic control and diabetes-related complications (66,69). Additionally, variations in the definition and classification of periodontitis, as well as differences in methods used to evaluate periodontal outcomes, further restrict the generalizability of findings and complicate the development of standardized treatment guidelines (18,62). These limitations highlight the need for well-designed, longitudinal, and multicenter studies with standardized periodontal assessments to more accurately determine the relationship between diabetes and periodontal disease and the effects of therapeutic interventions.

Conclusion

The evidence consistently supports a bidirectional relationship between diabetes and periodontitis. Diabetes increases susceptibility to severe periodontal disease through mechanisms such as hyperglycemia-induced immune dysfunction, chronic inflammation, and AGE–RAGE signaling (54,63). Conversely, periodontal inflammation contributes to systemic inflammatory burden, insulin resistance, and impaired glycemic control (51,61). Clinical studies demonstrate that periodontal therapy, particularly non-surgical interventions such as scaling and root planing, can improve both periodontal outcomes and glycemic parameters, including modest reductions in HbA1c (62,66,69). Adjunctive anti-inflammatory or host-modulatory therapies, combined with lifestyle and metabolic interventions, may further enhance these benefits (51,68,70). These findings underscore the importance of integrating periodontal care into comprehensive diabetes management, promoting interdisciplinary collaboration between dental and medical professionals. Future research should focus on standardized diagnostics, long-term controlled trials, and personalized treatment approaches to optimize outcomes. Addressing periodontal disease as part of diabetes care not only improves oral health but also contributes to better metabolic control and potentially reduced risk of diabetes-related complications, highlighting the need for

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integrated healthcare strategies in clinical practice.

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