Archives of Dental and Medical Sciences
Year 2025; Issue 1

ADMS
ARCHIVES OF DENTAL & MEDICAL SCIENCES

Journal homepage-
adms.manipal.edu.m

Pathogenic Interplay Between Diabetes Mellitus and Periodontal Disease

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Article information
DOI: 10.71354/m3he2b44
Received 30 August 2025; Accepted 24 September 2025

Abstract

Diabetes mellitus and periodontal disease are both chronic inflammatory conditions that are intertwined with a bidirectional, well-observed association. More evidence is emerging by which metabolic dysregulation in diabetes exacerbates periodontal tissue homeostasis, and that periodontal inflammation will also worsen systemic glycaemic control. Clarification of the molecular and immunological processes underlying this relationship is needed to offer improved medical and dental management. This review addresses the epidemiological and mechanistic relationships between periodontal disease and diabetes, with a focus on immune dysregulation, action of pro-inflammatory cytokines, development and influence of advanced glycation end-products (AGEs) and their receptors (RAGEs). It also identifies the clinical implications of concurrent patient management. A detailed literature review was performed using the assistance of MEDLINE and PubMed databases to scan for appropriate studies between 1990 and 2025. Experimental and clinical data were both evaluated to identify the manner in which immune dysfunction resulting from hyperglycaemia contributes to periodontal tissue breakdown. Epidemiological data have substantiated enhanced risk and severity of periodontitis in diabetes in a number of populations. Hyperglycaemia impairs the function of neutrophils and macrophages, enabling poor bacterial clearance and increased production of inflammatory cytokines, specifically TNF-α, IL-1β, and IL-6. Concurrently, AGEs develop in diabetic tissues and trigger RAGE on numerous cell types and promote oxidative stress and inflammation through NF-κB and JAK/STAT signaling. These alterations facilitate periodontal deterioration and further jeopardize glycaemic control. A two-way interaction between periodontal disease and diabetes is supported by shared pathogenic processes including dysregulation of the immune system and chronic inflammation.

Keywords: *diabetes mellitus, periodontal disease, immune dysregulation, AGE product, proinflammatory cytokines*

Introduction

Diabetes mellitus (DM) is a group of metabolic abnormalities characterized by the presence of persistent hyperglycaemia resulting from a defect in insulin secretion, insulin action, or both.[1] Persistent hyperglycaemia results in the occurrence of diabetic complications and induces progressive damage, dysfunction, and failure of multiple

organs and systems with extensive impact on overall well-being and quality of life.[2] Early clinical manifestations are usually polyuria, polydipsia, blurred vision, and accidental weight loss.[3] Diabetes diagnosis can be established by a variety of tests, including fasting blood glucose, post prandial blood glucose and glycated haemoglobin tests.[4] Type 2 diabetes mellitus (T2DM), one of its numerous systemic complications, has been revealed to have a harmful effect on the metabolism of bones and oral health.

Chronic hyperglycaemia inhibits osteogenesis, leading to reduced bone mineral density and osteoporotic fractures, particularly in those with poorly controlled glycaemic levels.[5] It has been demonstrated that patients who have an HbA1c level greater than 9.0% are at significantly higher risk of fracture of the hip, and it underscores the adverse impact of metabolic disturbance on bone.[6] This impaired bone remodeling has a direct impact on periodontal status as well. Alveolar bone supporting the teeth is particularly vulnerable to the effects of diabetes-mediated changes in bone turnover. Impaired osteoblast function, increased osteoclast function, and prolonged inflammation in the T2DM increase alveolar bone resorption, a hallmark of periodontitis.[7] The consequence is that diabetic patients especially those with unstable glycaemic control are most vulnerable to excessive periodontal loss, e.g., clinical attachment loss and increased tooth mobility.[8] This highlights the critical crosslinks between oral illness and systemic bone health in T2DM and highlights coordinated medical and dental management. Other important complications include dehydration, hyperosmolar hyperglycaemic coma, impaired healing of wounds, and vascular complications such as myocardial infarction, stroke, limb ischemia, and renal failure.

Diabetes can also lead to retinopathy with blindness,[9-11] peripheral neuropathy, impairment of neurocognition,[2] and infection of the feet that may require amputation.[12] Diabetes is a well-seated risk factor for periodontal disease, with diabetic individuals having higher prevalence, severity, and distribution of gingivitis and periodontitis compared with non-diabetic individuals.[13] This association is bolstered by several shared pathogenic pathways, including systemic inflammation, immune dysfunction, and microvascular alterations. Interestingly, recent findings have also proven a bidirectional relationship between periodontal disease and diabetes, periodontitis can impair glycaemic control in diabetic patients, while poorly controlled diabetes accelerates periodontal disease. Diabetes and periodontal diseases are categorized on multifactorial grounds such as age at diagnosis, pattern of presentation, progression of disease, and systemic or local factors modifying risk.

Periodontal diseases comprise entities such as gingivitis, reversible inflammation limited to the gingiva, and periodontitis, with destruction of more inwardly located tissues and alveolar bone loss.[14] The increasing evidence for periodontitis-diabetes interaction has important clinical implications, requiring integrated treatment strategies in order to maximize results in those affected. Thus, the current review shall attempt to explain the association between diabetes and periodontal disease by highlighting their epidemiological relationship, molecular and cellular mechanisms, and clinical importance, particularly in diabetic patients.

Methodology

A rigorous review of the literature was conducted in order to collate and critically evaluate available evidence for the bi-directional association of diabetes mellitus with periodontal disease. Electronic searches were performed via the PubMed and Web of Science (WoS) databases, from January 1990 through February 2025. Search strategy included utilization of combinations of Medical Subject Headings (MeSH) and free-text keywords like: "diabetes mellitus," "type 2 diabetes," "periodontal disease," "periodontitis," "immune dysregulation," "inflammation," "advanced glycation end-products (AGEs)," "RAGE," "cytokines," "macrophage polarization," "oxidative stress," and "neutrophil extracellular

traps (NETs)." Boolean operators (AND, OR) and truncations were used to maximize retrieval of pertinent studies.

Exclusion criteria were original research articles, clinical trials, systematic reviews, meta-analyses, and significant mechanistic experimental research in humans or relevant animal models specifically addressing the interaction between hyperglycaemia, immune impairment, and periodontal tissue disease. Data by which not in English, case reports, conference abstracts with poor data, and poorly methodologically specific studies were excluded. The reference lists of included papers were also searched to identify further relevant studies.

Data were extracted with a focus on experimental and clinical evidence, including: (i) diabetic cell immune dysfunction (e.g., neutrophil chemotaxis, phagocytosis, and NETosis), (ii) pro-inflammatory cytokine profiles of diabetic and non-diabetic periodontitis, (iii) molecular mechanisms that include RAGE and AGEs, and (iv) clinical outcomes that link periodontal treatment to glycaemic control. Special care was taken to identify areas of convergence between systemic hyperglycaemia and local periodontal inflammation, and pathways that may be regarded as therapeutic targets.

Epidemiological Correlation Between DM and Periodontal Disease

There are new studies that show a two-way interaction between disturbed glycaemic control and the onset of periodontal disease. Diabetes patients, particularly over the age of 30 years, have a higher likelihood of having severe symptoms of periodontitis than non-diabetic individuals. Out of 1331, 282 men (21.2%) had moderate periodontitis, and the remaining 271 men (20.4%) had severe periodontitis.[15] The interaction is of clinical significance because diabetes mellitus and periodontitis have been shown to influence each other in a two-way manner.

Periodontitis can negatively impact glycaemic control by enhancing systemic inflammation, whereas poorly controlled diabetes is responsible for causing periodontal tissue loss through dysfunction of the immune system and delayed healing. Periodontitis can raise HbA1c in non-diabetic individuals by about 0.16% compared to those without periodontitis.[16] Whereas in patients with type 2 diabetes, non-surgical periodontal treatment has been shown to reduce HbA1c by approximately 0.4 to 0.6%.[17] On the other hand, poorly controlled diabetes increases periodontal tissue destruction with 3-folds greater risk of periodontitis, by which diabetes impairs new bone formation, delays wound healing and causes greater attachment and bone loss.[18]

The World Health Organization (WHO) estimates that diabetes will be the seventh major cause of death in the world by 2030, primarily because it has a strong linkage to cardiovascular disease, stroke, and renal failure.[19] According to global epidemiological reports, an estimated 529 million people had diabetes in 2021 with an age-standardized prevalence of 6.1%.[20] Meanwhile, the total burden of severe periodontitis remains relatively high, and an estimated 71.48 million cases existed in 2017.[21] Among the Asian countries, China has experienced the most dramatic rise in incidence and prevalence of severe periodontitis, compared with Japan, South Korea, Thailand, and India.[22] In the Western Pacific region, Malaysia is one of the countries with the highest prevalence of diabetes, with estimates that more than 7 million adults will have diabetes by 2025.[23] Diabetic patients are far more prone to getting periodontitis, and the hyperglycaemic environment that is characteristic of diabetes results in an exaggerated inflammatory response in periodontal tissues. The environment suppresses tissue repair and leads to rapid disease progression, which makes joint management of both the disorders essential.

Interdependent Molecular Mechanisms Between DM and Periodontal Disease

As periodontitis progresses, the host immune system responds to the disease-causing bacteria through the induction of an inflammatory response locally. The immune-inflammatory interaction results in cementum loss, destruction of the

periodontal ligament (PDL), and resorption of alveolar bone.[24] In diabetic patients, this is further exacerbated by the generation of advanced glycation end products (AGEs) and their interaction with AGE receptors (RAGE), along with microbial flora modification, dysregulated cytokine expression, and dysfunctional immune cells. All of these contribute to increased inflammation, increased oxidative stress, and the generation of apoptotic signals, further speeding periodontal tissue destruction. It must be noted, however, that inflammation alone is not sufficient to induce periodontal bone loss, but certain destructive mechanisms and host susceptibility are required within the process of disease progression (Figure 1).

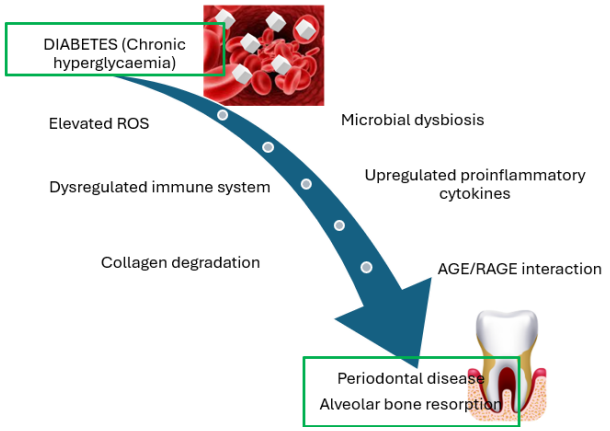

Figure 1: Pathogenesis of diabetes and periodontal disease

Immune system dysregulation

DM's hallmark, chronic hyperglycaemia, drastically compromises host immunoregulation and is the principal causative factor in periodontitis development. The interaction between chronic hyperglycaemia and inflammation in the periodontium highlights the multifactorial cause of the disease where microbial dysbiosis and immunodysfunction synergistically induce insidious tissue destruction.[25] One of the most significant immunological dysfunctions associated with diabetes is neutrophil dysfunction, which impairs critical processes such as recruitment, chemotaxis, and phagocytosis. These impairments compromise the host's ability to kill periodontal pathogens effectively, leading to microbial persistence and disruption of immune homeostasis in the periodontal environment.[26] Moreover, the diabetic environment enhances oxidative stress in periodontal tissues. Hyperactivity of neutrophils by hyperglycaemia results in excessive production of reactive oxygen species (ROS) leading directly to the destruction of surrounding cells and extracellular matrix components. Excessive ROS is further directly proportional to the severity of inflammation of periodontium and forms a cycle of oxidative damage and immunity activation leading to speeding up of periodontal tissue loss.[27]

The initial immunological defence of the host against subgingival bacterial biofilms is primarily mediated through the collaborative action of neutrophils, antibodies, and the complement system. Neutrophils are rapidly mobilized to the site of infection, where they engulf incoming pathogens, thereby limiting their apical and lateral migration within the periodontal pocket. Concurrently, complement cascade activation enhances opsonization and bacterial lysis, and preformed antibodies developed upon previous antigen exposure enhance specific microbial neutralization. Under ideal function, this innate immune response compartmentalizes inflammation to gingival tissues, most typically to reversible gingivitis.[28] In immune dysregulation conditions, however, such as in uncontrolled diabetes mellitus, this initial line of defense is defeated.

Hyperglycaemia undermines natural immune function, allowing periodontal pathogens to avoid destruction and gain entry to periodontal tissues at a deeper level. Recruitment and activation of the adaptive immune system, including macrophages, T cells, B cells, and a wide range of pro-inflammatory cytokines, ensue. Activated macrophages release cytokines such as interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNF-α), which sustain the continuation of local inflammation. T-helper cells coordinate the immune response, and B-cells secrete antigen-specific antibodies to enhance pathogen clearance.[29]

Macrophages, notably, are phenotypically plastic and polarize towards either classically activated (M1) or alternatively activated (M2) phenotypes, with each having particular functional roles. M1 macrophages are pro-inflammatory, inducing tissue damage by releasing cytokines like TNF-α and IL-1β, while M2 macrophages induce anti-inflammatory responses and tissue repair. In diabetes, chronic hyperglycaemia increases M1 polarization by activating signaling pathways such as NF-κB and STAT1.[30] This results in excessive production of inflammatory mediators leading to periodontal tissue injury. The hyperglycaemic state disrupts the polarization of M2 macrophages by disrupting signaling pathways important for anti-inflammatory reactions and regeneration processes. Thus, the homeostasis of the M1 and M2 macrophage populations is disrupted in the direction of inflammation, thereby inhibiting resolution and healing of periodontal tissues. The imbalance further sustains the chronic inflammatory state characteristic of diabetic periodontitis.[31]

Neutrophil dysfunction is a feature of the skewed immune response observed in diabetic periodontitis (DP) that is accountable for heightened susceptibility to pathogenic oral microbiota and prolonged chronic inflammation. Hyperglycaemia has a detrimental effect on various neutrophil functions, including phagocytosis, formation of neutrophil extracellular traps (NET) and regulation of apoptosis. Additionally, increased expression of cytokine signalling inhibitors like Src homology region 2 domain-containing phosphatase-1 (SHP-1) and suppressor of cytokine signaling (SOCS) proteins also dampen neutrophil and macrophage-mediated host response. These combined defects not only compromise microbial clearance but also perpetuate a pro-inflammatory state in the periodontium.[32] Studies have emphasized the role of NETs in the regulation of immune functions under a diabetic condition. NETs, composed of DNA, histones, and antimicrobial peptides, are typically released by activated neutrophils to entrap and disable pathogens. In a diabetic condition, however, excessive or unorganized NET release may be implicated in tissue damage and deregulation of the immune system. A key paper by Wen et al. investigated the influence of NETs on macrophage polarization during diabetic periodontitis. NETs were isolated from neutrophils cultured under high-glucose conditions in this research, and their function was explored with a diabetic mouse model of periodontitis. Periodontal tissue deposition of NETs was significantly promoted under hyperglycaemic conditions and was associated with increased secretion of pro-inflammatory cytokines by macrophages.[30]

Mechanistic insight through western blotting experiments revealed that NETs repressed expression of Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) both in vivo and in vitro. Repression of these effects led to suppressed anti-inflammatory macrophage polarization (M2 phenotype) and enhanced pro-inflammatory M1 polarization. These findings suggest that NETs are involved in the sustained inflammatory reaction of diabetic periodontitis by disrupting the JAK/STAT pathway, an important regulator of immune cell function and cytokine release.[33] Collectively, these results underscore the central role of NETs in bridging neutrophil impairment with macrophage-driven inflammation in diabetes-associated periodontal disease. Through promotion of an imbalanced immune response through inhibition of JAK/STAT signaling, NETs do not just increase local inflammation of tissue but also prevent resolution and repair. Aiming at the inhibition of NET formation or JAK/STAT reestablishment could then be a new immunomodulatory approach to treating diabetic periodontitis.

While these reactions aim at sequestering infection, repeated immune stimulation within the diabetic environment enhances periodontal loss. Chronic inflammation causes osteoclastogenesis leading to alveolar bone resorption, a characteristic feature of periodontitis. In addition, bacterial products such as lipopolysaccharide (LPS) from dental plaque cause systemic immune activation, raising circulating pro-inflammatory cytokines and

immune cell aggregation.[34] This also causes insulin resistance and exacerbated glycaemic control in diabetic patients. Collectively, these processes exemplify the central importance of immune dysregulation in the bidirectional interaction between diabetes and periodontitis. The hyperglycaemic environment not only prevents the resolution of inflammation but also permits the activation of destructive mechanisms speeding up periodontal degradation. A complete understanding of such immunopathological events is essential for the design of integrative therapeutic strategies for improving both metabolic and periodontal health outcomes.

Pro-inflammatory cytokines

In view of the intricate relationship between diabetes mellitus and periodontal disease, inflammatory mediators used are responsible for the progression of the disease and tissue loss. Hyperglycaemia in DM helps promote macrovascular and microvascular complications, and activated pathways can lead to increased inflammation, oxidative stress, and apoptosis. Periodontitis is a chronic inflammatory disease in which inflammation of the periodontal tissues is initiated by the continuous presence of subgingival biofilm. Uncontrolled host-mediated secretory tissue damage and inflammation are characteristic of the inflammatory response.[35] Among these, IL-1β, IL-6, and matrix metalloproteinase-8 (MMP-8) are particularly pertinent as they directly affect periodontal tissue homeostasis.

IL-1β is a potent pro-inflammatory cytokine that augments the inflammatory process by facilitating leukocyte invasion and osteoclast differentiation stimulation, initiating alveolar bone loss and periodontal tissue loss.[36] Increased concentrations of IL-6 and TNF- have been identified in DM and obesity.[37] The onset of type 2 DM has been anticipated from serum IL-6 and C-reactive protein (CRP) levels.[30,38] Higher levels of IL-1β in gingival crevicular fluid and saliva correlate strongly with increased severity of periodontal disease, particularly in diabetic individuals, whose hyperglycaemia heightens its synthesis, which causes chronic inflammation.[39] IL-6 is also a key figure in immune regulation by its ability to stimulate osteoclast genesis and facilitate soft tissue destruction. High IL-6 levels have been correlated with increased periodontal damage, especially in individuals with compromised glycaemic control, indicating a mutual enhancement of the effects between periodontal disease and diabetes.[40] High CRP is also correlated with insulin resistance, type 2 DM and cardiovascular disease. Acute-phase proteins such as CRP are mainly induced by TNF- and IL-6, which also lead to intracellular damage of insulin signaling, potentially developing insulin resistance.[41] Serum concentrations of IL-6 and CRP are elevated in periodontitis patients, and there is a positive correlation between the values of IL-6 and the severity of the periodontal infection. The most well-characterized are interleukin (IL)-1, IL-6, prostaglandin E2 (PGE2), tumour necrosis factor (TNF), RANKL and matrix metalloproteinases (MMPs, particularly MMP-8, MMP-9 and MMP-13), and regulatory T cells that secrete cytokines (e.g. IL-12 and IL-18) and chemokines.

The cytokine network of periodontal disease pathogenesis is rather complex, and moreover, much heterogeneity in the quality of the inflammatory response also exists among individuals. MMP-8, a neutrophil-released enzyme, is responsible for collagen degradation of the extracellular matrix, which in turn results in periodontal ligament damage.[42] Studies have shown that higher MMP-8 levels correlate with higher pocket depth and tissue destruction, making it a possible biomarker for periodontal disease activity.[43] The chronic elevation of such inflammatory mediators in periodontitis, particularly with the condition of co-existence with diabetes mellitus, underscore their status as top therapeutic targets for treatment aimed at reducing periodontal inflammation and further disease progression. Although diagnostic and pathogenic relevance of IL-1β, IL-6, and MMP-8 has been reported to a greater extent, their inclusion in

routine clinical risk evaluation of diabetic patients remains limited.

Saliva as a readily available non-invasive fluid for diagnosis is an easily accessible, patient-convenient vehicle for periodontal surveillance based on biomarkers. However, well-defined sampling, interpretation, and clinical application protocols are yet to be found, and this is a significant gap between experimental evidence and clinical practice. Further research is needed to establish threshold levels, assess longitudinal change, and explore how salivary cytokine profiling might be employed to enhance personalized risk stratification and early intervention in diabetic patients with periodontal disease.

Accumulation of AGEs and interaction with RAGE

AGEs are harmful compounds formed by non-enzymatic glycation of proteins or lipids by reducing sugars, with the reaction favored under conditions of hyperglycaemia. While AGEs are typically generated during ordinary metabolic reactions, their excess accumulation is aggravated in diabetes due to hyperglycemia per se over time. AGEs may either directly cross-link extracellular matrix proteins disrupting their structural and functional organization or indirectly cause disease by generating ROS and pro-inflammatory cytokines. Systemic AGE burden is also caused by dietary intake because these compounds are taken up from the gastrointestinal tract and accumulated in tissues.[44] AGEs carry two significant functions in tissue damage by binding to specific cell-surface receptors, namely the receptor for advanced glycation end products (RAGE), and by cross-linking long-lived structural proteins such as collagen. Both pathways activate altered protein function and induce intracellular signaling cascades that elevate oxidative stress and inflammation.[45] In the periodontium, AGE accumulation is especially detrimental to alveolar bone structural integrity.

Their production inhibits osteoblast proliferation and differentiation, which leads to reduced expression of key bone matrix proteins such as osteocalcin and alkaline phosphatase. This impairs bone growth and regenerative capability, ultimately aggravating periodontal tissue destruction.[46] The hyperglycaemic diabetic environment enhances AGE production, and consequently their action is particularly significant in diabetic patients.[44] The AGE–RAGE pathway lies at the core of the inflammatory process that defines diabetic periodontitis. RAGE is a multiligand receptor present on multiple cell types including endothelial cells, fibroblasts, immune cells, and osteoblasts. Through ligand binding, various downstream signal transduction pathways are activated that most significantly nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and the Janus kinase/signal transducer and activator of transcription (JAK–STAT) pathway. These collectively enhance the production of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, all of which play an essential role in pathogenesis of periodontal tissue inflammation and destruction.[47] Experimental and clinical studies validate the involvement of AGEs and RAGE in periodontal disease during a diabetic condition.

AGE levels are elevated in gingival tissue and saliva of diabetic periodontitis patients and are associated with plaque formation and severity of disease. Furthermore, serum AGE levels strongly correlate with periodontal injury in patients with type 2 diabetes.[48,49] In diabetic animal models, increased RAGE expression in gingival tissues has correlated with increased inflammatory cytokines and MMP activity, which further contribute to extracellular matrix breakdown and loss of alveolar bone.[50,51] Relevantly, therapeutic blockade of RAGE signaling has been shown to reduce the expression of both receptor and receptor ligands in gingival tissues. These effects were observed independently of systemic glycaemic control, such that the pathogenic relevance of RAGE activation per se is underscored. This renders the AGE–RAGE axis a valuable target for therapy in preventing periodontal inflammation and tissue damage in diabetic patients. In addition to their inflammatory effects, AGEs exert deleterious effects on bone metabolism. They suppress the

osteoblast precursor pool, induce periodontal ligament cells and mesenchymal stem cells (MSCs) apoptosis and osteogenic differentiation suppression, and suppress bone formation and enhance bone resorption.[52,53] Cumulatively, all of these actions cause defective bone formation and augmented bone resorption.

Porphyromonas gingivalis (P. gingivalis) is a Gram-negative, anaerobic keystone pathogen strongly associated with the onset and progression of periodontitis. Its virulence factors, including gingipains and lipopolysaccharides, enable it to dysregulate host immunity and promote chronic inflammation. Diabetes also enhances the host immune response to P. gingivalis by elevating the production of TNF-α and inducing fibroblasts to secrete MMPs and initiate osteoclast-mediated bone loss. Furthermore, P. gingivalis-induced inflammation can interfere with insulin signalling, particularly in obesity, also contributing to further metabolic as well as periodontal disease.[54] Together, these findings illustrate the central role of the AGE–RAGE pathway in mediating the complex, bidirectional crosstalk between periodontitis and diabetes mellitus and warrant the discovery of novel therapeutic approaches for blocking this pathway to avoid tissue damage and systemic metabolic derangement.

Clinical implications

The bidirectional relationship between diabetes mellitus and periodontal disease holds important clinical importance for the diagnosis, treatment, and management of patients with either or both conditions. Hyperglycaemia is an important factor in the pathogenesis of periodontal tissue destruction by several different mechanisms such as impaired host defence, increased oxidative stress, altered tissue metabolism, and enhanced inflammatory activity. Thus, periodontal disease should therefore not be considered solely a local oral disease in diabetic patients, but rather an emergent complication of the systemic effects of metabolic derangement. Early diagnosis and management of periodontal disease may therefore become a vital part of reducing the systemic effects of diabetes and promoting general health improvement.

Clinically, from a diagnostic perspective, poorly controlled diabetic patients present with greater prevalence and severity of periodontitis and typically exhibit more elevated periodontal pockets, higher clinical attachment loss, and more rapid alveolar bone resorption. All these presentations can be observed even in excellent oral hygiene, and therefore the role of metabolic control in disease development. Dental professionals should therefore screen for the presence of periodontal infection in all diabetic patients, particularly those with a poorly managed glycaemic profile (HbA1c >7%). Conversely, dentists may also play crucial first-contact health professionals in making the diagnosis of concealed diabetes, especially in patients with severe or treatment-resistant periodontitis.

In terms of treatment, periodontal treatment using mechanical debridement, scaling and root planing (SRP), and appropriate adjunctive antimicrobial treatment has been noted to reduce systemic inflammation markers by a considerable amount and improve glycaemic control. Several clinical trials have reported minimal but clinically relevant reductions in HbA1c levels (range 0.3% to 0.6%) following complete periodontal treatment.[55,56] While not a substitute for medical care, these findings underscore the systemic impact of healthy oral health in diabetic patients. Furthermore, host-modulation therapies, such as sub antimicrobial-dose doxycycline (SDD), have been used to inhibit inflammatory mediators and possibly favourably alter prognosis in diabetic patients.[57]

Collaboration between dental and medical professionals is essential to effective treatment of patients with diabetes and periodontitis. Care models that are systematic in nature wherein endocrinologists, family medicine physicians, and dentists share patient data and coordinate care are necessary to address the shared pathophysiological pathways of both disorders. Proper patient education is also necessary; diabetic patients must be educated regarding the heightened risk of

periodontal disease complications as well as in following periodic periodontal maintenance visit schedules, ideally every three to four months for active disease. In addition, progression in the knowledge of the molecular pathways linking diabetes and periodontal inflammation, such as the AGE–RAGE axis, macrophage polarization, and NETs, is an avenue towards future therapeutic innovation.

These pathways can be targeted to deliver adjunctive therapies to reduce inflammation, promote tissue regeneration, and improve glycaemic control. For instance, modulators of the JAK/STAT signaling pathway or inhibitors of AGEs can be novel means of inhibiting hyper-activation of the immune system in diabetic periodontitis. In general, clinical management of periodontal disease in diabetes patients is a rigorous process consisting of strict oral hygiene, metabolic control, professional periodontal care, and long-term interprofessional collaboration. Identifying periodontitis as an effect and a cause of diabetes emphasizes the need for integrative medical-dental care to maximize patient benefits on both oral and systemic health fronts.

Future Directions

Deeper mechanistic understanding of diabetes mellitus-periodontal disease immunoinflammatory interactions remain in high demand. The evidence currently dictates advanced glycation end-products (AGEs), neutrophil extracellular traps (NETs), and macrophage polarization as leading mediators but explains their interrelatedness and control checkpoints only partially. Progressive research must go beyond the descriptive correlations and employ integrative approaches such as single-cell transcriptomics, proteomics, and metabolomics to create high-resolution immune dysfunction maps of diabetic periodontitis. By pinpointing the nodes of signaling that perpetuate unresolved inflammation, such research could provide targetable molecular locations for new therapeutic strategies that progress from symptom treatment to disease modification.

Identification and validation of authentic biomarkers are another grand frontier.[58] Despite the repeated association of IL-1β, IL-6, TNF-α, and MMP-8 with periodontal tissue destruction, clinical diagnosis has been thwarted by variability in interpopulation and sampling protocol. Large longitudinal cohorts of general diversity are needed to set biomarker levels indicative of disease progression and systemic metabolic degradation. Salivary and gingival crevicular fluid assays, once standardized, can be employed as non-invasive, chairside tests of double screening for glycaemic control and periodontal disease. Proper application of such biomarkers would shift practice from reactive treatment of established disease to predictive and personalized management.

Innovation in treatment is equally essential. Systemic glycaemic control and mechanical debridement remain the pillars of management but have limited and frequently short-term impacts. The AGE–RAGE axis, JAK/STAT pathway, and oxidative stress pathways represent promising molecular targets to intervene, yet pharmacologic modulator clinical trials are scarce. The development of targeted inhibitors, biologics, or host-modulating agents specifically addressing the inflammation has the power to transform the treatment outcomes.[59] Likewise, regenerative medicine strategies like mesenchymal stem cells and bioengineered scaffolds must be optimized in the healing environment of diabetes. These strategies, if realized, would restore periodontal support lost to disease and simultaneously reduce systemic inflammation.

Equally important is the integration of medical and dental care into logical, patient-centered models. In the present paradigm, diabetes and periodontal disease are often treated in isolation, leading to disjointed care and lost chances for early intervention. Future research needs to critically assess the outcomes of shared models in which endocrinologists, family physicians, and dentists share diagnostic platforms, care plans, and follow-up data. Not only clinical efficacy but also health economics studies need to value potential cost savings of comprehensive care in preventing

diabetes complications such as cardiovascular disease, nephropathy, and amputation. The argument for medical-dental cooperation is also not merely biological but pragmatic from the point of view of a global reduction in health burdens.

Population-specific factors are also due for greater attention. Most mechanistic studies have been carried out in Western populations, while Asia, Africa, and Latin America carry a disproportionate share of diabetes and periodontal disease burdens.[60] Genetic predisposition, dietary patterns, microbiome diversity, and access to care can in theory modulate disease expression and responsiveness to therapy. Large longitudinal, multiethnic studies need to uncover these differences so that new diagnostics and therapies will be universally applicable and not region specific. In the absence of this knowledge, there is a risk that new therapies will exacerbate current disparities in health rather than stop them.

Finally, the possible impact of patient empowerment and digital health technologies to manage the diabetes–periodontitis axis must be critically evaluated. Mobile health (mHealth) apps, continuous glucose monitoring, and artificial intelligence-aided risk calculators will revolutionize patient self-management.[61] To determine whether they do improve compliance, reduce complications, and affect long-term outcomes effectively, robust trials are the order of the day. Importantly, solutions must be designed with inclusivity so that digital solutions can be used by older patients and low-resource environments. Using technology without bridging the gaps risks widening the care gap in exactly those populations most vulnerable to the double burden of diabetes and periodontal disease.

Conclusion

The relationship between diabetes mellitus and periodontal disease is a fascinating demonstration of bidirectional systemic–oral health relations. Chronic hyperglycaemia contributes to the pathogenesis and progression of periodontal disease by impairing immune competency, augmenting oxidative stress, and causing chronic inflammation through mechanisms such as advanced glycation end-product (AGE) accumulation and dysregulation of significant signaling pathways such as NF-κB and JAK/STAT. Chronic periodontal infection, on the other hand, raises systemic inflammation, which may enhance insulin resistance and glycaemic control, promoting the progression of diabetes and its complications. Both mechanistic and epidemiological investigations continually attest to the existence of a synergistic relationship, such that each condition negatively affects the other.

This dependency underlines the importance of early detection, multidisciplinary management, and care models that blur medical and dental practice. Therapeutic interventions addressing both glycaemic control and periodontal care are likely to improve patient outcomes across the board. Lastly, the identification and recognition of the two-way connection between periodontal disease and diabetes are important not only for oral health but also for reducing the systemic problems of diabetes and optimizing overall quality of life.

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