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ORIGINAL ARTICLE

Interrelationships of periodontitis and diabetes: A review of the current literature

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Abstract Diabetes and periodontitis are common chronic diseases in the world, and abundant epidemiological evidence implies a bidirectional relationship between the two diseases. It appears that diabetes is a risk factor for greater periodontal destruction, whereas managing periodontitis can also contribute to better glycemic control. The underlying regulatory mechanisms are also bidirectional. The hyperglycemic status may directly alter subgingival microbial compositions, impair cellular function, and change collagen metabolism. The formation of advanced glycation end-products (AGEs) can further modify the extracellular matrix, and establishment of cellular receptor binding can amplify inflammation. Moreover, periodontitis also induces hyperlipidemia and insulin resistance. This cyclical relationship converges via overproduction of proinflammatory cytokines, such as tumor necrosis factor- α and interleukin-1 β . Thus, this article highlights the importance of maintaining periodontal health to eliminate systemic complications and meticulous metabolic control to prevent further periodontal destruction. From a systemic aspect, targeting proinflammatory cytokines or receptors of AGEs could be a potential modality for treating periodontitis.

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Introduction

Diabetes is a disease of metabolic dysfunction characterized by hyperglycemia, giving rise to the risk of several

complications including retinopathies, neuropathies, nephropathies, cardiovascular complications,¹ and delayed wound-healing.² It is associated with a reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications, such as ischemic heart disease, stroke, and peripheral vascular disease, and a diminished quality of life. Currently, there are three types of diabetes recognized by the World Health Organization (WHO)³: (1)

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type I diabetes, previously known as insulin-dependent or childhood-onset diabetes (IDDM), is characterized by a lack of insulin production due to destruction of β -cells; (2) type II diabetes, formerly termed non-insulin-dependent diabetes (NIDDM), or adult-onset diabetes, is caused by increasing insulin resistance. It is the major type of diabetes in the adult population and is closely related to obesity⁴; (3) a third category, hyperglycemia secondary to systemic diseases or conditions,⁵ includes gestational diabetes³ and diabetes associated with diseases involving the pancreas and destruction of β -cells,⁶ endocrine diseases,⁷ tumors,⁸ a pancreatectomy,⁹ and drug- or chemical-induced insulin insensitivity or resistance.¹⁰

Periodontitis is the consequence of local infections in the oral cavity resulting in irreversible destruction of the tooth attachment apparatus (i.e., alveolar bone, root cementum, and the periodontal ligament).¹¹ One clinical manifestation of periodontitis is the appearance of periodontal pockets, enabling further microbial colonization and challenge. Other manifestations include redness and gingival swelling, pain, and tooth hypermobility. At present, periodontitis is one of the major reasons for adult tooth loss. Based on the 1999 American Association of Periodontology (AAP) classification, periodontitis can be further divided into six categories: (1) aggressive periodontitis; (2) chronic periodontitis; (3) periodontitis as a manifestation of systemic diseases; (4) necrotizing periodontal diseases; (5) periodontitis associated with endodontic lesions; and (6) periodontitis from the developmental or acquired deformities and conditions.¹²

An epidemiological link between diabetes and periodontitis was established in 1960, and the interaction is classified by age and type of diabetes in most studies.¹³ For example, studies showed that when comparing diabetic and non-diabetic Pima Indians, higher-aged diabetic individuals had greater periodontal attachment and bone loss than younger diabetic subjects.¹⁴ Findings from the Third National Health and Nutrition Examination Survey (NHANES III) in the US indicated that the prevalence of diabetes among people with periodontal disease was about two-fold higher than that of periodontally healthy diabetic subjects.¹⁵ Studies also showed an association between the severity of periodontitis and glucose intolerance, signs of metabolic syndrome, and additional diabetes-related complications, such as cardiovascular problems.^{16,17} As such, some have proposed periodontal disease as the sixth complication, due to the almost omnipresence of diabetes along with periodontal disease,^{18–21} and some evidence also supports a marked bidirectional correlation between periodontal disease and diabetes.^{13,22,11}

Epidemiological evidence of an association of diabetes with periodontitis

Attachment loss is frequently used as one of the parameters to measure periodontal health, and numerous studies agreed that patients with poorly managed type I or II diabetes have significantly worse periodontal health, including increased attachment loss, compared to patients with better or well-managed diabetes and healthy individuals.^{14,18,23} Other factors, such as the bleeding index and

pocket depth, were also considered in those studies, which also pointed towards poorer periodontal health in diabetic patients (Table 1).^{24–38} Furthermore, those studies indicated that there were other diabetes-associated factors that also affected attachment loss: (1) the duration of the patient being afflicted with diabetes appeared to affect periodontal health, namely, the longer the duration is, the worse the periodontal health and more clinical attachment loss there is.^{31,23} However, Sandberg and co-workers³⁹ demonstrated that the duration of diabetes was more closely correlated with the number of caries lesions than the periodontal status; and (2) patients with diabetic complications (i.e., retinopathies, neuropathies, nephropathies, and cardiovascular complications), also showed increased susceptibility to periodontal disease with increased attachment loss.¹⁸

Although some studies found no statistical difference in probing depths or attachment loss between diabetics and non-diabetics, most investigators agreed that some periodontal changes like increased gingivitis could be observed in diabetic subjects. One must also note that in those studies, most used type I diabetes (IDDM) as a selection criterion, implying a weak correlation between type I diabetes and periodontal breakdown. However, more extensive research needs to be conducted to support this claim. Other variables that may have confounded the results of those studies include a younger-than-average age (adolescents as test subjects) and a small sample size.^{27,34} With regard to other studies, most of them suggested a correlation between diabetes and increased periodontal breakdown (i.e., increased bone loss and probing depths).

Some studies were not able to confirm a link between diabetes causing increased periodontal breakdown, possibly due to the presence of confounding factors such as the age of the patients, the duration of diabetes, the presence of calculus, and smoking. Furthermore, some subjects, whose diabetes was under control, still experienced periodontal problems, implying that diabetes-induced periodontal alterations may be irreversible and cannot be recovered with glycemic control.⁴⁰

Effects of periodontal therapy on periodontal health and glycemic control

Perhaps the good news is that studies also showed that subjects with good metabolic control [measured in terms of glycated hemoglobin levels (HbA1c)] exhibited a slower rate of attachment loss than their poorly controlled counterparts. By contrast, studies also revealed that better glycemic control could be achieved after periodontal treatment (Table 2),^{41–46} and the relevance was further confirmed by several recent meta-analyses.^{47,48} Those studies addressed the importance of controlling infection in diabetic patients, where a combination of mechanical debridement (i.e., scaling and root planing) and systemic antibiotics allowed better glycemic control.^{44,46} Doxycycline, a tetracycline derivative, appeared to be the most potent modifier of all antibiotics, possibly due to the effect of preventing glycation of the extracellular matrix (ECM).¹¹ However, there are also studies that demonstrated no

Table 1 Susceptibility of periodontal diseases in accordance with glycemic control (HbA1c level).

Research Team	Periodontal parameters	Sample size and physiological conditions (age)	Periodontal response
Arrieta-Blanco et al ²⁴	PI	70 (T1DM&T2DM) 74 healthy (25–81 y/o)	PI↑ in DM subjects, and no significant difference between T1DM and T2DM. HbA1c level did not significantly influence PI
Campus et al ²⁵	TN, PPD, PI, GI, Microbiology	49 (T2DM, good control) 22 (T2DM, poor control) 141 healthy (35–75 y/o)	TN↓, PPD > 4 mm↑, PI↑, GI↑, <i>P. gingivalis</i> ↑, <i>T. forsythus</i> ↑ in T2DM patients PPD > 4 mm↓ in well-controlled than poorly-controlled subjects
Cianciola et al ²⁶	CAL	263 (T1DM) 208 healthy (11–18 y/o)	Prevalence of periodontitis is 9.8% T1DM and 1.7% in healthy controls. CAL↑ in T1DM
de Pommereau et al ²⁷	ABL, CAL, PI, GI	85 T1DM adolescents 38 healthy (12–18y/o)	None of the subjects demonstrated signs of periodontitis GI↑ in T1DM
Emrich et al ²⁸	CAL, ABL, PI, GI, CI	1324 Pima Indians 254 with T2DM 158 with impaired glucose tolerance (> 15 y/o)	CAL↑, ABL↑, and CI↑ in T2DM subjects
Guzman et al ²⁹	CAL	100 DM (19–78 y/o)	66% had 2 or more CAL > 5 mm, of which 43% had 2 or more CAL > 7 mm Prevalence of severe CAL increased in higher HbA1c subjects
Hove & Stallard ³⁰	PPD, CAL	28 DM, 16 healthy (20–40 y/o)	PPD↑ and CAL↑ in DM patients. Severity of diabetes had little effect on periodontal breakdown. Duration of diabetes not related to increased breakdown
Hugoson et al ³¹	PPD, ABL	82 (long duration T1DM) 72 (short duration T1DM) 77 healthy (20-70 y/o)	ABL↑ in long duration T1DM; PD > 6 mm↑ in both groups of T1DM
Pinson et al ³²	PPD, CAL, PI, GI, GCF flow, BOP	26 T1DM children 24 healthy (7–18 y/o)	Overall no statistically significant differences between cases and controls; GI↑, PI↑ in T1DM subjects
Safkan-Seppala and Ainamo ³³	PPD, CAL, ABL, PI, GI, BOP, GR	T1DM, 44 poorly controlled and 27 controlled (17–63 y/o)	With similar plaque control, CAL↑ and ABL↑ in poorly-controlled DM
Sastrowijoto et al ³⁴	PPD, CAL, PI, GI, Microbiology	6 T1DM receiving insulin treatment (18–50 y/o)	PI↓, GI↓, <i>Streptococcus</i> ↑ in with improved glycemic control, but has no effect on other periodontal parameters
Shlossman et al ³⁵	CAL, ABL	3219 T2DM Pima Indians	CAL↑ and ABL↑ in T2DM subjects
Silva et al ³⁶	TN, Medical diagnosis	86 (T1DM) 212 (T2DM) (>30 y/o)	Gingivitis (68%) and periodontitis (25.3%) among DM individuals. Higher prevalence of periodontitis among T2DM, males, and those with more than 8 years DM history
Tervonen & Knuuttila ³⁷	PPD, CAL, BOP	50 DM 53 healthy (30–40 y/o)	No significant difference between DM and healthy Well-controlled DM demonstrated improved PPD than poorly-controlled DM Poorly controlled diabetes increased attachment loss
Tervonen & Oliver ³⁸	PPD, CAL, PI, GI, CI	75 DM for 2–5 years HbA1c monitoring	CI↑, PPD↑, CAL↑ in poorer-controlled DM subjects

ABL = alveolar bone loss from radiograph; BOP = bleeding on probing; CAL = clinical attachment loss from probing; CI = calculus index; DM = diabetic mellitus; FBG = fasting blood glucose; GI = gingival index; GR = gingival recession; HbA1c = glycated hemoglobin; N/A = not available; PI = plaque index; PPD = probing pocket depth; T1DM = type 1 DM; T2DM = type 2 DM; TN = number of tooth; y/o = year-old.

Table 2 Glycemic response to periodontal intervention (all in type II diabetes).

Research Team	Sample size (physiological condition-periodontal treatment)	Time points (mo)	Glycemic parameters	Periodontal parameters	Periodontal response	Systemic response
Faria-Almeida et al ⁴¹	Exp: 10 (DM-SRP) Con: 10 (Healthy-SRP)	3, 6	FBG HbA1c	CAL PPD GR	PPD↓, CA ↓, and GR↓ (in both groups) No significant difference between groups	Hb1Ac in DM subjects↓ No significant change in FBG
Grossi et al ⁴²	Exp 1: (DM-SRP + doxycycline) Exp 2: (DM-SRP + CHX + doxycycline) Exp 3: (DM-SRP + povidone iodine + doxycycline) Exp 4: (DM-SRP+CHX) Con: (DM-SRP)	3, 6, 12	Serum glucose HbA1c	PPD CAL Microbiology	PPD↓, CAL↓, and <i>P. gingivalis</i> ↓ in all Exps. Doxycycline treated group (Exp 2) showed greatest improvement	HbA1c↓ in all groups without significance
Katagiri et al ⁴³	Exp: 32 (DM-SRP + minocycline) Con: 17 (DM-OHI)	1, 3, 6	FBG HbA1c Hs-CRP	PPD BOP	PPD↓ and BOP↓ Significant improvement in Exp group	HbA1c and FBG ↓ in Exp but no significant change in Con No significant change in Hs-CRP
O' Connell et al ⁴⁴	Exp: 15 (DM-SRP + doxycycline) Con: 15 (DM-SRP)	3	FBG HbA1c systemic inflammatory markers	PPD CAL PI BOP Suppuration	PPD↓, CAL↓, PI↓, BOP↓, and no suppuration in both groups No significant difference between groups	HbA1c in both groups↓, and significant decrease in Exp than Con No significant change in FBG Reduction in levels of 16 of 24 inflammatory markers, including IL-6, IP-10, sFasL, G-CSF, RANTES, and IL-12
Rodrigues et al ⁴⁵	Exp: 15 (DM-SRP+ amoxicillin) Con: 15 (DM-SRP)	3	FBG HbA1c	CAL PPD	PPD in both groups↓ No significant change in CAL No significant difference between groups	HbA1c in both groups↓ No significant change in FBG
Singh et al ⁴⁶	Exp 1: 15 (DM-SRP) Exp 2: 15 (DM-SRP + doxycycline) Con: 15 (DM-No Tx)	3	FBG HbA1c PPBG	PI and GI CAL PPD	All parameters improved in both Exp groups but no significant difference between Exp groups	FBG↓, HbA1c↓, and PPBG↓ in both Exp groups. HbA1c in Exp 2 significantly lower than Exp 1

BOP = bleeding on probing; CAL = clinical attachment loss; CHX = chlorhexidine; Con = control group; DM = diabetic mellitus; Exp = experimental group; FBG = fasting blood glucose; GI = gingival index; GR = gingival recession; HbA1c = glycated hemoglobin; Hs-CRP = high-sensitivity C-reactive protein; OHI = oral hygiene instruction; PI = plaque index; PPBG = postprandial blood glucose; PPD = probing pocket depth; y/o = year-old; SRP = scaling and root planing.

significant alteration in glycemic control after periodontal treatment.^{49,50} A 4-month report from Christgau and co-workers demonstrated that periodontal treatment improved clinical periodontal parameters, reduced periopathogenic bacteria, and reduced the oxidative burst response of inflammatory cells.⁵¹ However, no significant difference existed between systemically healthy and diabetic subjects. A meta-analysis from Janket and co-workers showed a tendency, but no significant improvement, in HbA1c levels after weight adjustment.⁵² A long-term, large-scaled follow-up study in Japan indicated no significant difference between periodontal treatment and the incidence of diabetes, but did suggest periodontitis as an increased risk for developing diabetes.⁵³ Taken together, of clinical relevance to us is that dentists should treat the periodontal condition in a patient's mouth and manage the patient's diabetic condition, in order to achieve optimal results after periodontal therapy. While good periodontal health might not necessarily be accompanied by a change in glycemic control, an improvement can potentially modify metabolic control, leading to an overall enhancement in the quality of life.

Proposed mechanisms of how diabetes affects periodontal health (Fig. 1)

Arising from the epidemiological association, diabetes was thought to affect the periodontal status through direct effects of hyperglycemia and be indirectly modulated by advanced glycation end-products (AGEs), adducts from the glycation and oxidation of proteins and lipids,⁵⁴ leading to an overall impairment of wound healing and changes in periodontal tissues.

Direct effects of hyperglycemia

Firstly, diabetes results in a rise of the concentration of glucose and a decrease in the level of epidermal growth

factor (EGF) in the saliva and gingival crevicular fluid (GCF),^{55,56} which contributes to alterations in the microbial profile in periodontal pockets. Clinical investigations demonstrated that the modified environment is more favorable for the growth of gram-negative anaerobes, including the periodontal pathogens *Capnocytophaga* spp., *Actinomyces* spp., and *Campylobacter* spp., and black-pigmented species including *Prevotella intermedia* and *Porphyromonas gingivalis*.^{57–60} However, results from *in vitro* studies revealed that the bacterial microflora at periodontally diseased sites in diabetic subjects is similar to that of non-diabetic subjects.^{59,60} The apparent lack of significant differences in the bacterial microflora suggests that alterations in the host immunological response may have a stronger influence on the increased prevalence and severity of periodontal destruction seen in diabetes.¹

Therefore, it was proposed that diabetes may elicit a cytokine-induced acute-phase response through activation of the innate immune system, which contributes to the pathogenesis of this disease and its associated complications such as dyslipidemia, atherosclerosis, and host inflammatory responses.⁶¹ One of the mechanisms causing periodontal destruction involves activation of the innate immunity, mainly by upregulation of proinflammatory cytokines in the presence of gram-negative microorganisms, potentially indicating that periodontitis can be systemically modulated by proinflammatory cytokines.⁶² Thus, Salvi and co-workers^{63,64} demonstrated the hyperresponsiveness of monocytic proinflammatory cytokines, including tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and prostaglandin (PG)E₂, in diabetic patients with periodontal diseases. In their later study, results revealed an elevation of proinflammatory cytokines in the GCF of diabetic patients, without significant changes in the microbial or plaque compositions.⁶⁵ Further investigations also demonstrated prolonged expression of TNF- α , resulting in greater periodontal damage and alteration of the lipopolysaccharide (LPS)-associated signaling pathways in diabetic animals.^{66,67} Taken together, cytokine dysfunction in

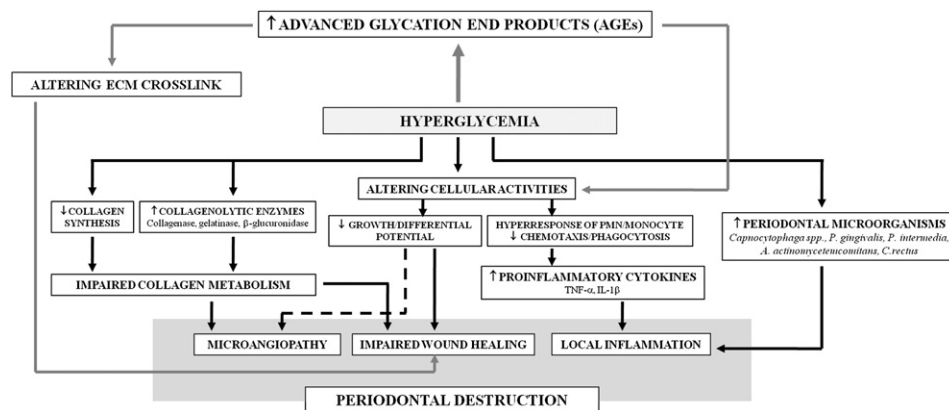


Figure 1 Mechanisms of diabetes-mediated periodontal tissue destruction. The hyperglycemic status can directly provide favorable environment for the growth of Gram-negative periodontal pathogens, impair cellular function and host defense, and induce overproduction of proinflammatory cytokines and secretion of collagenolytic enzymes (black lines). By facilitating the formation of advanced glycation end products (AGEs), diabetes can also indirectly alter the crosslink of the extracellular matrix (gray lines) as well as the cellular activities to amplify inflammatory reactions and decrease cell viability, leading to further wound healing impairment and potential vascular change (dash black lines) in periodontal tissue (gray box).

diabetes plays a more-predominant role in causing periodontal destruction than microbial changes.

As such, hyperglycemia appears to decrease the effect of chemotaxis and phagocytosis and increase apoptosis, the production of reactive oxygen species (ROS), and the expression of adhesion molecules of polymorphonuclear neutrophils (PMNs)^{68–70} and monocytes/macrophages.^{67,71} It is also known to reduce the proliferation, migration, and differentiation potential of periodontal ligament cells (PDLs),^{72,73} gingival fibroblasts (GFs),⁷⁴ and mesenchymal stem cells (MSCs).^{75,76}

Hyperglycemia also triggers a variety of collagen changes. One study showed reduced synthesis of both collagen and glycosaminoglycan in hyperglycemic culture conditions and fibroblasts from diabetic patients.⁷⁷ *In vivo* studies also demonstrated impaired production of collagen and the osseous matrix in a diabetic condition.⁷⁸ Increased collagenase and gelatinase activities in gingival tissues were also noted in some animal studies.^{79,80} The alteration of collagen metabolism can influence wound healing and the turnover capability and it also results in microangiopathy due to impaired metabolism of type IV collagen, which is the main component of basement membranes.⁸¹ Disruption of the basement membrane can impede oxygen diffusion, metabolic waste elimination, PMN chemotaxis, and diffusion of growth factors. In conclusion, vascular changes can result from the cumulative effects of altered collagen metabolism, glycation of the ECM, overproduction of ROS, and immune dysfunction.^{77,81}

Modulation by AGEs

In prolonged hyperglycemic states, AGEs form as a consequence of extensive glycation of proteins and lipids, with ROS as byproducts.^{54,82} Accumulation of AGEs in plasma and tissues was also reported in several pathophysiological conditions including metabolic dysfunctional, chronic inflammatory, and neurodegenerative diseases.⁸³ AGEs can modify the cross-linking of matrix molecules, impair the efficiency of growth factors, and contribute to oxidative stress in diabetic conditions.⁸⁴

Studies demonstrated that AGEs arrest cell cycles in fibroblasts⁸⁵ and attenuate the viability and differentiation potential of MSCs.⁸⁶ Increased levels of AGE-cross-linked collagen lead to altered osteoblastic activity and ECM productivity, which affects bone formation production.^{87,88} This alteration in collagen metabolism leads to a rapid degradation of newly formed collagen. AGEs crosslink with collagen, making it less soluble and less likely to be repaired or replaced. As a result, collagen in tissues of poorly controlled diabetics is aged and more susceptible to breaking down.⁸⁹ The storage of AGE-modified collagen molecules in tissues leads to decreased wound healing of the periodontium and accelerated degradation of both non-mineralized connective tissue and mineralized bone.⁹⁰ Impaired osteoblastic cell growth and collagen production cause bone formation reduction and a decrease in the strength of newly formed bone by osteocytes.^{91–93} As a result, AGEs undermine wound healing and lead to more-severe tissue destruction.

Therefore, AGEs are regarded as inflammatory initiators or amplifiers when binding to their cellular receptors, RAGEs.⁵⁴ Monocytes, macrophages, endothelial cells, and epithelial cells possess high-affinity RAGEs,^{77,94} and in our recent investigation, elevated expression of RAGEs was also noted in PDLs and MSCs when seeded on a glycated matrix.⁹⁵ This binding of AGEs to RAGEs will activate the nuclear factor (NF)- κ B-regulated pathway, resulting in the release of cytokines and induction of inflammation.⁹⁶ Upregulation of RAGEs in endothelial cells results in hyperpermeability and enhanced expression of vascular cell adhesion molecule (VCAM)-1, which further induces chemotaxis of monocytes.⁹⁷ AGE-RAGE binding can also lead to increased intracellular oxidant stress and reductions in detoxifying mechanisms.⁹⁸ Thus, the presence of RAGE is capable of converting transient proinflammatory reactions into sustained cellular dysfunction and impairment of immune responses.⁹⁶

Effects of diabetes on bone healing

Diabetes is also associated with skeletal complications, i.e., diabetic osteopathy,⁹⁹ which is characterized by a reduction in the bone mineral density, an increased risk of osteoporosis and osteopenia,¹⁰⁰ an increased risk of fracture,¹⁰¹ and impairment of osseous healing and regeneration potentials.¹⁰² For dental implant osseointegration, however, the results from clinical studies are still equivocal, whereas a positive correlation between the implant failure rate and a diabetic status was only seen in some studies^{103,104} but not in another one.¹⁰⁵ In animal models, a diabetic status led to 50% loss of bone-implant contact.¹⁰⁶ The failure rate tended to rise after functional loading, presumably associated with impaired bone remodeling.¹⁰⁷ The occurrence of these skeletal complications are high in type 1 but not obvious in type 2 diabetic subjects,¹⁰⁰ suggesting that these complications can be accounted for by systemic insulin levels. Clinical studies demonstrated that the fracture healing capability can be recovered after insulin treatment,¹⁰⁸ and animal studies demonstrated that insulin treatment is capable of maintaining the level of dental implant osseointegration for a longer period.^{108–110}

With regards to the micro-architecture of diabetic bone, poor trabecular connectivity, increasing porosity, a lower bone spicule/marrow ratio,¹¹¹ a lower calcium-to-phosphate composition,¹¹² and reduced ash content were found in experimental diabetic animals. Decreasing levels of matrix proteins and minerals,¹¹³ diminished alkaline phosphatase activity, disruption of hydroxyapatite crystal formation,¹¹⁴ and reduced collagen synthesis⁷⁸ were noted in diabetic rodents. Therefore, elevation of AGEs in osseous tissues alters interactions of the cell matrix and also disrupts the cross-linking of the ECM.⁵⁴ As a result, inferior mineralization and poor matrix formation properties can contribute to deteriorating biomechanical properties of diabetic bone.¹¹⁵

Histologically, decreased osteoblasts were found, presumably associated with deficits in the recruitment and proliferation of mesenchymal stem cells of an osteoblastic lineage.¹¹⁵ The activity of osteoblasts also decreased, resulting in reductions in collagen synthesis and osteoid surface formation.¹¹⁶ Excessive osteoclastic markers were

found in the urine, suggesting progressive bone loss in diabetic patients.¹¹⁷ However, in animal studies, many subjects displayed reductions in osteoclast numbers and activities,^{118,119} indicating the inability of bone turnover. On the other hand, Hie and co-workers also demonstrated an increasing number and activity of osteoclasts leading to bone resorption.¹¹⁶

Alterations of periodontal tissues with diabetes

Morphological changes in periodontal tissues under experimental diabetes were reported by Tesseromatis and co-workers.¹²⁰ Their results revealed mild inflammation limited to the lamina propria and perivascular region, with gingival epithelial hyperplasia and moderate-to-severe angitis 90 days after inducing diabetes. With the presence of plaque retentive factors (i.e., subgingival ligature placement), Silva and co-workers demonstrated a thickening of the gingival epithelium, with elongated dermal papilla, and the collagen alignment in connective tissue was loose and disorganized, with more prominent inflammatory cell infiltration in diabetic animals.¹²¹ Furthermore, in our current investigation, we also demonstrated that a diabetic condition can prolong the period of periodontal breakdown and delay mitogenesis.¹²²

Healing of periodontal destruction in diabetic animals was investigated by Liu and co-workers.¹²³ They reported that a diabetic condition can induce greater bone loss with ligature placement and may impair new bone formation after ligature removal. They also found that recovery from inflammation was delayed, apoptotic bone-lining cells exhibited prolonged expression, and the numbers of osteoblasts and periodontal ligament fibroblasts decreased in diabetic animals. Devlin and co-workers also evaluated the pattern of alveolar bone after tooth extraction.¹²⁴ They showed extensive necrosis of alveolar bone after extraction, and that reepithelization, mineralization, and tissue remodeling were delayed in diabetic animals. Desta and co-workers also suggested that the delayed healing of gingival wounds may have originated from decreased numbers of fibroblasts, due to increased apoptosis and reduced proliferation.⁷⁴ Taken together, preclinical studies confirmed that a diabetic status can augment and prolong periodontal destruction, while at the same time, impairing repair capabilities.

Proposed mechanisms for periodontitis affecting glycemia control (Fig. 2)

While the effects of diabetes on periodontal health are more clearly elucidated, there is still limited information regarding how periodontal diseases influence diabetic states. Periodontitis is primarily an oral infection caused by gram-negative anaerobes. The main virulence factors of these microorganisms are endotoxins in the form of lipopolysaccharides (LPSs),¹²⁵ and pathogenesis is triggered by recognition of pathogen-associated molecular patterns from Toll-like receptors (TLRs), which release ROS from defending cells and subsequently induce oxidative stress, proinflammatory cytokines, and immunoregulatory

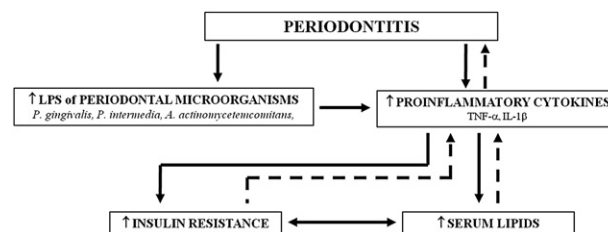


Figure 2 Mechanisms of periodontitis-mediated metabolic dysfunction. In response to LPS of periodontal microorganisms, elevation of systemic proinflammatory cytokines can disturb the lipid metabolism and insulin resistance, consequently leading to hyperlipidemia and hyperglycemia (solid lines). The systemic metabolic disturbance can further deteriorate local infection, such as periodontitis, via hyperlipidemia and proinflammatory cytokines (dashlines).

complexes through the NF- κ B pathway.^{126,127} Periodontitis may induce systemic conditions through translocation of periodontal microorganisms and their products from periodontal biofilms or direct cytokinemia from the GCF into the circulation.¹²⁸ Investigations showed the coincidence of elevated serum proinflammatory cytokines and attachment loss,^{129,130} implying the systemic involvement of periodontitis. Moreover, periodontal treatment not only reduced oral inflammation, but also decreased systemic levels of IL-6, TNF- α , and C-reactive proteins (CRP), indicating that periodontal diseases induce systemic alterations beyond the local periodontal environment.¹³¹ Since elevation of TNF- α and IL-1 β was observed in both the GCF and serum of subjects with periodontitis and diabetes, TNF- α and IL-1 β are thought to play major roles in developing systemic conditions.⁴⁰ TNF- α was shown to induce insulin resistance and potentially links the progression of periodontal disease destruction with worsening of the diabetic state.

There is evidence that exposing serum from periodontitis patients to LPS of periodontal pathogens leads to increased triglycerides and lower levels of high-density lipoprotein (HDL),^{132,133} which suggests that local infection, such as periodontitis, can alter systemic lipid metabolism. The mechanism is possibly due to activation of the 'cytokine cascade' in response to LPS.⁴⁰ The elevation of serum lipids may also influence immune cell function by upregulating proinflammatory cytokines and superoxide production by PMNs and altering surface marker antigens of monocytes.¹³⁴ In the meanwhile, periodontitis can potentially induce insulin resistance by the overproduction of systemic proinflammatory cytokines, such as TNF- α , IL-1 β , and IL-6. These cytokines will further ameliorate insulin insensitivity by destroying pancreatic β -cells, antagonizing insulin action, or altering intracellular insulin signaling through the NF- κ B and c-Jun N-terminal kinase (JNK) axes.^{13,40,135,136}

Potential applications

Based on the epidemiological link between diabetes and periodontitis, clinical guidelines were developed to predict undiagnosed diabetes cases based on the waist circumference, age, oral health status, ethnicity, and weight information.¹³⁷ The potential mechanistic interrelationships

between diabetes and periodontitis may also direct future therapeutic interventions from two aspects. Firstly, systemic glucose and lipid levels can be reduced to attenuate the systemic influence on periodontal health, and this can be achieved by medication or dietary changes. Periodontal treatment to control colonization of microbial pathogens and simultaneously reduce the level of proinflammatory cytokines is also essential to prevent a worsening of diabetic conditions. Secondly, while proinflammatory cytokines, such as TNF- α and IL-1 β , play key roles in this bidirectional relationship, it is also of interest to develop immunomodulators that target these cytokines. However, one must be cautious, because modulating these cytokines may also affect the body's homeostasis.

By contrast, while both TLRs and RAGEs solicit inflammatory reactions via NF- κ B-regulated pathways, recent studies demonstrated that RAGEs also interact with endogenous ligands other than AGEs to induce inflammation and regulate disease progression,¹³⁸ and the expression of RAGEs was also observed even in periodontally diseased gingival tissues from physiologically healthy subjects.¹³⁹ Furthermore, blockade of RAGEs in diabetic animals can significantly suppress periodontal bone loss without affecting the systemic metabolic status.¹⁴⁰ Those findings imply that RAGEs may be involved in the pathogenesis of periodontitis, and utilizing an antagonist of RAGEs may be a potential treatment modality to manage periodontal diseases.

In summary, an in-depth understanding of the possible mechanisms linking periodontal disease and diabetes, in terms of periodontal destruction and periodontal healing, is essential to the future development of treatment strategies for patients with diabetes and periodontal disease.

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