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Review Article

Periodontal Disease and Diabetes Mellitus: A Two-Way Road to Health

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Abstract

Periodontitis has been associated with diabetes mellitus and the discussion has resulted in conflicting conclusions. Both the diseases have a relatively elevated incidence globally in the general population as they have a number of common pathways in their pathogenesis. Both these diseases are polygenic disorders with some degree of immuno-regulatory dysfunction. A higher incidence of periodontitis in diabetics compared to healthy controls is indicated in a number of reports. The relationship between these two maladies appears bi-directional insofar that the presence of one condition tends to promote the other, and that the meticulous management of either may assist treatment of the other. However, the converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received little attention.

Keywords: *Diabetes Mellitus; Periodontal Diseases; Glycemic Control; Periodontitis; Bone Loss*

Introduction

Years of research have established a number of mechanisms by which diabetes can influence the periodontium. Many of these mechanisms share common characteristics with those involved in the classic complications of diabetes, such as retinopathy, nephropathy, neuropathy, macrovascular diseases and altered wound healing. Because periodontal diseases are infectious diseases, research initially focused on possible differences in the subgingival microbial flora of patients with and without diabetes. Although some early studies reported higher proportions of certain bacteria in the periodontal pockets of patients with diabetes, later studies involving cultures generally revealed few differences in periodontally diseased sites of subjects with diabetes and those of subjects who did not have diabetes [1].

Because the pathogens associated with periodontitis do not appear to differ greatly in people with and without diabetes, researchers have focused attention on potential differences in the immune inflammatory response to bacteria between people with diabetes and those without diabetes. Diabetes mellitus is a heterogeneous group of disorders and is characterized by high blood glucose levels.

Type 1 diabetes mellitus (T1DM) results from an absolute deficiency of insulin, which is most commonly due to auto-immunological destruction of the insulin producing pancreatic β cells but which can be caused by other etiologies. In type 2 diabetes mellitus (T2DM), muscle, fat and other cells become resistant to the actions of insulin. This results in the activation of a compensatory mechanism that induces β cells to secrete more insulin. T2DM occurs when the compensatory increase in insulin is insufficient to maintain blood glucose levels within a normal physiological range [2,3].

By 2025, 300 million people are projected to be afflicted with diabetes worldwide, with a prevalence of 6.4%. The countries with the most people suffering from diabetes by the year 2025 are predicted to be India, China and the United States. T1DM represents 5% - 10% of the total number of diabetes cases worldwide6 and is the main type of diabetes in youth, representing 85% or more of all diabetes cases in individuals younger than 20 years of age worldwide. On average, males and females are equally affected with T1DM in young populations. T2DM accounts for 90% of diabetes cases globally. This disorder has traditionally been considered a metabolic disorder of adults; however, it has recently become more common in young adults, adolescents and occasionally, in children [4].

Mechanisms by which Periodontitis May Influence Diabetes-Related Inflammatory State and Insulin Resistance

Evidence has consistently indicated that diabetes acts a risk factor and is responsible for increase in severity of gingivitis and periodontitis. Conversely, periodontitis may be a risk factor for worsening glycemic control among patients with diabetes and may increase the risk of diabetic complications. Periodontitis may initiate or propagate insulin resistance in a manner similar to that of obesity, by enhancing activation of the overall systemic immune response initiated by cytokines [5,6] (Figure 1).

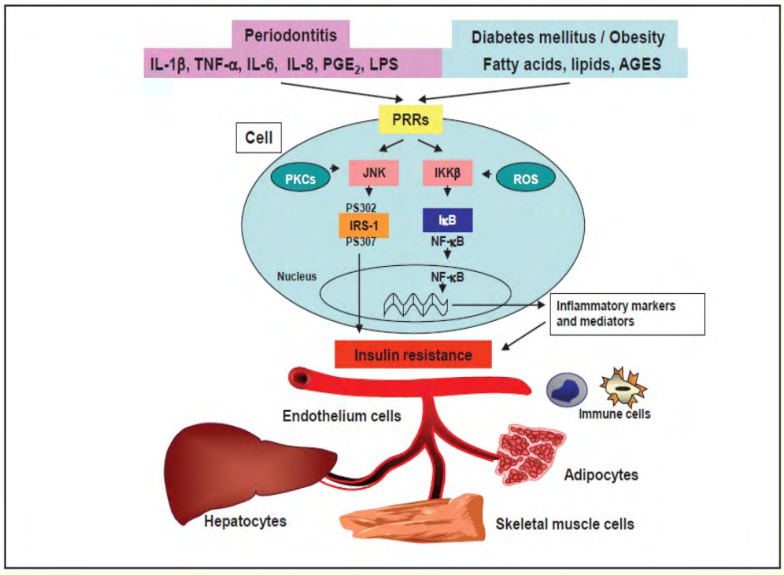

Figure 1: *Proposed mechanism by which periodontal inflammatory mediators may contribute to the development of resistance in individuals with both type 2 diabetes and periodontitis.*

Findings from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States showed that the prevalence of diabetes among people with periodontal disease (n = 1293) was 12.5%, whereas only 6.3% of periodontally healthy participants (n = 12 178) reported that they had diabetes, a 2-fold difference. Other studies have shown an association between the severity of periodontitis and glucose intolerance, signs of metabolic syndrome and additional diabetes-related complications, such as cardiovascular problems [7].

There is limited knowledge about the mechanisms through which periodontal diseases may influence the diabetic state. In untreated severe periodontal disease, the cumulative surface area of ulcerated pocket epithelium has been estimated to range from 8 to 20 cm^2,

which approximates the size of the palm of an adult hand [8]. Bacteremia and endotoxemia can be induced by dental procedures, as well as by usual daily activities (such as chewing), leading to an elevated inflammatory state and stimulating increases in the levels of serum inflammatory markers [9].

Thus, locally produced proinflammatory mediators, such as interleukin-1 (IL-1), IL-6, tumour necrosis factor alpha (TNF-α) and prostaglandin E2 (PGE2), move into the systemic circulation and may subsequently exert effects on distant organ systems, as would be the case with other chronic infections or inflammatory processes and resulting in an acute-phase response. Elevated levels of these serum markers and mediators of inflammation have been observed in individuals with periodontitis [10].

Moreover, patients with periodontitis, particularly those with gram-negative organisms such as *Porphyromonas gingivalis, Tannerella forsythia* and *Prevotella intermedia*, have significantly higher levels of C-reactive protein (CRP) and fibrinogen than those without periodontitis. Periodontal treatment not only reduces clinically evident inflammation, but also has been associated with decreases in IL-6, TNF-α and CRP, indicating that periodontal diseases have systemic effects extending beyond the local periodontal environment. Chronic inflammation through the action of inflammatory mediators is mainly associated with the development of insulin resistance, which is influenced by genetically modified environmental factors, including decreased physical activity, poor nutrition, obesity and infection [11].

In the obesity-related model of the development of insulin resistance, activated adipocytes release abnormal levels of bioactive molecules, such as lipids, fatty acids, monocyte chemoattractant protein-1 and various inflammatory mediators (e.g., CRP, plasminogen activator inhibitor-1, TNF-α and IL-6). The release of these cytokines and other mediators results in the local recruitment of monocytes within the adipose tissues. With differentiation of the monocytes into macrophages comes an increase in the release of inflammatory factors and chemokines locally within the adipose tissue but also systemically, such that the inflammatory response is propagated to various tissues, especially to insulin sensitive organs such as the liver and skeletal muscle, thus contributing to overall insulin resistance [12]. One of the earliest studies to link the release of inflammatory substances from adipose tissues to insulin resistance in type 2 diabetes showed that TNF-α, mRNA and protein were induced locally within adipose tissue and systemically in the plasma (Figure 2).

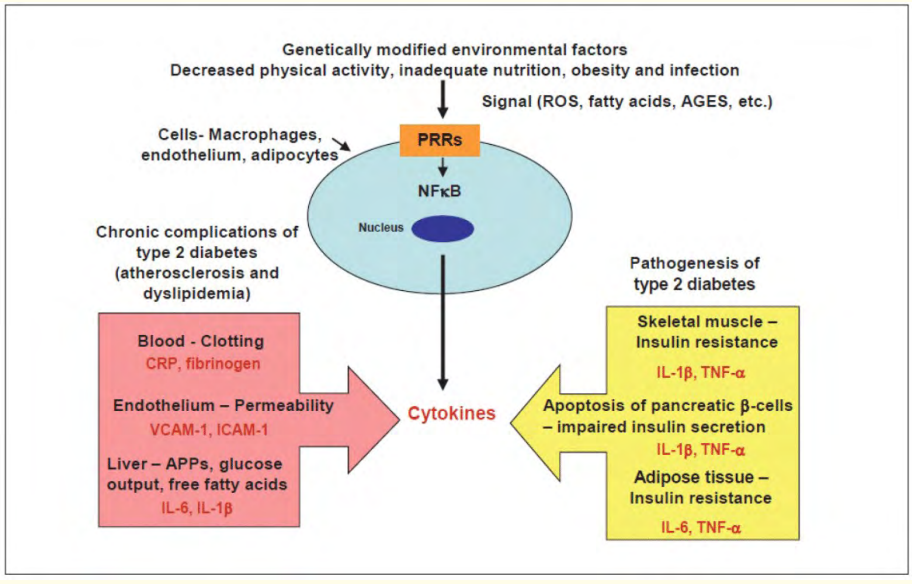

Figure 2: *Innate immunity and type 2 diabetes mellitus.*

When the expression of TNF-α was inhibited in a rodent model (fa/fa) by use of a recombinant TNF-α receptor– immunoglobulin G chimeric protein, insulin sensitivity improved, which suggested that this cytokine has a direct role in the development of insulin resistance. Thus, a mechanism was proposed that links the expression of TNF-α and other inflammatory mediators to the development of insulin resistance in obesity and type 2 diabetes [12].

In this model, receptor ligands, such as inflammatory cytokines, bacterial lipopolysaccharides, lipids, free fatty acids, other microbial products and advanced glycation end products, activate the intracellular pathways, such as the I-kappa-B (IκB), I-kappa-B kinase-β (IKKβ), nuclear factor-kappa B (NF-κβ) and the protein c-Jun N-terminal kinase (JNK) axes.

JNK has been shown to promote insulin resistance through the phosphorylation of serine residues in the insulin receptor substrate. Insulin receptor signalling, which normally occurs through a tyrosine kinase cascade, is inhibited by counter-regulatory phosphorylation of serine and threonine. Unlike JNK, IKKβ causes insulin resistance through transcriptional activation of NF-κB. This protein transcription factor is known to initiate the transcription of a variety of genes for compounds involved in insulin resistance, such as the genes for cytokines (TNF-α, IL-1, IL-6 and IL-8), growth factors, adhesion molecules and acute phase proteins. Activation of IKKβ leads to the phosphorylation of IκB, a cytosolic inhibitor of NF-κB. Phosphorylation targets IκB for ubiquitination and proteasomal degradation, freeing NF-κB to translocate to the nucleus where it regulates the transcription of target genes promoting insulin resistance.

Other cellular stressors may activate these pathways, such as protein kinase C activators and oxidants. Once activated in the tissues, especially in the adipose tissue and associated immune cells, these processes may become self-perpetuating through a positive feedback loop created by the proinflammatory cytokines [12].

Given these mechanisms promoting insulin resistance, it seems that in individuals with type 2 diabetes and periodontitis, an elevated chronic systemic inflammatory state induced by periodontal disease may contribute to insulin resistance through a “feed-forward” mechanism, worsening glycemic contro [5,6] (Figure 3).

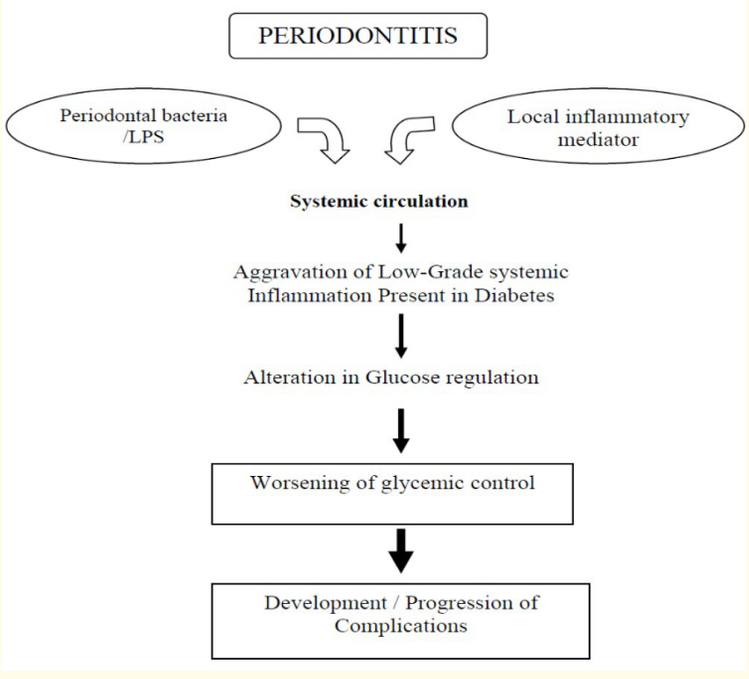

Figure 3: *Potential mechanisms for the influence of periodontitis on the diabetic status (Andersen., et al. 2007).*

This might explain why periodontitis increases the risk of poor glycemic control among patients with type 2 diabetes [5]. Periodontitis may also contribute to the elevation of serum inflammation mediators through enhanced *in vitro* production of TNF-α, IL-1β and PGE2 by monocytes, as has been shown in patients with both diabetes and periodontitis. This may indicate an innate hyperresponsiveness of these monocytes to periodontal bacterial challenge [1,6,7]. Periodontitis may also play a role through the translocation of gram-negative species and their products from the periodontal biofilm into the circulation and through direct cytokinemia from the gingival crevicular fluid (i.e., translocation of cytokines from the periodontal space into the circulation) [13].

With regard to the last of these mechanisms, poorer glycemic control was associated with increased levels of cytokines, especially IL-1β, in the gingival crevicular fluid [14]. In individuals with type 2 diabetes and periodontitis, serum levels of TNF-α were significantly correlated with the severity of periodontal destruction, plasma endotoxin and IL-1β levels in the gingival crevicular fluid, but not with body mass index (BMI), serum glucose or hemoglobin A1c (HbA1c) levels. Furthermore, there was a dose–response relationship between the severity of periodontitis and serum TNF-α levels, which suggested that periodontal disease may play a major role in elevating levels of this cytokine, which is closely linked to insulin resistance [13].

An examination of NHANES III data from participants without diabetes revealed a positive association between BMI and clinical attachment loss. Moreover, those in the highest quartile of body mass (BMI ≥ 30.8 kg/m^2) had significantly higher serum levels of TNF-α and soluble TNF-α receptors than those in the lowest quartile of body mass (BMI < 24.6 kg/m^2). These data suggest that obesity is associated with both systemic inflammation and periodontal disease and that insulin resistance may mediate this relationship [15].

Specific Molecules in the Interaction

The strongest relationship was found between the intensity of periodontal pathology markers and the activity of β-glucuronidase of neutrophilic leukocytes in patients with type 1 DM and periodontitis. It was speculated that if periodontal impairment is severe, DM possibly causes a faster destruction of periodontal tissues, increasing the risk of periodontitis.

Diabetic patients exhibited significantly higher mean salivary levels of alkaline and acid phosphatase, osteopontin, and osteocalcin than healthy controls [16].

Substance P, a potent proinflammatory neuropeptide present in sensory neurons, is important in initiating and sustaining inflammation. Serum substance P levels were higher in the poorly-controlled diabetic group than in well-controlled patients; within the poorly-controlled group, patients with severe attachment levels had the highest circulating substance P levels [17].

Lipid peroxidation (LPO) evaluated by malondialdehyde in plasma and GCF is increased in diabetes and may be related to modulation of inflammatory response. Significant correlations between LPO markers and periodontal parameters suggest a direct relationship between these two entities [18].

Plasma adrenomedullin level is elevated in pathophysiological conditions such as arterial hypertension, acute coronary syndrome, renal diseases, DM and periodontal diseases. The periodontal clinical indices were higher in Type 2 DM patients with/without periodontitis than the non-diabetic control groups. Chronic periodontitis and type 2 DM group had significantly higher total adrenomedullin level [19].

Human β-defensins (hBD-1 and hBD-3) have strong antibacterial action against various microorganisms, especially periodontal pathogens. Patients with type 2 DM and chronic periodontitis had worse clinical periodontal parameters, they also had significantly higher GCF levels of total hBD-1 and hBD-3 than systemically healthy patients with periodontal disease [20].

Toll-like receptor (TLR) 2, 3, 4, and 9 levels in gingival tissue were higher in individuals with diabetes, possibly due to an exacerbated inflammatory reaction. Levels of osteoclastogenesis-related factors (soluble receptor activator of nuclear factor-kappa B ligand [sRANKL] and osteoprotegerin [OPG]) have been evaluated in GCF from poorly or well-controlled type 2 diabetes and chronic periodontitis before and after periodontal therapy. Levels of sRANKL and RANKL/OPG ratios were higher in poorly-controlled group at baseline and after therapy [21].

Visfatin which is secreted by the adipocytes of the body, is a human pre-B cell colony-enhancing factor and induces the production of IL-1β, TNF-α, and IL-6 during infection and inflammation. The mean visfatin concentration was increased in both serum and GCF in type 2 DM patients with chronic periodontitis [22].

Diabetes Induce Periodontitis and Bone Loss

Anaerobes bacteria are the dominating pathological bacteria of periodontitis. Periodontal bacteria and secretion leading to inflammatory response resulted in periodontal tissue breakdown. Alveolar bone has the ability for bone remodelling and regeneration. Bacterial plaque accumulated on the tooth surface can stimulate the host response in the adjacent gingival and resulted in the destruction of periodontal tissue, and periodontal bone loss is the critical characters of periodontitis. Periodontal bone loss appeared when the bone absorption exceeds new bone formation. Diabetic represented inflammatory response result of hyperglycemia. A study showed that T1DM reduced the formation of new bone and decreased bone mineral density leading to osteopenia. The impact of T1DM on bone is reflected by a significant delay in fracture healing. Both T1DM and T2DM increased the risk of periodontitis 3 to 4 times [23].

There is reduced fracture healing or osseous repair after marrow ablation in diabetics compared with normal's. Bacterial insuling can induce the apoptosis of bone-lining cells and diabetes had an intense effect on apoptosis of bone-lining cells. Bone surfaces in diabetic mice are lined by fewer cells than bone in normal and the increased apoptosis of bone-lining cells decreased the bone formation. The soft tissue wounds in diabetic mice indicated that they had increased levels of apoptosis, and the influence of diabetes on apoptosis of matrix-producing cells and limiting the repair of injured tissue. Tuominen indicated that the reduced bone mass in T1DM had a higher bone loss and a profound effect on bone remodeling than T2DM. An inflammatory stimulus in animal model of T2DM showed the inhibition of osteoclastogenesis represented reducing new bone formation [23].

The mechanisms of hyperglycemia on periodontitis described as following. Firstly, hyperglycemia leading to increase gingival crevicular fluid influences the microbial flora such as biofilm and accelerates the inflammatory processes in the mouth and alters the immune response of the periodontal bacteria infectious leading to the breakdown of perodontium. Secondly, hyperglycemia increases the sensitivity of bacteria to diabetes patients and alters the chemotaxis and adherence to neutrophil resulting in producing much inflammatory cytokine.

Hyperglycemia increased the levels of AGEs leading to pathological biochemical processes such as glycation of protein-like collagens or lipids and non- enzymatic oxidative destruction. AGEs can influence normal protein functions directly or act by reacting with receptors indirectly on the different cell membrane. The glycated products had the potential to create molecular complexes reducing the solubility of the target protein- like collagens and alter the functional properties of type 1 collagen and lamina. Interactions between AGEs and receptors mediated the expression of cytokines and growth factors by macrophages. Inflammatory responses induced by AGEs contribute to systemic degradation of periodontal tissue in diabetic patients [23].

Blockade of receptors for the AGEs reduced alveolar bone loss and the effects of oxidative stress by blocking the activation of innate immunity may be used to treat periodontitis. Thirdly, increased inflammatory cytokines and secretion resulted in insulin resistance and in turn caused periodontal infection stimulate immune activity cell to release a number of inflammatory cytokine TNF1α and IL-1. TNF1α

inhibited phosphorylation of insulin receptor and lessen the sensitivity of insulin leading to insulin resistance. Diabetes mellitus are associated with altered collagen metabolism and increased bacteria pathogenic to periodontal tissue and thereby increased the severity of periodontitis. Matrix metalloproteinase involved in a number of physiological events and as the major option in collagen breakdown and periodontal tissue destruction [23].

Increased levels of matrix metalloproteinase 8 and 9 in the gingival tissue of diabetic with periodontitis suggested that expression of matrix metalloproteinase's contributes to failure of the healing in the diabetic. Periodontal therapy could improve tissue healing in chronic periodontitis by inhibition of matrix metalloproteinase. Periodontitis with diabetics enhanced susceptibility to infection due to diminished neutrophil recruitment and function and increased formation of inflammatory cytokines and delayed wound healing after bacterial inbreak. Bone loss increased because the effects of diabetes inhibited new bone formation and the apoptosis of bone lining cells increased. Enhanced expression of cytokines *in vitro* is capable of stimulating bone absorption in diabetics and enhanced inflammation and bone absorption may increase risk and severity of periodontitis with diabetes [23].

Mechanisms of Diabetic Influence on Periodontium

A number of possible mechanisms have been proposed by which diabetes may affect the periodontium. These mechanisms are primarily related to the alterations in subgingival microbiota, GCF glucose levels, periodontal vasculature, host response, and collagen metabolism. While early studies showed possible differences in subgingival bacterial colonization between diabetic and nondiabetic patients with periodontitis, more recent research has demonstrated few differences. Periodontally diseased sites in diabetic patients harbor similar species as comparable sites in nondiabetic individuals [24,25].

This lack of significant differences between diabetic and nondiabetic individuals in the primary bacterial etiologic agents of periodontal disease suggests that the increased prevalence and severity of periodontitis in diabetes may be due to differences in host response factors. Increased blood glucose levels in diabetes are reflected in increased levels of GCF glucose [25].

In vitro studies show decreased chemotaxis of periodontal ligament fibroblasts to PDGF when placed in a hyperglycemic environment compared with normoglycemic conditions. Thus, elevated GCF glucose levels in diabetes may adversely affect periodontal wound healing events and the local host response to microbial challenge. Changes affecting the renal, retinal, and perineural vasculature in diabetes also occur in the periodontium. Increased thickness of gingival capillary endothelial cell basement membranes and the walls of small blood vessels may be seen in diabetic individuals [26].

This thickening may impair oxygen diffusion and nutrient provision across basement membranes. Increased thickness of small vessel walls results in narrowing of the lumen, altering normal periodontal tissue homeostasis. The formation of AGEs occurs in the periodontium as it does in other tissue sites. Schmidt and colleagues have demonstrated a two fold increase in AGE accumulation in diabetic gingiva compared with gingiva from nondiabetic subjects. Increased oxidant stress was also noted in diabetic tissues. Enhanced oxidant stress has been targeted as the underlying mechanism responsible for the widespread vascular injury associated with diabetes. The formation of AGEs stimulates arterial smooth muscle cell proliferation, increasing thickness of vessel walls.

In the capillaries, enhanced cross-linking of AGE-modified collagen in the basement membrane inhibits the normal degradation of these proteins, increasing the thickness of the basement membrane. Higher levels of LDL, especially seen in type 2 diabetes patients, may cause alterations in the gingival vasculature [27].

The AGE modified arterial collagen in gingival blood vessel walls can bind circulating LDL, resulting in atheroma formation and further narrowing of the vessel lumen. All these events may play a role in altering the tissue response to periodontopathic bacteria, resulting in

increased severity and progression of periodontitis. Altered host defenses have long been considered important in the pathogenesis of periodontitis associated with diabetes.

In some diabetic individuals, the defects in polymorphonuclear leukocyte (PMN) adherence, chemotaxis, and phagocytosis have been observed. Many of these PMN abnormalities can be corrected with improved glycemic control. Defects affecting this first line of defense against subgingival microbial agents may result in significantly increased tissue destruction. The function of PMNs in normal in most of the diabetic patients. Oliver and colleagues have even suggested hyper-responsiveness or increased numbers of PMNs within the gingival crevice of poorly controlled diabetic patients as indicated by elevated levels of the PMN-derived enzyme β-glucuronidase [28].

The monocyte/macrophage cell line is critical to cell-mediated host defense in periodontal diseases. Studies suggest that many diabetic patients possess a hyper-responsive monocyte/macrophage phenotype in which stimulation by bacterial antigens such as lipopolysaccharide (LPS) results in dramatically increased proinflammatory cytokine production.

Salvi and colleagues have demonstrated significantly increased production of proinflammatory cytokines by monocytes derived from patients with diabetes compared with nondiabetic subjects. The levels of TNF- α produced in response to LPS from the periodontal pathogen *P. gingivalis*, by the diabetic monocytes were 24 to 32 times the level seen when compared with nondiabetic monocytes. Also, the LPS-stimulated monocyte production of PGE2 and IL-1β increased four folds in diabetic subjects than in nondiabetic subjects [29].

The gingival crevicular fluid levels of PGE2 and IL-1b were significantly higher in diabetic patients with periodontitis than in nondiabetic subjects with a similar degree of periodontal destruction.

It is likely that there is a genetic component to the development of a hyper-responsive monocyte/ macrophage phenotype in some diabetic patients. Not all individuals with diabetes have this phenotype. The formation of AGEs also plays an important role in the upregulation of the monocyte/ macrophage cell line. Accumulation of AGEs in the periodontium stimulates influx of monocytes. Once in the tissue, AGEs interact with the receptor RAGE on monocyte cell surfaces. This halts the migration of the monocytes, fixing them at the local site. The AGE-RAGE interaction then induces a change in monocyte phenotype, upregulating the cell and significantly increasing proinflammatory cytokine production. This provides another explanation for increased GCF production of TNF-α, PGE2 and IL-1β noted in diabetic patients with periodontitis. As previously discussed, there is a great deal of heterogeneity in AGE formation within the diabetic population.

Thus, these AGE-associated changes may be present in some patients but absent in others. Those individuals at greatest risk for increased AGE accumulation and its adverse effects are those with poor glycemic control, who may accumulate large deposits of AGEs within target tissues. Similarly, the patient with poorly controlled diabetes is most likely to suffer more rapid and advanced periodontal destruction. However, just as some individuals with poorly controlled diabetes do not develop classic vascular complications of the disease, some such patients have little, if any, significant periodontal disease. The variability in AGE formation may provide some explanation for the variance in risk of periodontal complications of diabetes.

Collagen is the primary constituent of gingival connective tissue and the organic matrix of alveolar bone. Changes in collagen metabolism contribute to alterations in wound healing and to periodontal disease initiation and progression. Proteinases are enzymes involved in matrix degradation. In the periodontium, these matrix metalloproteinases (MMPs) include collagenases, gelatinases, and elastases [30].

The MMP family consists of atleast 12 distinct members, and these enzymes are responsible for the breakdown of bone and connective tissue during periodontal disease. Matrix metalloproteinases are produced by all of the major cell types in the periodontium when activated by various cytokines and growth factors, including PMNs, fibroblasts, macrophages, endothelial cells, osteoblasts, and osteoclasts [30].

Increased collagen breakdown through stimulation of collagenase activity has been observed in the periodontium of diabetic patients. Collagenases primarily degrade more newly formed and, therefore, more soluble collagen macromolecules. Sustained hyperglycemia results in AGE modification of existing collagen, with increased cross-linking. The net effect of these alterations in collagen metabolism is a rapid degradation of recently synthesized collagen by host collagenase and a predominance of older, highly cross-linked, AGE modified collagen. Since collagen production and degradation exist as a highly balanced homeostatic mechanism, changes in collagen metabolism result in altered wound healing in response to physical or microbial wounding of the periodontium. Impaired wound healing is a well-recognized complication of diabetes and may affect any tissue site, including the periodontium. Reduction in host collagenase production can be achieved by tetracycline therapy [1,8,4].

This is accomplished via mechanisms which are independent of the antimicrobial properties of these agents. Low-dose tetracyclines and chemically modified tetracyclines (CMTs), which have no antimicrobial effect, have been shown to significantly decrease collagenase production and collagen degradation.

Although CMTs are not yet available for routine use, tetracyclines such as doxycycline, minocycline, and tetracycline HCl have been used for many years. Low-dose doxycycline is now available as well although its use in diabetic patients has not yet been reported. Due to their anticollagenolytic effect, tetracyclines and CMTs have potential benefits in inhibiting the onset and progression of periodontitis, arthritis, and osteoporosis, among other conditions [31].

In a disease such as diabetes, where collagenase production is significantly increased, these agents may have even greater beneficial effects by normalizing collagen metabolism and wound healing events.

Conclusion

Evidence is emerging to suggest that periodontal disease is associated with increased risk for diabetes complications. Because periodontal diseases are “silent” in nature, most patients do not realize they have such conditions until significant destruction has occurred. Likewise, physicians may not know that their patients have a condition that could alter glycemic control and make diabetes management more difficult. It is important for clinicians to discuss with their diabetic patients the increased risk for periodontal diseases. Treating periodontal infection in people with diabetes is clearly an important component in maintaining oral health. It may also have an important role in establishing and maintaining glycemic control and possibly in delaying the onset or progression of diabetic complications.

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Volume 9 Issue 2 April 2017