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PERIODONTAL DISEASE, INSULIN RESISTANCE, AND DIABETES MELLITUS:

A REVIEW AND CLINICAL IMPLICATIONS

Alan J. Moritz, DDS, MS† and
Brian L. Mealey, DDS, MS‡

Abstract
This review examines the unique relationships between periodontal diseases and diabetes mellitus (DM). Scientific literature related to possible mechanisms of interaction, with a focus on potential common pathophysiologic pathways, including those associated with inflammation, altered host responses, and insulin resistance, is reviewed. Current evidence suggests that insulin resistance may be a major shared metabolic abnormality linking the interaction of periodontal disease and type 2 DM. As insulin resistance in type 1 patients is less prominent, this relationship may be most significant for type 2 patients. A model is proposed by which chronic inflammation resulting from periodontal disease may contribute to increased insulin resistance in type 2 DM, thus worsening glycemic control. Subsequently, a reduction in periodontal inflammation through treatment may possibly result in enhanced insulin sensitivity and better glycemic control. Understanding these processes will allow health care providers to gain further insight into additional features these diseases share: both conditions are ultimately treatable and in many ways preventable.

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Key Words: Periodontal disease, diabetes mellitus, inflammation, insulin resistance, obesity

Introduction

Periodontal disease and diabetes mellitus (DM) are chronic disorders that rely on a major inflammatory component to affect host tissue damage. Both conditions have major impacts on the health and well-being of millions of individuals worldwide. Because these diseases are both ubiquitous and insidious, it is important that health care professionals fully understand the risks that these conditions pose to patients and are able to provide the most relevant, up-to-date treatments grounded in the scientific literature. Although associations between a variety of oral health conditions and chronic systemic diseases have been observed in recent years, an interaction between periodontal disease and DM has been documented most consistently.[1,2] Current evidence suggests that DM is associated with an increased prevalence and severity of gingivitis (inflammation of the gingiva around the teeth) and periodontitis (inflammation and destruction of the tooth-supporting structures of the periodontal ligament and bone).[3,4] Conversely, periodontitis may increase the risk for worsening glycemic control in diabetic patients,[5] as well as increasing the risk for diabetic complications.[6,7]

Epidemiology of Periodontal Disease and Diabetes Mellitus

Advanced periodontal disease with deep pockets and destruction of periodontal ligaments and alveolar bone afflicts approximately 10%-15% of adults worldwide.[8] In the United States, approximately 13% of adults have severe periodontitis, and 35% of those over age 30 have some form of periodontitis.[9] The prevalence of periodontitis in the U.S. is

† Director, Department of Periodontics, 52nd Dental Squadron, United States Air Force, Spangdahlem Air Base, Germany

‡ Associate Professor, Department of Periodontics, Effective June 2006: Head, Specialist Division and Graduate Program Director, University of Texas Health Science Center at San Antonio, TX

greatest in individuals of African and Hispanic descent.[9] Gingivitis is seen in approximately 75% of U.S. adults.[9] Based on epidemiological studies, gingival health in the U.S. appears to be improving at a slow but steady pace because of increased public health awareness of dental disease and improved treatment efforts.[10]

Diabetes represents a huge health problem worldwide. In 2002 in the U.S. alone, approximately 20 million people were estimated to be affected by both diagnosed and undiagnosed DM, representing over 9% of the adult population.[11,12] Type 2 DM is by far more common than Type 1, constituting approximately 85%-90% of cases and may currently affect over 150 million people worldwide.[13] The U.S. prevalence of type 2 DM is greatest in the Native American, Hispanic-American, and African-American populations.[14] In contrast to the improving gingival health trends in the U.S., diabetes incidence has increased at an alarming rate of nearly 500,000 new cases every year from 1998 through 2002, and the rate continues to climb at a staggering pace.[15] Coupled with the estimate that over 6 million people in the U.S. with diabetes are undiagnosed, this is a public health crisis of massive proportions.[15] The documented increase in DM incidence parallels enhanced diabetes screening methods but also is very much coincident with the increasing incidence of obesity in the American population.

The Periodontal Disease–Inflammation Connection

Periodontal diseases are initiated by biofilm infections of the gingival sulcus at the interface of the gingival tissues and the tooth. Over 400 different species of bacteria reside in these plaque biofilms, many of which are gram-negative and anaerobic.[16] With disease onset, the sulcus transforms into a pathologically deepened pocket, where a delicate balance is struck between the bacteria and the host's immune system, which attempts to destroy them. The bacteria directly invade the soft tissues or release their toxic products, including endotoxins from the cell walls of gram-negative bacteria, chemotactic peptides, organic acids, and protein toxins, into the pocket, causing inflammation.[17] As the pocket epithelium proliferates in response to the ongoing inflammation and becomes ulcerated, the compounds released from the biofilm readily enter the gingival tissues and further stimulate the host's immune response. Significantly, the majority of the destruction seen in periodontal disease results from this stimulation of the immune system and the exuberant host inflammatory response, which leads to the activation of host enzymes.[17] These compounds, produced by many different immune cells but most notably from monocytes (tissue macrophages), include proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), IL-6, and prostaglandin E_2 (PGE_2).[18] These compounds influence multiple inflammatory processes, including recruitment and chemotaxis of neutrophils, increased permeability of gingival blood vessels, and bone resorption.

Perhaps more significantly, however, the ulcerated pocket epithelium may serve as an entry portal for these bacteria, their byproducts, and host-derived cytokines into the systemic circulation, from where they have the potential to exert effects throughout the body. In untreated severe periodontal disease, the cumulative surface area of ulcerated pocket epithelium has been estimated to be from 8 to 20 cm^2 (approximately 3 in^2 or about the size of the palm of a hand).[19,20] In these patients with severe disease, bacteremia can be induced by dental procedures as well as by normal daily activities like chewing.[21] In one study, chewing was shown to cause systemic endotoxemia in 40% of patients with periodontitis compared with only 12% of periodontally healthy patients, and the concentration of endotoxin in the bloodstream was 5 times higher in those with periodontitis.[22] Thus, the effects of inflammation can spread from the localized periodontal lesion into the systemic circulation.

Serum inflammatory markers are elevated in the peripheral blood of patients with periodontitis. Periodontal inflammation may directly increase the concentrations of these substances in the blood or indirectly stimulate their formation as part of the acute-phase response.[23] Acute-phase reactants are proteins produced in the liver during the innate immune response to bacterial challenge and serve a variety of proinflammatory functions, including complement activation, bacterial phagocytosis, and stimulation of tissue repair and regeneration.[24] Acute-phase proteins such as C-reactive protein (CRP), serum amyloid A, and fibrinogen appear not only in acute disease processes but also in chronic diseases. These proteins also may have deleterious effects on end organs. CRP, which along with fibrinogen is an accepted risk factor for major cardiovascular events, may exert its effects by modulating coagulation and atherosclerosis.[25,26] Studies have further suggested that periodontitis patients harboring *Porphyromonas gingivalis (P. gingivalis)*, *Tannerella forsythia*, and *Prevotella intermedia*, all highly virulent gram-negative bacteria, have significantly higher serum levels of CRP, IL-6, and fibrinogen than patients with-

out periodontitis.[23,27,28] Periodontal treatment decreased serum levels of IL-6 and CRP in intervention trials, and the decrease was greatest in patients who had significant clinical reductions in periodontal inflammation.[29] Those who showed little clinical improvement in periodontal parameters after treatment also showed little change in serum acute-phase reactant levels. Thus, localized periodontal inflammation has the potential to perpetuate a chronic systemic inflammatory state, which may impact other inflammation-related conditions in the body, such as DM.

Diabetes Mellitus and Insulin Resistance

Diabetes mellitus comprises a clinically and genetically diverse group of hormonal diseases that are characterized by alterations in carbohydrate, protein, and lipid metabolism, the primary manifestation being abnormally high blood-glucose levels.[30] This hyperglycemia is attributed to a lack of insulin secretion by the pancreas, a reduction in insulin activity, or a combination of both. The resultant elevated systemic glucose levels affect almost all organs in the body, including the cardiovascular system, eyes, nerves, kidneys, and the periodontium.

Type 1 DM comprises about 5%-10% of all cases and usually has an early age of onset. Type 1 DM results from autoimmune destruction of the β-cells of the pancreas, which renders the patient incapable of producing endogenous insulin.[31] Without adequate insulin to allow glucose from the bloodstream to enter cells, cellular starvation takes place at the same time glucose levels build up in the bloodstream. Fat then is broken down through lipolysis as the body seeks a secondary energy source. Large amounts of free fatty acids accumulate in the bloodstream and are converted into ketones, which may result in ketoacidosis, a potentially life-threatening condition.

Type 2 DM, the most common form, results from altered insulin action on cells. Unlike patients with type 1 DM, patients with type 2 DM retain the ability to produce some insulin, although this production decreases with disease duration. Diabetic ketoacidosis is uncommon in type 2 DM because enough endogenous insulin is produced to keep ketone formation low. In patients with type 2 DM, increasing cellular energy demands cause insulin receptors to be displayed on the surface of nearly all cells (except brain cells), which facilitates glucose loading from the bloodstream into the cells. However, certain events, such as acute bacterial or viral infections, can cause cells to become insulin-resistant, resulting in increased pancreatic insulin production in an effort to force glucose into the cells.[32] This insulin resistance represents the major underlying pathophysiologic abnormality of type 2 DM and differentiates it from type 1 DM. In type 1 DM, insulin resistance plays much less of a role in the pathogenesis of disease, but insulin resistance associated with illness or infection can make type 1 DM more difficult to control as well. Even after the resolution of the acute illness, tissues may remain resistant to insulin for many weeks or months, further exacerbating the diabetic condition.[33,34] With persistent infection and after oral glucose intake, hyperglycemia and hyperinsulinemia develop. These are the hallmarks of insulin resistance and are associated with the many systemic complications of diabetes, including blindness, kidney failure, myocardial infarction (MI), stroke, infection, and the need for limb amputation.[35]

As noted earlier, the increase in type 2 DM incidence parallels an increase in obesity, with more than 30% of U.S. adults being obese.[36] Obesity, defined as body mass index (BMI) >30 kg/m^2, is a major risk factor for both type 2 DM and cardiovascular disease (CVD).[37] Adipocytes are highly metabolically active cells and produce various substances important in energy regulation in the body. These include cytokines such as TNF-α, which contribute to insulin resistance by inhibiting cell surface insulin receptor action through the suppression of tyrosine-kinase phosphorylation of insulin receptor substrate-1 (IRS-1), thereby blocking the translocation of glucose-transporting proteins.[38,39] Additionally, elevated serum levels of free fatty acids produced by adipocytes may contribute to insulin resistance by lowering glucose uptake, synthesis of glycogen, and glycolysis, and by raising hepatic glucose production.[40] With weight loss, insulin resistance often improves but usually does not return to normal.

Gestational diabetes occurs in approximately 4% of all pregnancies in the U.S.,[41] usually with onset in the third trimester. Similar to type 2 DM, gestational diabetes is associated with insulin resistance. Proper diagnosis and management significantly improve pregnancy outcomes. After delivery, most patients return to a normoglycemic state; however, women with a history of gestational diabetes have a significantly increased chance of developing type 2 DM later in life.

Insulin resistance has been implicated as a key factor in the development of the metabolic syndrome, a condition that may effect at least 1 in 5 overweight people.[42] Patients with this syndrome, also known as the "insulin

resistance syndrome," present with several disorders of metabolism, including obesity, hypertension and hyperlipidemia. This syndrome may raise the risk for diabetes and cardiovascular events.[26] A 2-year study of 750 patients showed that subjects with metabolic syndrome were >2.5 times more likely to suffer from stroke, chest pains, MI, or heart failure,[43] but questions remain as to whether this indeed constitutes a true syndrome.[44] It is not clear whether metabolic syndrome represents a greater risk for CVD than any of its component parts, all of which require treatment.

Short of overt diabetes lie the pre-diabetic conditions known as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), which together affect over 40 million Americans.[15,45] Insulin resistance underlies both conditions, with endogenous insulin secretion being relatively normal. Patients with IFG are hyperglycemic during periods of fasting, with serum glucose levels returning to normal after eating. Those with IGT become hyperglycemic after glucose intake, but are otherwise normoglycemic. Both conditions are significant risk factors for future development of type 2 DM, and IGT has also been identified as a risk factor for MI and stroke.[46]

Periodontal Disease: Potential to Impact Metabolic Control of Diabetes Mellitus

As noted earlier, acute infections may increase insulin resistance and thereby reduce metabolic control in DM. Periodontal diseases have the potential to cause a chronic systemic inflammatory state,[20] and chronic gram-negative periodontal infections increase insulin resistance and negatively impact glycemic control.[47] In a 2-year longitudinal study of type 2 DM subjects, patients with severe periodontitis were at 6 times greater risk for worsening of glycemic control over time than patients without periodontitis, a finding attributed to increased insulin resistance.[5]

Additional evidence for an association between periodontal disease and metabolic control of diabetes comes from studies evaluating other diabetic complications. In a case-control study over a period of 11 years, 82% of patients with diabetes and severe periodontitis had 1 or more macrovascular complications, such as angina, MI, heart failure, transient ischemic attack, and stroke.[6] Only 21% of DM patients without periodontitis had macrovascular complications. A more recent prospective longitudinal trial of 628 patents examined the effect of periodontal disease on overall as well as CVD mortality in patients with type 2 DM.[7] After adjusting for other common risk factors, it was found that patients with severe periodontal disease had a death rate from ischemic heart disease 2.3 times higher, and a death rate from diabetic nephropathy 8.5 times higher, than patients with mild, moderate, or no periodontal disease. These findings parallel data from several studies suggesting that periodontal disease may be a significant independent risk factor for atherosclerosis-mediated events such as MI and stroke.[48-50]

The best evidence for evaluating the influence of periodontal disease on metabolic status comes from intervention trials evaluating the effects of periodontal treatment on glycemic control. These studies are heterogeneous, and it is important to examine them in light of their limitations, including small sample sizes, mixing of type 1 and type 2 DM patients, confounders such as smoking and body mass index, and varying methods of assessing glycemic control. Nevertheless, the studies suggest that periodontal therapy may have a positive effect on glycemic control in DM. More than 45 years ago, periodontal therapy consisting of systemic antibiotics, extraction of hopeless teeth, scaling and root planing, and limited gingivectomy was shown to reduce the insulin requirements of subjects with type 1 DM.[51] These results have been corroborated in a prospective fashion more recently.[52] Scaling and root planing alone have also been shown to significantly improve glycemic control in patients with type 2 DM,[53,54] although other studies have shown improved periodontal conditions but no improvement in glycemic control in both type 1 and 2 DM patients.[55,56] Several studies have demonstrated that scaling and root planing in combination with systemic tetracycline antibiotics, most notably doxycycline, improve glycemic control in type 1 and type 2 DM patients.[57-59] Tetracyclines are increasingly used as an adjunct to mechanical treatment of periodontal disease in DM patients because they reduce production of matrix metalloproteinases, in particular the enzyme collagenase, which is known to be produced to a greater degree in DM patients.[60] In these studies, clinically and statistically significant decreases in glycated hemoglobin (HbA1c) from baseline paralleled a reduction in periodontal inflammation. The best results were seen in patients with the poorest diabetic control and with the most advanced periodontitis. However, this has not been replicated in all studies, and recently a study in patients with poorly controlled type 2 DM showed only a nonsignificant reduction in glycemic control, although periodontal parameters improved significantly.[61]

Perhaps the best reflection of the current knowledge comes from a recent meta-analysis of 10 intervention trials showing that periodontal therapy without antibiotics reduced HbA1c levels 0.4% from baseline on average, and the addition of systemic antibiotics resulted in an average reduction of 0.7%, neither of which reached statistical significance.[62] Although the studies to date are conflicting, it appears that periodontal treatment may have the ability to influence glycemic control in some patients, and those with poorer diabetic control and severe, generalized periodontitis are likely to benefit the most.

The exact mechanisms by which a reduction in periodontal inflammation following treatment may affect insulin resistance and glycemic control are not well established. It has been noted that local as well as systemic dissemination of inflammatory mediators, most notably the cytokines TNF-α and IL-6, may increase insulin resistance. IL-6 itself acts to further stimulate TNF-α production, which may lead to additional insulin resistance. Chronic periodontal infection can contribute to insulin resistance by up-regulating these cytokines.[63] In addition, monocytes from DM patients produce up to 32 times more TNF-α than monocytes from patients without DM when stimulated by periodontal pathogens, leading to higher systemic cytokine levels.[64]

Obesity is a risk factor for type 2 DM and also may be a potential risk factor for periodontal disease.[65,66] Obesity was shown to be associated with periodontal disease in a cohort study of 241 patients, where the additional risk for periodontitis was 3-fold higher in patients with BMI 25 to 29.9 kg/m^2 than in patients with BMI ≤20 kg/m^2.[ref 65] Patients with BMI ≤30 kg/m^2 had an 8.6-fold higher risk than controls. A recent study using data from 12,367 subjects in the National Health and Nutrition Examination Survey (NHANES III) showed that insulin resistance appears to mediate this relationship,[47] which may begin to explain the association between periodontal disease and DM. The study further suggested that high plasma TNF-α levels associated with enhanced adipocyte secretion in obesity may account for further increases in insulin resistance. A model was proposed in which increased cytokine levels, along with additional cytokine production triggered by advanced glycation end products (AGE) in DM patients, create a systemic hyperinflammatory state and prime the periodontal tissues to respond in an exaggerated manner to infecting microorganisms. Further data are needed to substantiate this theory. However, periodontal therapy not only reduces local inflammation and cytokine levels but also reduces TNF-α levels systemically, and this correlates with a significant improvement in glycemic control in patients with type 2 DM, with a significant reduction in HbA1c levels from 8.0% to 7.1%.[67] Further work is needed to determine exactly how periodontal treatment and the subsequent reduction in periodontal inflamma-

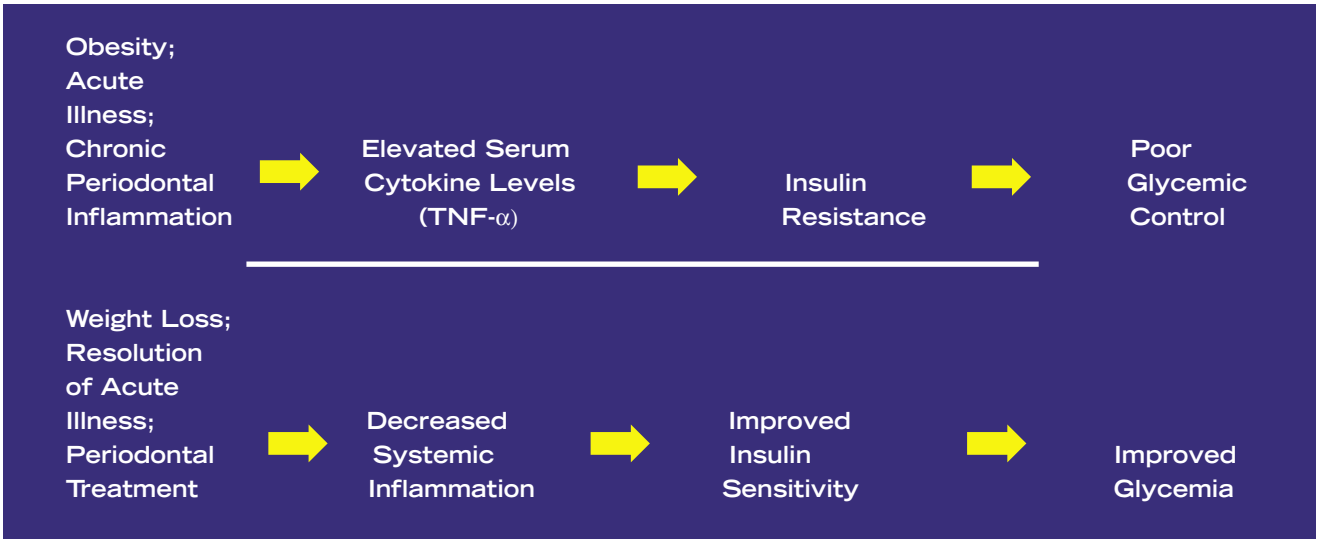

Figure 1 – Proposed model for effects of inflammation, infection, and obesity on glycemic control

Obesity, acute illness (such as upper respiratory tract infection), or chronic periodontal inflammation may result in a state of systemic inflammation, with increased serum levels of cytokines, such as TNF-α, that cause an increase in insulin resistance. The result is worsening of glycemic control. Weight loss, resolution of an acute illness, and periodontal treatment that reduces inflammation may improve the systemic inflammatory status of the patient, resulting in enhanced insulin sensitivity and better glycemic control.

tion may reduce insulin resistance and thus lead to improved glycemic control.[38]

Diabetes Mellitus: Potential to Impact Periodontal Disease Severity

Diabetes mellitus has long been known to have a significant influence on the periodontium and is viewed as a risk factor for both gingivitis and periodontitis, although it is clear that not all patients with DM have periodontal disease. The relationship seems highly dependent upon the level of glycemic control.[68] Just as DM patients with poor control are more likely to exhibit retinopathy, neuropathy, and nephropathy, they are also at greater risk for destructive periodontal disease. The current periodontal disease classification lists "diabetes mellitus-associated gingivitis" as a distinct disease entity.[69] Although there is no distinct diabetes-associated periodontitis in the current classification, uncontrolled or poorly controlled DM is considered a modifier of preexisting periodontitis that adjunctively enhances its severity.

Both children and adult patients with DM tend to have more plaque-induced gingivitis than healthy individuals, although this has not been shown in all studies.[70] Given similar levels of plaque accumulation, gingivitis is more prevalent and severe in type 1 and type 2 DM patients than in non-diabetic controls,[71-73] with significantly more gingivitis seen in patients with poorly controlled DM than in those with well-controlled DM or without DM.[73-76] Supporting this relationship, gingival inflammation tends to subside as glycemic control improves.[52,75,76] More recently, a study of experimental gingivitis in type 1 DM patients found that even patients with relatively well-controlled DM develop gingivitis more readily than non-diabetic individuals because of a hyperinflammatory immune response, despite similar plaque levels and bacterial composition,[77] again implicating the systemic inflammation present in the diabetic state as an etiology for periodontal disease.

Most evidence also suggests that type 1 and type 2 DM increase the risk of periodontitis. Of 21 epidemiological studies in children, adolescents, and adults with type 1 DM, 95% found a greater prevalence, severity, or extent of periodontal destruction in DM patients than in non-DM controls.[78] Age is a factor in the prevalence of periodontitis: type 1 DM did not affect prevalence in subjects under age 12; however, during adolescence and middle age, the prevalence increased more in DM patients than in controls.[71] Another systematic review and meta-analysis examining over 3,500 adult DM patients found that patients with DM had more severe periodontitis than those without DM in the majority of studies.[4] In large epidemiological studies of the Pima Indians of Arizona, who have the world's highest prevalence of type 2 DM,[79,80] patients with DM had a risk for developing periodontitis that was about 3 times higher than the U.S. average. Other studies of DM patients corroborate the greater extent and severity of periodontal destruction in these patients versus non-DM controls when all other risk factors are taken into account.[81,82] This higher prevalence and severity of periodontitis may also put these patients at higher risk for continued progression of periodontal destruction,[83] with type 2 patients having up to a 4-fold greater risk of progressive periodontal bone loss than non-DM control patients.[84]

As with gingivitis, the association between DM and increased risk for the development and progression of periodontitis appears to be related to the level of glycemic control. Although the evidence is not complete,[68] longitudinal studies have shown that patients with poorly controlled type 2 have 2.9 times the risk of periodontitis[85] and 11 times the risk of progressive bone loss[84] that non-DM patients have, whereas patients with well-controlled DM have no increased risk for periodontal morbidity. DM patients with poor or worsening control suffer greater increases in pocket depths, attachment loss, or bone loss than patients with well-controlled or relatively well-controlled DM.[82,86-90] Other studies have shown nonsignificant associations between diabetic control and periodontal parameters,[91,92] and some older studies found no relationship at all.[93,94] The varied results may reflect improvements in treatment and assessment methodologies over the years, although many patients with poorly controlled DM have no major complications,[95-97] just as good glycemic control is not a guarantee against developing periodontitis.

The association between glycemic control and periodontitis may parallel the relationship between DM and other classic complications. In the Diabetes Control and Complications Trial (DCCT), 1,441 type 1 DM patients on a tight glycemic control regimen had less retinopathy, nephropathy, and neuropathy over 6.5 years than DM patients using conventional glycemic-control methods.[95] Subsequently, similar reductions in the risk of diabetic complications have been shown in over 5,000 intensively-managed type 2 patients.[96,97]

The proposed mechanisms by which diabetes may affect the periodontium also parallel the pathophysiological routes by which diabetes can result in classic diabetic complications. Because of this, some have suggested that periodontitis be included as the "sixth complication of diabetes" along with retinopathy, neuropathy, nephropathy, macrovascular diseases, and altered wound healing.[98] The main influences of DM on periodontal disease appear to be related to alterations in host immunoinflammatory reactions and tissue homeostasis. Diabetes alters the function of immune cells directly involved in the host's response to periodontal infection, such as neutrophils, monocytes, and macrophages.[99] Neutrophils, the first line of immune cell defense in the periodontal pocket, demonstrate reduced adherence, chemotaxis, and phagocytosis in diabetic patients.[100,101] Diabetic patients with severe periodontitis have less neutrophil chemotaxis than patients with DM and mild periodontitis or non-DM patients with severe periodontitis.[100,102] The result is reduced bactericidal activity, which favors increased bacterial proliferation and may enhance periodontal inflammation and destruction.

In contrast to down-regulated neutrophil activity, monocytes and macrophages in DM patients are hyperresponsive to periodontal infection, resulting in increased production of proinflammatory cytokines, especially IL-1β, TNF-α, and PGE_2.[64,103,104] Potent bacterial products in the periodontal lesion, such as *P. gingivalis* endotoxin, enhance TNF-α production significantly more in peripheral blood monocytes from DM patients than in monocytes from non-DM patients.[64]

The increased response of monocytes and macrophages from DM patients may be related to the interaction of elevated levels of AGE in the periodontium with AGE receptors on these immune cells.[105] AGEs, such as non-enzymatically glycated proteins, lipids, and nucleic acids, form in direct relationship to glucose concentration and time in the hyperglycemic environment. Besides playing a significant role in diabetic complications, AGEs modify extracellular matrix activity and cell-matrix interactions.[105,106] AGEs and cytokines also are able to enter the gingival crevicular fluid, a serum transudate, in elevated quantities when serum levels increase.[104] Cytokine levels of IL-1β in gingival crevicular fluid also increase with worsening glycemic control.[107] AGEs in gingival crevicular fluid may induce changes in the periodontium, such as elevation of oxidant stress, that may lead to vascular injury, and together with elevated cytokine levels, may increase the risk that poorly controlled DM patients will suffer from accelerated periodontal tissue destruction.[108]

Just as inflammatory mediators alter gingival crevicular fluid composition, excess serum glucose also may enter periodontal pockets in hyperglycemic patients.[109,110] At one time, this was thought to change the subgingival microbiota of DM patients and to be a possible explanation for increased periodontal destruction. However, most studies have demonstrated no real differences in the subgingival microbiota between DM and non-DM patients with gingivitis or periodontitis.[78,111-113] Nevertheless, an increased glucose concentration in the gingival crevicular fluid has been shown to prevent attachment and spreading of fibroblasts and may thus impact periodontal wound healing.[114]

Blood vessel alterations secondary to AGE accumulation are evident in the periodontium and may contribute to the classic macrovascular and microvascular complications of DM.[115,116] AGEs produced in the periodontium of DM patients may form on collagen resulting in increased collagen cross-linking. This results in highly cross-linked collagen macromolecules with reduced solubility that accumulate in the walls of periodontal blood vessels, binding low-density lipoprotein and leading to atheroma formation and vessel lumen reduction.[99] Vascular smooth muscle cells proliferate in the presence of AGEs and increase vessel wall thickness. In addition, because the basement membranes of capillaries also are thickened by AGE accumulation, oxygenation and perfusion of nutrients from the vasculature into the periodontium are reduced.[108] These changes result in decreased tissue vascular supply and ultimately may affect the progression of periodontitis and the potential for homeostatic repair.

In diabetes, collagen metabolism is significantly disrupted, which affects tissue homeostasis and wound healing. AGE modification of collagen in the periodontium inhibits normal tissue turnover.[108] In addition, formation of new collagen is reduced and matrix metalloproteinases such as collagenase are elevated, resulting in a fundamental alteration in wound-healing capacity.[117,118] Neutrophils appear to be the primary source of collagenase in the gingival crevicular fluid of DM patients, whereas in non-DM patients most collagenase is derived from fibroblasts,[119] and more of the collagenase in DM patients is in the active form.[119] Importantly, the solubility of collagen can be returned to near-normal with insulin treatment and normal glycemic control.[120,121]

Conclusion and Treatment Considerations

Although treatment of DM and periodontal disease is covered in detail in other articles in this publication, some general considerations in the clinical management of DM and periodontal diseases can be made based on the pathophysiological interrelationships discussed in this article. Diabetes mellitus and periodontal diseases are chronic, treatable conditions, although neither has a cure, and each requires long-term follow-up and reinforcement for maximum treatment results. From the medical side, all patients diagnosed with and treated for DM should be routinely referred to a dentist to evaluate their periodontal condition as part of the overall treatment for DM. Physicians should be aware of the potential impact of periodontal inflammation on achieving ideal glycemic control and should concern themselves with their patients' periodontal status. Medical providers should also educate their DM patients about the potential role of conditions affecting insulin resistance, including periodontal diseases, and the importance of controlling such conditions.

Dentists should screen a patient's medical history for the possibility of DM; order or refer the patient for appropriate laboratory tests to verify glycemic status when needed; and refer the patient to medical providers for definitive diagnosis and treatment, if indicated. Dental professionals should educate their DM patients that the control of blood glucose is important in establishing and maintaining periodontal health and that periodontal health has the potential to enhance glycemic control. Excellent oral hygiene and consistent compliance with dental examinations and preventive care should be emphasized to these patients as the keys to achieving overall health.

Finally, patients with DM and periodontal disease must endeavor to educate themselves about their conditions and must work closely with their healthcare providers to control these chronic diseases. Patients should strive to achieve maximal glycemic control through diet, exercise, medications, and periodontal health in order to realize the best possible outcomes.

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