

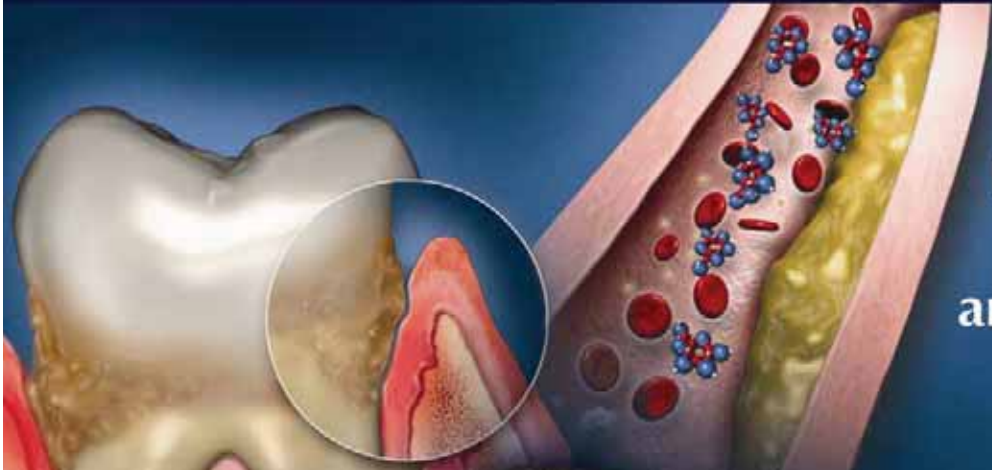
GRAND ROUNDS

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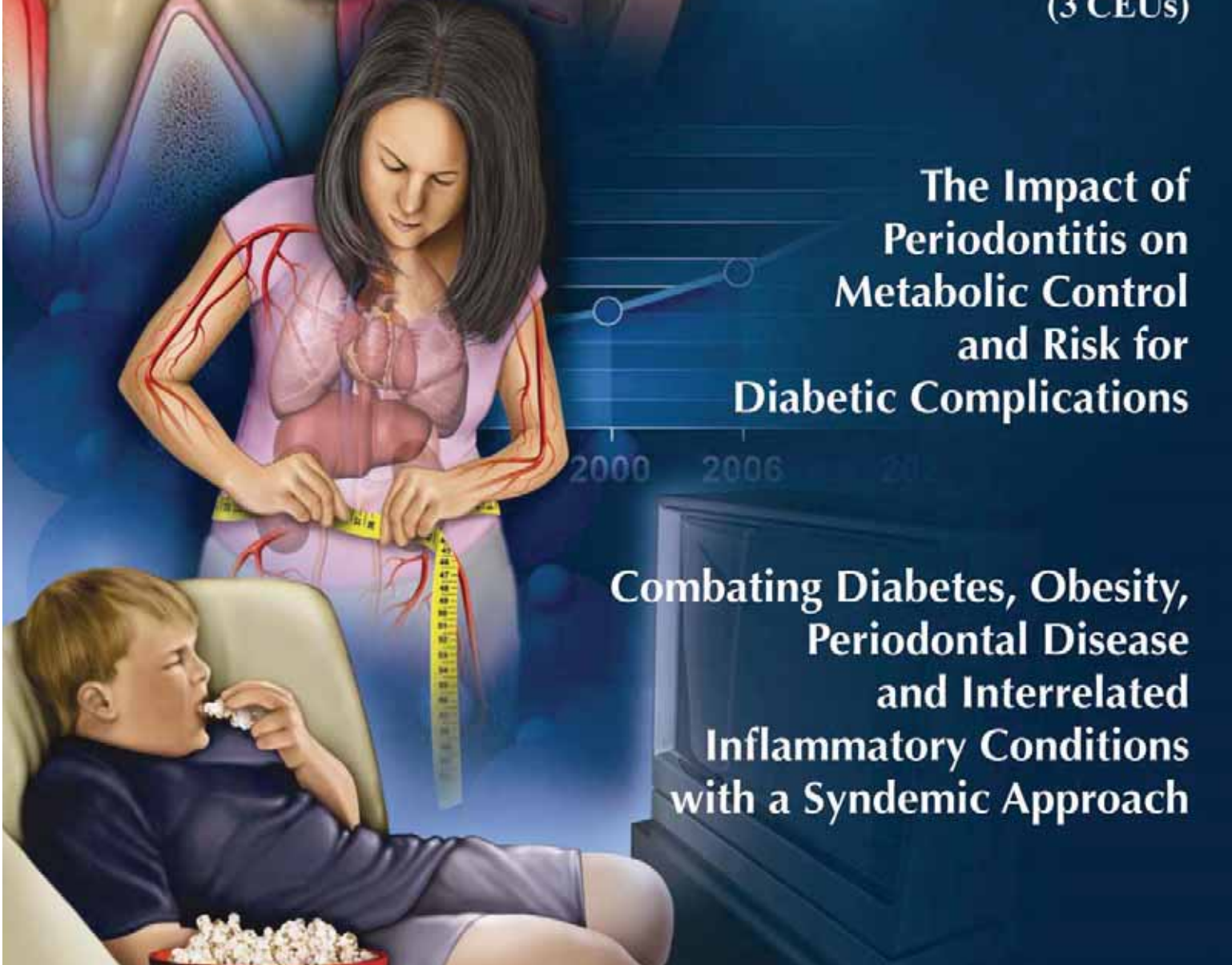
PenntWell

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Periodontal Disease, Insulin Resistance, and Diabetes Mellitus

A review and
clinical implications
(3 CEUs)



The Impact of Periodontitis on Metabolic Control and Risk for Diabetic Complications

Combating Diabetes, Obesity, Periodontal Disease and Interrelated Inflammatory Conditions with a Syndemic Approach

GRAND ROUNDS WITH DR. BRIAN L. MEALEY

Brian Mealey

As a periodontist, I see the devastating effects that periodontal diseases can have in advanced stages - loss of teeth, poor esthetics, inability to eat or function well. It's hard to tell a patient that they are going to lose their teeth. Try telling a 25-year-old woman 2 months before her wedding, or your local TV newscaster, whose smile is critical to his business, that they are going to lose their front teeth. To some, losing teeth seems to be "no big deal." To others, it has the same effect on the psyche as an amputation or mastectomy would have. In my practice, I also see the efforts that have to be made by my patients to treat periodontal diseases before they reach these late stages, and to maintain oral health over the long-term. It takes money, time, and persistent motivation, things that are often seem in short supply. What helps my patients most? My technical expertise? Probably not. I think what helps them most is education. The patient with knowledge of his disease is the easiest patient in the world to work with, and the one most likely to have successful outcomes.

I do not have periodontal disease, but I do have diabetes. When I was first diagnosed over 20 years ago, I went through the same thing every other newly diagnosed patient goes through. If you don't have this disease, you can't really understand it. Believe me. The mental images that confronted me as I first learned about my diabetes were stark: images of my young family without their father, or of them having to drive Dad to the dialysis center every other day, or the black emptiness of blindness before my eyes as my daughter's wedding march is played. Over the past 20 years, this picture of doom has been replaced by one of... sameness. My life is the same kind of life as my non-diabetic wife, kids, friends, and colleagues have. Yes, I use an insulin pump that can be a pain in the neck. Yes, I have my moments when I still feel sorry for myself over the inconveniences that my diabetes causes. But overall, I'm pretty much the same as you are. Having the greatest doctors in the world has been a huge part of that for me. So has technological evolution. But most importantly, so has education. Learning about diabetes and having a sound knowledge base has been my best weapon in the fight.

Education is what we do every day. Physicians, dentists, dental hygienists, nurses and other healthcare providers must accept responsibility for establishing and maintaining a current knowledge base in order to help their patients along the path to health. What we know today about the relationships between diabetes and periodontal diseases means absolutely nothing if that knowledge is not disseminated throughout our professions and to our patients. We know that the oral cavity is a source of inflammation that can have effects extending well beyond the boundaries of the lips and the posterior oropharynx. As a profession, we simply must get ourselves out of the days where the mouth was considered a disembodied part. The historical legacy of the barber-dentist must end.

I recently attended a continuing education course with my wife, who is a nurse. The course, given by a neurophysiologist, was on the inflammatory nature of obesity, diabetes, and Alzheimer's disease. Toward the end of the course, the speaker spent 30 minutes discussing periodontal diseases and their associations with these other conditions. I imagine I was the only dentist in this audience consisting of over 100 physicians and nurses, and I was pleased to hear the outstanding questions from those in attendance. It was clear that for most in the room, this was the first time they had heard of the oral condition, periodontitis, being associated with systemic conditions like diabetes. What was encouraging to me was that the audience had no difficulty making the link, once they understood the inflammatory nature of periodontal diseases.

In medicine, there has been widespread dissemination of research demonstrating the inflammatory nature of obesity and its link to insulin resistance and type 2 diabetes. Medical professionals know that adipocytes are a highly metabolically active source of pro-inflammatory cytokines like TNF- α and IL-6, and that obesity leads to elevated serum levels of these cytokines, which then can directly induce insulin resistance.^{1,2} They know that elevated acute phase reactants such as C-reactive protein and fibrinogen are found in people with inflammatory disease.³ They also know that elevated C-reactive protein levels are a major risk marker for acute cardiac events.⁴ But are medical professionals also aware that periodontitis can induce elevated production of pro-inflammatory cytokines?⁵ Do they know that people with periodontitis often have elevated serum levels of TNF- α , IL-6, and C-reactive protein compared to periodontally healthy people?^{6,7} Do they realize that periodontal treatment aimed at reducing the microbial bioburden present in the oral cavity and decreasing inflammation locally within the periodontium also results in reduced serum markers and mediators of systemic inflammation?⁸

The periodontium is unique in an important sense. In no other region of the body is an intact mucosal lining, similar in many respects to the lining of the genitourinary tract and gastrointestinal tract, interrupted by the presence of calcified structures that penetrate the mucosal lining. The presence of teeth protruding through the oral mucosal surface establishes a dynamic wound healing state that is unlike other regions in the body, and is analogous to inserting a cannula or ostomy through an intact skin surface. The presence of teeth results in establishment of a sulcus or pocket in the mucosa adjacent to the teeth, which becomes colonized by microorganisms that induce an inflammatory response. If not cared for properly, inflammation can increase in intensity and result in production of massive quantities of pro-inflammatory cytokines, local destruction of the adjacent tissues, and penetration of bacterial products through the ulcerated pocket epithelium into the systemic circulation.

The potential impact of this inflammatory response is now being recognized. As the articles in this issue discuss, periodontal inflammation can result in elevated serum levels of inflammatory mediators that may increase insulin resistance similar to obesity, and may worsen glycemic control in people with diabetes.⁹ Likewise, periodontal treatment that reduces inflammation may also result in improved glycemic control. One study recently made me pause to consider the potential clinical implications of the interrelationship between periodontal inflammation and systemic health. This longitudinal trial of over 600 subjects with type 2 diabetes examined the effect of periodontal disease on mortality.¹⁰ After adjusting for other known risk factors, the death rate from ischemic heart disease was over 2 times higher in subjects with severe periodontitis than in subjects without periodontitis or with only mild periodontitis. The death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis, and the overall cardiorenal mortality rate was 3.5-fold higher, suggesting that the presence of periodontal disease poses a risk for cardiovascular and renal mortality in people with diabetes. This is important information for all of us to know.

I do not have periodontal disease, but I do have diabetes. I plan to control the disease that I have to the best of my ability, and to prevent the disease that I don't have. I plan to do the same for my patients.

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THE IMPACT OF PERIODONTITIS ON METABOLIC CONTROL AND RISK FOR DIABETIC COMPLICATIONS

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Abstract

Over the last decade there have been numerous studies providing compelling evidence that periodontal therapy can improve metabolic control in diabetes, reduce pre-term birth in high risk pregnant females, and reduce pneumonia in patients in intensive care units. In contrast, and despite the strong data confirming the relationship between diabetes and periodontitis, many practitioners in both medicine and dentistry have failed to convert these findings into clinical actions. There is no doubt that poor glycemic control, as assessed by glycated hemoglobin levels (HbA1c), increases the risk for developing the long-term complications of diabetes, including periodontitis. This article presents 4 case studies that demonstrate the importance of achieving and sustaining optimal oral care in the diabetic patient and offers scientifically supported recommendations for treatment of periodontal disease, and strategies for progressive disease management to achieve metabolic control of diabetes and decrease risk for diabetic complications.

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Key words: Diabetes, periodontal disease, inflammation, insulin resistance, glycemic control

Introduction

The bridge between systemic disease and oral inflammation, primarily the role of periodontal disease, has been the focus of a multitude of publications in both medical and dental journals. The strongest data supporting an oral-systemic link exists for diabetes and periodontitis with reports of this connection traced back to the 1920s¹ and 1930s.² In addition, an uncontrolled oral infection such as periodontitis will increase the risk for poor metabolic control and certain long-term complications of diabetes, particularly nephropathy³ and cardiovascular disease (CVD).⁴ Recent research has shown that improving oral health is important to optimizing metabolic control of diabetes;⁵⁻⁷ therefore, the treatment of periodontal diseases should not be considered optional or elective, but instead a standard of care integral to diabetes management.

In 1993 Dr. Harold Loe, former director of the National Institute for Dental and Craniofacial Research,⁸ identified periodontitis as the sixth long-term complication of diabetes. Today, adults with diabetes have heart disease death rates about 2 to 4 times higher than those without diabetes; and the risk for stroke is 2 to 4 times higher among diabetic people. Despite these dismal statistics, evidence of a bi-directional relationship between diabetes and periodontal disease, and the potential of unattended periodontal infection to increase diabetic complications, there still exists a practice gap in dentistry and medicine in the recognition and/or proactive management of diabetic patients with periodontal disease. A recent survey of general dentists and periodontists revealed that dental practitioners' rates of proactive management of diabetic patients, e.g., willingness to change/adjust treatment plans, and referring patients for evaluation of suspected diabetes or screening for diabetes with a finger-stick test, may actually be quite low.⁹ It is unfortunate that oral health was barely addressed in the 2006 Clinical Practice Recommendations of the American Diabetes Association for the Standards of Medical Care in Diabetes.¹⁰ Currently there is no cure for diabetes and periodontitis, but with the appropriate therapy and regular follow-up care of motivated patients, these diseases can be controlled. Successful management of these diseases requires frequent monitoring and careful attention to therapeutic responses, both glycemic control and periodontal status. This level of diabetes care is best facilitated by a team of healthcare providers from both medicine and dentistry including physicians, nurses, diabetes educators, dietitians, dentists, dental hygienists, and a number of other specialists.

Diabetic Patients? Unique Dental Needs and Opportunities for Intervention

The Center for Disease Control and Prevention (CDC) currently estimates 20.8 million people have diabetes, accounting for 7% of the United States population (2005).¹¹ This represents an increase of 2.6 million Americans from the 2004 estimates, and a dramatic jump in prevalence in just one year. Of this large population, 14.6 million people have been diagnosed with diabetes; however, most disturbing are the 6.2 million individuals with diabetes that have not been diagnosed.¹¹ It is estimated that an additional 41 million adults between the ages of 40 and 74 are considered pre-diabetic; once pre-diabetic, individuals have a significantly increased risk of developing type 2 diabetes, heart disease, and stroke. Evidence described later in this article indicates that chronic inflammation may play a role in converting pre-diabetic individuals to diabetics. Screening for both undiagnosed diabetes and prediabetes among dental patients represents a valuable opportunity for dental practitioners to become involved in helping to identify diabetes in individual patients and reversing these alarming epidemiologic trends.¹¹ For guidance on referring an asymptomatic adult or child for diabetes testing, readers may download the American Diabetes Association (ADA) Criteria for testing for diabetes in asymptomatic adults and ADA Criteria for testing for type 2 diabetes in children, which may be accessed in the Clinical Decision-Making Tools section at www.thesystemiclink.com.

From 1980-2004, the number of Americans with diabetes more than doubled.¹² In the year 2004, about 1.4 million adults between 18 and 79 years of age were diagnosed with diabetes.¹³ Why was there such a rise? The reasons include increasing awareness, longevity, change in demographics, and genetic predispositions. The rise in urbanization and changes in lifestyle play a role as well as an increased prevalence of obesity. In the United States, obesity is known to play a major role in increasing the risk for diabetes.^{14,15} With more than 60% of the adult population now considered overweight or obese, addressing obesity in our dental patients can no longer be considered an optional practice.

There are a number of systemic diseases and conditions that can increase a patient's susceptibility to periodontitis, with significant data supporting a 2 to 3 times greater risk for developing periodontal disease in diabetic patients.¹⁶ Poor metabolic control of diabetes may render an individual more susceptible to developing periodontitis and, once developed, may lead to more aggressive disease.¹⁷⁻²⁶ It should be noted that well-controlled adult diabetic patients generally do not exhibit the periodontal destruction commonly associated with poorly controlled diabetes.¹⁶

It is also important to astutely watch for oral manifestations of underlying disease. The presence of significant periodontitis with no evident risk factors such as smoking or poor oral hygiene may be a sign of underlying systemic disease such as diabetes. Dental practitioners should be very suspicious of rapidly progressing cases of periodontitis with no apparent risk factors. Periodontal risk assessment needs to be conducted on a regular basis since a patient's non-genetic risk may change due to environmental and systemic factors. Accordingly, suspicious cases of periodontitis should be referred to a physician for evaluation of underlying systemic contributions such as those seen in diabetes.

Diabetic patients may also experience diminished salivary flow and increased sugar in both saliva and the gingival crevicular fluid. These factors, in turn, may lead to increased plaque and calculus formation, thereby increasing the risk of developing periodontal disease and dental caries. Xerostomia can contribute to the development of candidiasis and burning mouth and tongue. Palliative interventions for xerostomia or dry mouth include saliva substitutes and stimulants. The administration of antifungal agents may be necessary for the management of candidiasis. The management of oral burning sensations may include the maintenance of adequate oral hydration and restrictions on the intake of caffeine and alcohol. Because diabetic individuals have a greater risk of infection and impaired wound healing, patient education and preventive measures need to be incorporated into diabetic case management at the earliest recognition of diabetes. Preventive measures include frequent dental visits to assess plaque control, conducting risk assessment before surgical procedures are planned, postoperative antibiotic therapy if necessary, and elimination or modification of compounding risk factors such as smoking.

The Systemic Impact of Oral Infection and Inflammation in Diabetes

The potential for an infectious challenge to the oral and/or pocket epithelium is well illustrated in Case 1 of a poorly controlled type 1 diabetic patient with extensive periodontal disease (Figure 1).

If a patient had an equivalent bacterial challenge anywhere else on the body, such as a nonhealing ulcer on the foot of a diabetic patient, it certainly would be of concern as it is easily visible. A bacterial infection of the gingival tissues and the ensuing inflammation resulting in periodontitis can complicate the management of diabetes in the same fashion as other unresolved infections in the body.

If periodontitis is left untreated, bacteria will eventually enter the bloodstream, interacting with platelets and putting patients at greater risk for a number of systemic diseases, including CVD, the number one killer of people with diabetes.¹² The systemic exposure to microbial pathogens results from loss of epithelial integrity within the periodontal pocket, allowing bacterial and endotoxin penetration into the tissues and translocation into the blood stream, resulting in possible bacteremia and endotoxemia. Recurrent transient bacteremias can occur every time a person with untreated periodontitis masticates or brushes their teeth.²⁷

When gingival inflammation is present, there is more vascularity in the surrounding tissues, a greater chance for bacteremia and endotoxemia to occur, and a greater likelihood that inflammatory mediators will enter the bloodstream. Many of the pro-inflammatory mediators present in patients with periodontitis can be found locally within the gingival crevicular fluid but also within the gingival tissues and alveolar bone. When these pro-inflammatory mediators eventually enter the blood stream, this results in systemically elevated levels of interleukins (IL-1 and IL-6), tumor necrosis factor- α (TNF- α), and prostanooids, all known to have a profound effect on diabetic patients, leading to insulin resistance, and resulting in difficulties in achieving glycemc control.²⁸

Case 2 (Figures 2 and 3), demonstrates the severity of oral disease that can occur in a poorly controlled diabetic patient and its potential for systemic injury. This case involves a 46-year-old obese female, registered nurse, with type 2 diabetes. She also has a history of hypertension

and hypothyroidism and reported smoking one pack of cigarettes or less per day. She was referred by her physician to a radiologist for a mandibular and maxillary computerized tomographic scan (CT scan) (2003) to determine the extent of dental disease. She has a history of multiple oral abscesses. Her physician noted a large draining abscess in the left maxillary incisor region and was concerned about paranasal sinus involvement. The CT scan indicated a mild maxillary and mandibular osteopenia of the maxilla and mandible; however, the paranasal sinuses were normal without involvement of dental disease. (Other intra-oral images and a panorex radiograph of this case may be accessed and viewed in the Collateral Case Study Information section at www.thesystemiclink.com.) The physician referred the patient to the faculty practice of the School of Dental Medicine at State University of New York at Stony Brook.

The patient presented with generalized caries, multiple abscesses, and the presence of fistulas. She reported using a sterile needle and pressure to drain the abscesses. She was diagnosed with periodontitis and caries in 2003. Her current medications included: metformin, Lantus[®]i (insulin glargine), Synthroid[®]ii (levothyroxine sodium), Altace[®]iii (ramipril), atenolol, aspirin, and folic acid. The patient developed a penicillin allergy due to repeated use for acute dental infections. Antibiotic coverage included clindamycin (300 mg t.i.d.) or levofloxacin (500 mg q.d.). Her history revealed both parents have type 2 diabetes and wore dentures by the age of 40. Genetics, diabetes, obesity, and smoking were clearly risk factors to be considered in this patient. The patient also reported a history of gestational diabetes with all 3 of her pregnancies from 1980-1992 (many gestational diabetics eventually develop type 2 diabetes).²⁹ She was diagnosed with diabetes in 1999 and managed solely with oral hypoglycemics until 2005, when insulin therapy was initiated.

Her HbA1c was 8.8% (4.1-6.5% is normal) and her C-reactive protein level (CRP) was 12.60 (low risk = <1.0 mg/L, average risk = 1.0 to 3.0 mg/L, high risk = >3.0 mg/L) indicating a significant pro-inflammatory status contributing to insulin resistance and increased risk for CVD. She was referred to an oral surgeon and restorative dentist for consultation but was unable to pursue the recommended dental treatment plan due to a lack of insurance and financial resources. The lack of regular dental care impeded the patient's attempts to improve her diet. She attempted to comply with the recommendations of a nutritionist but the patient was unable to eat fruits and vegetables due to the status of her dentition. She met with a surgeon to determine if she was a candidate for gastric bypass, but the procedure was contraindicated due to her dental condition. She was hospitalized twice in the first 3 months of 2006 with bilateral pneumonia which was treated with intravenous antibiotics. It was suspected that her dental diseases contributed to her respiratory condition.

In discussions with the patient she indicated she was very worried about the possibility of dying from her dental infections, and it was difficult to reassure her otherwise. The physician recognized the need for dental care but none of her healthcare providers were able to assist in securing the funds to obtain appropriate care. This case presents us with many unanswered questions regarding the optimal management of the diabetic patient. This patient's dental disease likely contributed significantly to her medical needs, which begs the question: Should medical insurance cover dental treatment as an integral part of diabetes management? Recognizing this patient was at an impasse, the School of Dental Medicine at Stony Brook made a commitment to support her complete oral rehabilitation, regardless of ability to pay. Sadly, for many cases like this one, there are no financial mechanisms in place to cover critically needed dental care in diabetes management, including provisions within medical insurance.

The Challenge of Metabolic Control (HbA1c) Associated with Periodontal Infection

The cornerstone of medical management of a diabetic patient is centered on achieving and sustaining glycemic (metabolic) control at the same level as a healthy, non-diabetic individual.³⁰ Improved control of blood glucose reduces the risk of a number of long-term complications, particularly retinopathy, nephropathy, and neuropathy.^{3,31-36} Evidence is emerging that intensive glycemic control may reduce CVD,³⁴⁻³⁶ although this has not yet been demonstrated in a randomized clinical trial.

The major marker of metabolic control for physicians is the level of HbA1c (abbreviation previously referenced), which is a long-term marker of metabolic control measuring the patient's average glycemia over the past 2 to 3 months³⁷ (unlike blood glucose which fluctuates daily and as we eat). HbA1c levels of 4% to 6% are normal, <7% is considered good diabetes control, 7% to 8% is moderate control, and >8% is considered poor metabolic control. Clinical practice recommendations of the ADA for the standards of medical care in diabetes¹⁰ suggests a general goal for patients is <7% but for the individual patient <6% is preferred if this can be accomplished without significant hypoglycemia. The less stringent goals are for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young or old individuals, and those with comorbid conditions. It has been estimated that every percentage point drop in HbA1c (e.g., from 8% to 7%) reduces risk of microvascular complications (eye, kidney, and nerve diseases) by 40%.¹¹ Accordingly, it is the primary objective of most physicians to keep the levels of HbA1c low to prevent long-term complications. HbA1c testing is recommended at least twice a year for patients with stable glycemic control and quarterly for those who do not meet the goals for glycemic control.¹⁰

Periodontal infections, like other chronic infections, can impair a diabetic patient's ability to process and/or utilize insulin. This leads to less optimal diabetic control. Monitoring HbA1c against periodontal status may provide key information in assigning appropriate periodontal maintenance intervals, or provide evidence that definitive periodontal treatment must be reinstated. Diabetic patients who are well controlled may not require the frequency of maintenance visits and the careful monitoring required for poorly controlled diabetic patients. One way of gathering information about diabetic patients' glycemic control is to request from their physicians a history of HbA1c lab values and the results of most recent lab tests. A template for dentist communication to a physician requesting this information is included in Templates of Letters for Dentist-Physician Communications, which may be accessed and downloaded at www.thesystemiclink.com. Another way of obtaining this information is for the dentist to directly refer the patient to a medical laboratory, i.e., hospital or treatment center laboratory. Also emerging is the use of point-of-care monitoring of HbA1c with chairside/bedside analyzers that are now available. This allows for on-the-spot decisions that may result in alteration of treatment plans. On-site availability of this technology may not only apply to physicians but also dental practitioners considering more invasive surgical procedures. The use of HbA1c testing for the diagnosis of diabetes is not recommended at this time since the vast majority of people who meet the diagnostic criteria for diabetes by oral glucose tolerance test (OGTT), but not by fasting plasma glucose (FPG), will have an HbA1c <7%.¹⁰ Improvements in biochemical diagnostics for periodontitis might soon allow physicians, nurses and even patients to send samples to a centralized laboratory for evaluation and preliminary detection of periodontal inflammation and breakdown with subsequent referral to the oral healthcare provider for a complete oral evaluation and treatment.

Progressive Disease Management Benefits Both Periodontal Status and Glycemic Control

Diabetic patients with poor glycemic control most often experience delayed and impaired wound healing.¹⁰ Consequently, there are challenges to achieving and sustaining optimal therapeutic outcomes. In addition to traditional mechanical therapy of scaling and root planing, a progressive treatment regimen for periodontally involved patients with poor glycemic control may also require the use of adjunctive therapies such as systemically administered or locally applied antimicrobials (i.e., Arestin[®]iv, Atridox[®]v or Periochip[™]vi). Another valuable therapeutic addition to scaling and root planing is prescription of Periostat[®]vii (sub-antimicrobial dose of doxycycline hyclate), a pharmaceutical product that targets the non-microbial, host response component of periodontal disease. Recently reported pilot clinical studies using the two-pronged approach of scaling and root planing in addition to Periostat demonstrated excellent clinical results³⁸ of periodontal treatment with simultaneous improvements in the glycemic control of diabetic patients, as assessed by significant reductions in HbA1c levels.^{38,39}

Without such progressive therapies, there is a risk that an unresolved periodontal infection and the related pro-inflammatory response may lead to insulin resistance.⁴⁰ This cascade of events makes it difficult for patients and their physicians to achieve and sustain optimal glycemic control which reinforces the importance of collaboration between dentists and physicians in monitoring diabetic patients, via HbA1c testing, for changes in glycemic control and oral health. Education of diabetic patients regarding the significance of active periodontal disease and preventive measures need to be incorporated into diabetic case management at the earliest recognition of diabetes. Patient self-care regimens may include toothpastes that contain antiseptic agents such as triclosan/copolymerviii in addition to automated toothbrushes for optimal plaque removal, and the use of oral irrigation. It is also essential that patients are thoroughly educated about the hyperinflammatory response related to diabetes, and the importance of a plaque-free mouth.

Assessment of all risk factors for periodontitis and implementation of risk reduction strategies (e.g., smoking cessation programs, nutritional counseling, and exercise/weight loss programs) is important for the optimal management of the diabetic patient and should be incorporated into dental practice settings. Monitoring diabetic patient compliance to medication regimens is also part of proactive diabetes management in dental practices. All of these preventive measures are aimed at maintaining control of blood glucose levels, since this will help diabetic patients be more resistant to periodontal infection and allow for improved wound healing and therapeutic responses.

More advanced cases of periodontal disease may require surgical intervention, which should be preceded by optimal metabolic control since the healing response is critical for optimal post-surgical responses. Case 3 (Figure 4) involving a 66-year-old, type 2 diabetic male demonstrates how periodontal therapy may reduce the systemic levels of the pro-inflammatory cytokines that contribute to insulin resistance. This facilitates improved glycemic control, as evidenced by reductions in HbA1c levels. This case is an example of what happens to a poorly controlled diabetic patient with periodontal disease and illustrates the therapeutic potential of progressive disease management in bringing about greater periodontal health and metabolic control of diabetes. Radiographs and periodontal charts of this case may be accessed for viewing in the Collateral Case Study Information section available at www.thesystemiclink.com.

This patient was referred to our faculty practice in 1999 by a general dentist who had placed the patient on the antibiotic Cleocin[®]ix (clindamycin) for a periodontal infection (Figure 4). Five years previously this patient had been treated by a periodontist who performed 4 quadrants of periodontal surgery. The patient reported his diabetes was well controlled; concomitant medications included Vasotec[®]x (enalapril) and glyburide. Periodontal evaluation revealed the presence of 5-10 mm probing depths with radiographic evidence of significant bone loss. (This patient's periodontal chart and radiographs may be accessed for viewing in the Collateral Case Study Information section at www.thesystemiclink.com.) This case was diagnosed as generalized severe periodontitis. Blood samples were drawn from the patient to assess glucose and HbA1c levels as well as systemic levels of pro-inflammatory cytokines. The baseline and post therapy (4 months) blood chemistry test results are listed in Table 1.

Clearly, with serum glucose levels at 288 mg/dL and HbA1c at 9.1% at baseline, the patient mistakenly believed that his diabetes was well controlled. When contacted, the patient's physician reported the patient did not visit the physician's office regularly for medical checkups and although he was referred back to his physician for medical evaluation the patient did not comply with the referral. Elevated serum levels (TNF- α and IL-6) are associated with insulin resistance.²⁸ To that end, it is reasonable to surmise that the elevated levels of cytokines at baseline (Table 1) contributed to this patient's lack of metabolic control.

This patient became an extremely compliant dental patient, never missing an appointment with relatively good oral hygiene. Treatment consisted of extraction of hopeless teeth, full mouth scaling and root planing and host modulatory therapy with sub-antimicrobial doxycycline hyclate (Periostat). This treatment protocol resulted in a decline in the systemic levels of the pro-inflammatory mediators (IL-1 β , IL-6 and TNF- α) without a concurrent drop in the blood glucose or HbA1c levels after 4 months of initial periodontal therapy (Table 1). Significant clinical improvements in probing depths encouraged us to move to the next stage of therapy to further reduce probing depths which was achieved with the use of locally applied antimicrobials at localized sites, surgical intervention and adjunctive use of Periostat. When there was evidence of improved glycemic control, regenerative surgical procedures were performed at certain sites. One year later the periodontal therapy was successfully completed and an HbA1c level of 7.5% was achieved. Both the physician and the patient were impressed by the final clinical and systemic outcome of this case.

Periodontitis, C-reactive Protein, and Diabetes

The persistent chronic inflammation associated with untreated periodontitis ultimately results in elevations of the systemic inflammatory marker C-reactive protein (CRP). CRP is produced by the liver in response to bacterial challenge and chronic inflammation.⁴¹⁻⁴⁵ The relevance of CRP with regard to risk for CVD was described in depth in a previous issue of Grand Rounds in Oral-Systemic Medicine.⁴⁶ High sensitivity C-reactive protein (hsCRP) is one of the best indicators of risk for CVD, and along with cholesterol levels, provides the most accurate risk assessment for future cardiovascular events.⁴⁷ It is important to keep levels of hsCRP low in diabetics and patients with metabolic syndrome

since these are patient populations known to be at greater risk for death from CVD. The Minnesota Heart Survey has monitored the trends in coronary heart disease morbidity since 1970.⁴⁸ The odds ratio for in-hospital death after a myocardial infarction (MI) for individuals with diabetes was 1.5 ($p < .01$) times that of persons without diabetes, after controlling for age, sex, and year of MI occurrence.⁴⁸ Among the MI survivors from this study, the risk of death after 6 years of follow-up was 40% ($p < .01$) higher in patients with diabetes compared to those without diabetes and was more pronounced in women than men. In a cross-sectional study⁴⁹ of 3,873 subjects from the National Health and Nutrition Examination Survey (NHANES) the reported odds ratio for CVD was 1.99 (95% CI, 1.10-3.59) in subjects with neither metabolic syndrome nor diabetes with high CRP levels. For those subjects with metabolic syndrome and intermediate CRP levels, the odds ratio jumped to 2.67 (1.30-5.48). Subjects with metabolic syndrome and high CRP had a similar odds ratio for CVD of 3.33 (1.80-6.16) compared to those with diabetes and a low CRP level at 3.21 (1.27-8.09). Finally, the data demonstrate that the likelihood of CVD was highest in those with diabetes and either intermediate or high CRP levels with reported odds ratios for CVD of 6.01 (2.54-14.20) and 7.73 (3.99-14.95), respectively.

The Insulin Resistance Atherosclerosis Study (IRAS) provided evidence demonstrating that inflammation is associated with insulin sensitivity even in patients without diabetes.⁵⁰ The study found a strong independent association between the levels of CRP and insulin sensitivity. Higher levels of CRP are associated with a greater degree of insulin resistance. Serum concentrations of CRP and other markers of inflammation were significantly related to the development of type 2 diabetes in 1,047 non-diabetic subjects followed for 5 years in the IRAS.⁵¹ The IRAS investigators concluded that chronic inflammation has emerged as a new risk factor for type 2 diabetes. Within its context, this research could imply that untreated periodontitis, which is a well known chronic inflammatory condition, might increase a person's risk for the development of type 2 diabetes. Future studies should be designed to address this issue.

The Importance of Managing Periodontal Disease to Prevent Diabetic Complications

Two studies have demonstrated that diabetic subjects with severe periodontitis are at greater risk for developing nephropathy and CVD, which can both affect mortality in this patient population. In an 11 year follow-up of subjects, diabetics with severe periodontitis had a greater prevalence of proteinuria indicative of nephropathy and a greater number of cardiovascular complications.⁴ These oral-systemic connections in diabetic patients have been confirmed most recently by Saremi and colleagues,⁵² who reported periodontal disease is strongly predictive of mortality from ischemic heart disease and diabetic nephropathy in a population of Pima Indians with type 2 diabetes. In an 11 year follow-up, the age and sex-adjusted death rates of type 2 diabetic patients increased with severity of periodontitis.⁵² There is no doubt that optimal oral health is essential to the medical management of the diabetic patient.

This final presentation, Case 4, demonstrates how the management of periodontal disease may not only be effective at reducing HbA1c levels but may also significantly reduce the development or progression of additional complications such as kidney and CVD. A 34-year-old type 1 diabetic female (Figure 5) was referred for possible participation in a clinical study funded by the National Institute of Health (NIH), but she was ineligible to participate in the study because she was being treated for rheumatoid arthritis with prednisone.

Review of the patient's medical history revealed she was diagnosed with type 1 diabetes at the age of 9, had laser treatment to slow the progression of retinopathy 17 years ago, and was diagnosed with periodontal disease 10 years ago, at the age of 28. The patient reported a family history of periodontitis in both parents who had type 2 diabetes. When asked about her dental history, the only dental care she had received was a superficial prophylaxis. One year after the patient was diagnosed with periodontal disease, she delivered her first daughter at 37 weeks. This first infant weighed 6 lbs, 1 ounce, and 5 years later a second daughter was prematurely delivered at 33 weeks weighing 3 lbs, 1 ounce. She had not received any dental treatment for 10 years because she was under the impression that her periodontal disease had been addressed. In retrospect, one might question the contribution of periodontal disease in addition to her diabetes to 2 preterm deliveries.

About 2 years after the patient was diagnosed with periodontal disease, she was diagnosed with rheumatoid arthritis. Since that time, she has also suffered from hypertension. Her medications included: Lente human insulin (morning and bedtime) and Humalog[®]xi (insulin sliding scale), captopril, Lasix[®]xii (furosemide), folic acid, Zoloft[®]xiii (sertraline), methotrexate, and prednisone. Full mouth charting revealed generalized 5-7 mm probing depths and radiographs revealed mild to moderate bone loss. (This patient's radiographs, periodontal charts, and other intra-oral images may be accessed for viewing in the Collateral Case Study Information section at www.thesystemiclink.com.) A diagnosis of generalized moderate periodontitis with localized severe periodontitis on tooth #10 was made. The patient was given oral hygiene instructions and prescribed Periostat. This was followed by 4 visits of deep scaling and root planing with anesthesia, reevaluation, and maintenance therapy at 3 and 6 months, at which time all probing depths were <5 mm. Blood, urine and gingival crevicular fluid samples were obtained at baseline and 6 months and were evaluated for HbA1c, hsCRP, microalbuminuria, albumin/creatinine ratio, proteinuria, the presence of the cytokines IL-1 β , IL-8, and vascular endothelial growth factor (VEGF). The data collected at baseline and 6 months is listed in Table 2.

It is evident that periodontal therapy resulted in improvements in the patient's metabolic control and may have reduced her risk for CVD, as supported by the significant reduction in hsCRP levels from a high risk level to a low risk level. It is interesting to note that this same dental host modulatory therapy was used in a pilot medical trial to assess its usefulness as an agent to prevent acute coronary syndromes.⁵³ In this study it significantly reduced systemic levels of the cytokine IL-6, consequently reducing hsCRP levels, and it also significantly inhibited the enzymes responsible for the disruption of atheromatous plaques.

Although a normal range was not achieved for the urinary markers of nephropathy, significant reductions in microalbuminuria, the albumin/creatinine ratio and proteinuria were evident along with the reductions in the urinary levels of cytokines. Finally, reductions in the GCF level of cytokines reflect the significant reduction in inflammation in the gingival tissues as a result of the periodontal therapy provided.

Conclusion

Consider periodontitis the sixth complication of diabetes,⁸ an important risk factor that needs to be controlled in order to improve overall health.

It is known that the more complications a diabetic individual may have the more likely he/she is to develop other complications of diabetes. Periodontitis has been linked to other well-known complications such as retinopathy, angiopathy, and nephropathy.^{3,54,55} A recent study in Type 2 diabetic patients has linked periodontitis to mortality in diabetic patients from nephropathy and CVD.⁴ Just as physicians closely monitor diabetic patients for metabolic control, compliance, and overall systemic health, it is necessary for the dental providers to do the same. Periodontal disease may be monitored and controlled with careful attention to patient compliance to self-care, and regular care from dental practitioners who are diligent in monitoring periodontal status and glycemic control. With newly developed treatment modalities that target both the microbial and host response components of periodontal disease, it is reasonable to expect that metabolic control may improve in diabetic patients simultaneous to improvements in periodontal health. This type of progressive care may provide great promise in decreasing the risk for complications of diabetes.

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COMBATING DIABETES, OBESITY, PERIODONTAL DISEASE AND INTERRELATED INFLAMMATORY CONDITIONS WITH A SYNDEMIC APPROACH

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Abstract

This article discusses the standard of care-practice gap in diabetes care and makes a compelling case for why dental and medical professionals need to collaborate in integrating oral care in diabetes management. Epidemiologic trends and the etiological rationale for adopting a syndemic orientation to the epidemic of obesity, insulin resistance, diabetes and related inflammatory conditions are presented. The term "syndemic" describes a set of 2 or more linked health problems that interact synergistically to contribute to the excess burden of disease in a population with a specific focus on the forces that bind the problems together. The authors suggest that instead of approaching prevention and treatment of chronic disease states as discrete, individual problems, a syndemic perspective would allow healthcare providers to view chronic inflammatory diseases or conditions such as diabetes, obesity, insulin resistance, hypertension, hyperlipidemia, and infections like periodontal disease as an interrelated cluster of maladies with specific focus on the ties or forces (acquired and environmental risk factors) that bind these conditions together. The article also discusses possibilities for large scale population based intervention strategies and micro-systems of collaboration targeting obesity, diabetes, and periodontal disease through health promotion in childhood and adolescent populations. Also included are aggressive screening and risk reduction strategies targeting patients with risk factors for diabetes and patients who have undetected diabetes.

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Key words: Diabetes, obesity, syndemic, periodontal disease, collaborative treatment, prevention

Introduction

It is staggering to consider the threat that diabetes and obesity pose to our current healthcare system. The growing population of aging Americans with diabetes or unattended risk factors related to diabetes and the growing segment of the youth population that is overweight and already manifesting signs and symptoms of insulin resistance has begun to drain our economy of the resources needed to preventively avert this epidemic in younger generations. More disturbing is the realization that even the best attempts by healthcare providers to follow guidelines for diabetes care have fallen short. We are now at the tipping point where the unrestrained epidemics of obesity and other unattended risk factors for inflammatory conditions such as diabetes have outpaced the intervention strategies currently in practice. This places right at our doorsteps an unprecedented opportunity to change what has clearly become an obsolete model of healthcare delivery. Accordingly, the responsibility to prevent and treat obesity and diabetes can no longer fall solely to an overburdened medical community. The expectation that the medical profession can unilaterally implement wellness-promotion and risk-reduction strategies without enlisting the cooperation of other healthcare professionals is unrealistic. Indeed, referring to the increasing incidence of diabetes, a think tank recently concluded, "No single individual or group can meet these challenges alone."¹

It is widely recognized that the development of type 2 diabetes and its complications is highly correlated with being overweight or obese. Obesity is also an independent risk factor for hypertension and dyslipidemia in addition to cardiovascular disease (CVD)¹. Added to this cluster of obesity-related conditions is a newcomer: periodontal disease. Growing evidence suggests that obesity is a significant predictor of periodontal disease, which reflects yet another cascade of inflammatory events.^{2,3} It is theorized that chronic stimulation and secretion of proinflammatory cytokines associated with periodontal infection contribute to insulin resistance, which may further increase diabetes risk. Obesity appears to be a precipitating factor in this cascade.

The Obesity Pandemic

According to the Department of Health and Human Services, "Calling obesity in the U.S. an epidemic is more than rhetorical."¹ Five years ago, when the National Institutes of Health published clinical guidelines to identify, evaluate, and treat adult obesity, an estimated 97 million American adults were overweight or obese.² The classification of overweight and obesity now applies to more than 60% of American adults and nearly 80% of some high-risk subgroups, such as African-American women,¹ placing these individuals at greater risk for diabetes and subsequent CVD. Some authorities estimate that 2 out of 3 Americans are overweight or obese.¹ Obesity, which is now considered a chronic disease, substantially increases the risk of morbidity from hypertension; dyslipidemia; type 2 diabetes; coronary heart disease; stroke; gall bladder disease; osteoarthritis; sleep apnea and respiratory problems; and endometrial, breast, prostate, and colon cancers.⁵

The number of overweight children has more than doubled among 2- to 5-year-olds and more than tripled among 6- to 11-year-olds.¹ Approximately 10.4% of children 2- to 5-years-old and 15.3% of children 6- to 11-years-old are overweight.⁶ It is generally known that childhood adiposity tracks into adulthood and significantly influences adult mortality and morbidity.⁶ Some investigators note a "gap between current dietary practices and recommended diets for infants, children, and adolescents."³ For instance, the American Dietetic Association states that the percentage of diets that "need improvement" among children 2 to 3, 4 to 6, and 7 to 9 is 60%, 76%, and 80%, respectively.⁶ Furthermore, the diets of most American children do not meet the Food Guide Pyramid recommendations for fruit, grain, and dairy groups or the Dietary Guidelines for Americans recommendations for total and saturated fats. Both guidelines should be achievable for all American children over the age of 2.⁶ Thus, there is a pressing need to target young children for primordial obesity prevention. Given that dietary patterns and physical activity are largely established and weight gain and adiposity entrained by parents and guardians, this goal cannot be accomplished without targeting whole families.

A study of 1,740 students in 12 middle schools reported a high incidence of risk factors for diabetes, including impaired fasting glucose, hyperinsulinism suggestive of insulin resistance, and body mass index (BMI) \geq 85th percentile.³ Another nationwide epidemiologic study found that obese children were more than twice as likely to develop diabetes as normal weight children.³ These findings suggest the overwhelming need for population-based efforts to decrease overweight/obesity and diabetes risk in childhood and adolescence.

After almost 25 years of research, the conditions known collectively as the metabolic syndrome (MSyn), also referred to as "syndrome X," have become accepted as a leading cause of death for the obese, diabetics, and other subpopulations.³ Alarming, an estimated 24% of adult Americans have MSyn. This syndrome was derived from investigators' recognition that complications of obesity, such as diabetes, hypertension, insulin resistance and heart disease may be more related to central adiposity (waist circumference) than overall obesity. Also included in MSyn are hyperinsulinemia, abnormal blood lipids (dyslipidemia), a procoagulant state, vascular abnormalities, inflammatory markers, and hyperuricemia.¹⁰ Genetic predisposition may underlie susceptibility to MSyn.¹⁰ Central adiposity is associated with insulin resistance, and both are important predisposing risk factors for MSyn and are related to diabetes, high-fat diet, aging, certain medications, physical inactivity, polycystic ovary syndrome, and low birth weight with imprinting of the brain. Because of its association with insulin resistance, inflammatory markers, and the procoagulant state, MSyn is considered a major risk factor for CVD.¹⁰ With a quarter of the U.S. population with MSyn, it appears that a large number of individuals may not be aware of their increased risk for CVD.

The increase in diabetes rates in the overall population translates into higher rates of pregestational diabetes and a shift toward increased prevalence of diabetes at younger ages.³ This trickle-down effect places more women and fetuses at risk, resulting in a greater need for prenatal services.¹¹ What is also emerging is that the risk of death associated with diabetes may be correlated with abnormal birth weight (low birth weight defined as $<$ 6.5 lbs. and high birth weight defined as \geq 8.5 lbs.)³ Lower birth weight is associated with postnatal rapid weight gain and central adiposity, MSyn, diabetes, and CVD in adulthood.⁷ This population may represent a subset of at-risk diabetic individuals.¹² Babies who are large for gestational age because of consequences of maternal insulin resistance and glucose intolerance are at high risk for future obesity.⁷ Without intervention strategies targeting women of child-bearing age, particularly those in subgroups at greater risk for diabetes, an increase in gestation-related complications can be expected that may place future generations at greater risk for diabetes.

As if the present day epidemic is not devastating enough, current predictions suggest that by 2030 there will be 23 million individuals with diagnosed and 7 million with undiagnosed diabetes, with another estimated 70 million with impaired fasting or postprandial glucose.³ Direct costs of diabetes could be close to \$175 billion/year, with an additional \$75 billion/year in indirect costs.¹³ In reference to a potential pandemic, Bloomgarden recently wrote, "The economic and personal burden of diabetes will be almost overwhelming" and suggested the following measures to avert the pandemic:¹³

1. Continue to invest in research.
2. Abandon an acute-care model and adopt a chronic-care model.
3. Focus on early treatment and prevention.
4. Find a way to limit obesity.

Collectively, the previous statistics present a strong argument for multiple levels of preventive care. This is a departure from our current healthcare system which focuses on treatment of diabetes and other chronic diseases in an attempt to minimize related disability or loss of function. Implementing preventive strategies before risk factors develop in children and adolescents by promoting lifestyle changes that emphasize exercise, proper diet, weight loss, and the importance of being tobacco-free (primordial prevention) is key. Strategies aimed at reducing risk factors in individuals who are already insulin resistant (secondary prevention) is also essential. These preventive strategies cannot be realized as a population-based strategy without expanding the responsibility to prevent obesity and diabetes to all healthcare providers. Prevention holds the greatest promise in curbing the projections of diabetes and the chronic inflammatory conditions that parallel its etiology.

Efforts to curb the epidemic of chronic conditions associated with these disease trends can no longer rely primarily on treatment; rather, our

efforts must be concentrated on helping young people grow up with healthy lifestyles. This shift in healthcare priorities will provide interventions that liberate future generations from the harmful lifestyles that became the inevitable by-product of the detrimental environmental and societal influences of the 20th century. This shift in priorities requires cooperation of all healthcare providers and calibrated health promotion messages. Given the association of obesity-related conditions with periodontal disease, the dental profession must willingly play a role in such health-promotion and disease-intervention strategies. A key question is whether the dental profession is educationally prepared to expand its responsibility for diabetes prevention and treatment.

It is time for a new model of care which is grounded in promotion of healthy lifestyle before risk factors develop, as well as risk elimination or modification for insulin-resistant or pre-diabetic individuals. Mobilizing dental professionals to embrace this challenge could positively impact diabetes trends. Yet, can this level of care happen in real world practice?

Guidelines Meet Real World Practice

The American Diabetes Association (ADA) recently published revised standards of medical care for diabetes (January 2006).² Throughout the guidelines there is a range of interventions to improve diabetes outcomes, including screening of asymptomatic adults and children who may be at risk, progressive strategies to prevent and delay diabetes, and care of patients with diagnosed diabetes.² Nowhere in the guidelines does the ADA specify that its recommendations are the sole responsibility of the medical community. The guidelines state that the standards of care are intended for clinicians, without specific reference to any one healthcare profession.

In these revised standards, the ADA also made rather bold statements that question the ability of the current healthcare-delivery system to implement such standards of care for diabetes. Several statements are included below.

- “The implementation of the standards of care for diabetes has been suboptimal in most clinical settings.”
- “... the challenge of providing uniformly effective diabetes care has thus far defied a simple solution.”
- “A major contributor to suboptimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, often duplicates services, and is poorly designed for the delivery of chronic care.”

Despite efforts to translate research on diabetes care into primary medical care, it is increasingly apparent that there is a large gap between what is known about diabetes care and what is practiced.³

The Standards of Care-Practice Gap

Empirical evidence for a gap in standards of care and practice in treating diabetes has been cited in numerous professional journals. Some state that the level of diabetes care provided in primary care medical practices, where most patients are seen, consistently falls short of what is recommended.¹⁴ Even ordering blood tests or regularly checking HbA1c is performed less frequently than recommended.¹⁴ Saydah and colleagues reported other evidence of suboptimal diabetes care, as follows:³

- Only 37% of adults with diagnosed diabetes achieved an HbA1c of < 7% (goal).
- Only 36% of adult diabetics had a blood pressure < 130/80 mmHg (goal).
- Only 48% of adult diabetics had a cholesterol < 200mg/dL (goal).
- Fewer than 7.3% of diabetics achieved all 3 goals.

Other standards of care-practice gaps emerge when examining national diabetes-related objectives for year 2010. Three of the national objectives related to diabetes care include: increasing to 75% the proportion of adults with diabetes who undergo an annual dilated eye exam; increasing to 50% those who have an annual foot exam; and increasing to 50% those adults who have HbA1c measurements at least twice a year.³ To determine the percentage of adults with diabetes who received 1 or all 3 of these services, the Centers for Disease Control and Prevention (CDC) analyzed data from surveillance surveys collected from 2002 through 2004.¹⁶ Their findings indicate that only 4 out of 10 diabetic adults received all 3 preventive care services, and they concluded that continued interventions to ensure delivery of diabetes care are necessary.¹⁶ An even more startling finding is that of the estimated 7% of the U.S. population with diabetes, only 70% has been diagnosed.¹⁶

The standards of care-practice gaps cited above result from overwhelming demands for diabetes treatment. Until complications develop clinically, diabetes is mostly asymptomatic, and medical providers' attempts to fully implement guidelines for diabetes care often take a back seat to immediate concerns of diabetic patients. Before we take aim at the medical profession, we must consider the magnitude of the challenges inherent in reversing the trends in obesity and diabetes.

Dentistry's Current Capacity to Impact the Diabetes Epidemic

Managing diabetic patients' special needs is not new to dentistry. Oral manifestations of diabetes, treatment guidelines, and emergency protocols have been taught in dental schools and dental hygiene programs for decades. What also has been taught and extensively discussed in professional literature is that diabetic patients are at 2-4 times greater risk of developing periodontal disease than non-diabetic patients,³ and once periodontitis is established in a diabetic host, metabolic control of diabetes is complicated from the constant reservoir of periodontal pathogens responsible for infection.³ Thus, assessment and treatment of periodontal disease are essential for diabetic patients,¹⁸ and dental providers who treat diabetic patients with periodontitis should monitor serum glucose or HbA1c as part of patient management.³ Over the last decade, the American Academy of Periodontology has addressed appropriate care of the diabetic patient with periodontal disease in numerous position statements and parameters of care.³⁻⁷ However, the number of dental providers who incorporate these guidelines into

Everyday patient care has never been quantified. A well captured data on how diabetic patients are managed in dental practices may determine whether there is a standards of care-practice gap in diabetic patient management in the dental profession that parallels that within the medical profession.

What is less well understood by dental and medical professionals alike is the concept of the risk continuum of periodontal disease, namely, the risk periodontal infection poses to systemic health. Recent research³ suggests that obesity, mediated by insulin resistance, may increase the risk for periodontal disease; however, this risk continuum does not end here. Although traditional thinking within the broader healthcare arena is that periodontitis is an oral disease with tissue destruction which remains localized, the sequelae of periodontal disease appears significantly more threatening than simply a localized infection. Escalating evidence over 20 years of research suggests various inflammatory pathways that link oral infections such as periodontitis to systemic damage. These etiological mechanisms include metastatic spread of gram-negative bacteria that gain access to the vasculature through a breach of the compromised epithelial lining of periodontal pockets and metastatic injury from the effects of the circulating toxins of periodontal pathogens.²⁵ The result is metastatic inflammation caused by immunologic response to the pathogens and their toxins.²⁵ Infection within the periodontium may be the origin of vascular dissemination of large numbers of virulent pathogenic bacteria to distant sites in the body,²⁶ thereby increasing the burden of systemic inflammation seen in several chronic disease states, including diabetes.

Another pathobiological concept that may be unfamiliar to many within the dental and medical communities is the relationship between infection seen in periodontal disease, insulin resistance, and the risk of chronic inflammatory conditions. This relationship is best described by a conceptual model proposed by Donahue and Wu,²⁷ who theorized that there is a pathobiological mechanism to support a role for periodontitis and insulin resistance in increasing risk for diabetes and coronary heart disease (CHD). Simplified, oral infections such as chronic periodontitis could trigger low-level inflammation leading to increased cytokine production and enhanced insulin resistance.²⁷ Insulin resistance increases the risk for both type 2 diabetes and CHD.²⁷ Once established, diabetes and CHD may subsequently induce feedback which amplifies the immune and inflammatory responses.²⁷ If this hypothesis is proven, such a cycle of immuno-inflammatory events would provide multiple opportunities for interventions potentially mitigating the risk for diabetes and CHD.

The overarching precept is that medical and dental professionals have common goals: preventing chronic inflammation and enabling interventions that disrupt the cycle of immuno-inflammatory events. All healthcare providers need to understand the role of inflammation in the link between periodontal disease and systemic diseases such as diabetes and CVD. It is essential that medical providers recognize infections of oral origin as significant risk factors for systemic inflammation.

Utilizing a Syndemic Orientation to Devise Health-Promotion and Risk-Modification Strategies

Decades of research related to the sequelae of chronic inflammatory conditions such as diabetes and periodontal disease have provided significant evidence of interrelated etiological pathways. When carefully examined, these pathways yield multiple opportunities for preventive or early therapeutic intervention of a cluster of multi-factorial chronic diseases like diabetes, atherosclerosis-induced diseases, and periodontitis. Adopting a syndemic orientation to the epidemic of obesity, insulin resistance, diabetes and related inflammatory conditions may provide the best blueprint for health-promotion and risk-modification strategies that disrupt the cycle of immuno-inflammatory events. These types of interventions hold the greatest promise for sustainable healthcare.

Syndemic is a relatively new term introduced in 1994 by Singer²⁸ to describe a set of 2 or more linked health problems acting synergistically to contribute to the excess burden of disease in a population.²⁸ Although the term is generally used in a public healthcare context to describe intertwined and mutually enhancing health and social problems, Singer used it to describe mutually reinforcing connections between substance abuse, violence, and AIDS.²⁹ A syndemic orientation is primarily distinguished from other healthcare perspectives by its explicit emphasis on examining the connections between health-related problems.²⁹

Traditionally, research, disease prevention, public health practices, and healthcare policy have focused on a single disease, even when evidence suggested interrelationships.²⁹ The term syndemic may aptly apply to the interrelated cluster of chronic inflammatory disease states that may amplify one another and to the forces (environmental and acquired risk factors) linking those disease states together.²⁹ Diabetes, obesity, insulin resistance, hypertension, hyperlipidemia, and genetically-encoded hyperinflammatory response to infection (i.e., periodontal infection) are part of this cluster of diseases brought on by chronic inflammation. These syndemic relationships are represented in Figure 1.

A syndemic orientation has the potential to provide a framework that can guide initiatives of greater efficiencies and effectiveness because healthcare providers will no longer approach chronic diseases as discrete problems. Instead, diseases will be viewed as a cluster of chronic diseases resulting from multiple forces (environmental and acquired risk factors) that bind the conditions together. As long as outcomes are measured as reductions in specific diseases rather than as a cluster of interrelated chronic conditions, there will be no incentive to collaborate across professional boundaries and patients will be deprived of the creative energy unleashed through collaboration.²⁹ Such a focus will also fuel inefficiency.²⁹ A syndemic orientation provides a clearer picture of what forces cause chronic conditions to cluster together.²⁹ Because medical and dental providers are finally looking at disease relationships the same way, a syndemic perspective provides a catalyst for collaboration.²⁹ A syndemic orientation also promotes effective collaboration at a scale that better matches the complexity of multi-factorial chronic disease states.²⁹ As Donahue and Wu's²⁷ model suggests, there are multiple opportunities for intervention by disrupting the forces that link these conditions, and no single profession can tackle the cluster of the interrelated chronic conditions.

Some may question a syndemic approach, but their objections must be weighed against the known limitations of maintaining the status quo.²⁹ Specifically, preoccupation with a single disease, like diabetes or periodontal disease, rather than focusing on multiple forces that bind chronic inflammatory conditions together will handicap attempts to develop effective health-promotion and risk-modification strategies. Because a

syndemic orientation was used in this area of healthcare and professional boundaries still are fairly engrained, it is not yet known how powerful interventions can be if they are focused on disrupting forces that unite these chronic disease states.²⁹

The challenge of controlling diabetes can best be addressed by adopting a syndemic orientation and implementing a transdisciplinary approach combating diabetes. The term transdisciplinary is used to describe the importance of going across and beyond professional boundaries looking at these interrelated inflammatory events as a whole instead of discreet disease entities.

Prerequisites for Transdisciplinary Intervention

Before an intervention can occur, practitioners must decide whether they are willing to become involved in combating diabetes. In the concluding statements made by the ADA in Standards of Medical Care in Diabetes (2006), the authors wrote, "Evidence suggests that individual initiatives work best when provided as components of a multi-factorial intervention...it is clear that optimal diabetes management requires an organized, systematic approach and involvement of a coordinated team of healthcare professionals."² Optimal diabetes management also requires a commitment by both dental and medical providers. For large scale change in the delivery of diabetes care to take place, there are certain things that are a prerequisite, most importantly the factors necessary for dental and medical providers to become involved in health promotion and risk reduction of diabetes:

1. Adequate recognition that the role obesity, and other inflammatory conditions such as periodontal disease, may have in amplifying the risk for diabetes
2. A willingness to provide intervention
3. Adequate skills and resources to do so.

Most troubling is the speculation that this level of commitment may be lacking among dental providers.³⁰ If statistics from smoking cessation interventions by dental practitioners can be considered a measure of provider willingness to offer health promotion and risk reduction interventions for diabetes, it appears that dentists' and dental hygienists' willingness to provide interventions may be wanting.³⁰ National surveys suggest that only 30-50% of U.S. dentists and 25% of dental hygienists ask patients about smoking, and smoking cessation advice provided in dental offices has been described as "rather ad hoc and somewhat superficial."³⁰ Fewer than 20% of dentists used a system to identify patients who smoked, and fewer than 5% provided follow-up services to help patients quit.³⁰ One study concluded that among physicians, dentists, mental health counselors, and social workers, cessation interventions by dental providers ranked lowest in terms of both quantity and quality.³⁰ Lack of training and incentives were most often cited to explain the reluctance of dentists and hygienists to provide tobacco-cessation interventions.³⁰ If these findings hold true for dental practitioners' willingness to provide diabetes intervention, dentistry's impact on the pandemic of diabetes will be disappointingly small.

Rather than adding additional interventions to the workload of already overwhelmed medical providers, there are complementary roles and aspects of prevention and treatment that can be delegated to other healthcare professionals. Preventive care increasingly is being delivered by non-physician and non-dentist clinicians.³¹ In fact, nurse-led interventions to treat conditions such as diabetes-related hypertension and hyperlipidemia in clinical settings adjunctive to hospitals have been very successful,³²⁻³⁴ leading some to speculate that if standards of medical care in diabetes "are to be achieved, then such proven methods of delivery care must be adopted."³⁴

For large-scale population-based intervention strategies, the goal should be to develop highly-coordinated and well-trained provider teams that function as case-management teams to provide transdisciplinary care to diabetic patients. These teams could include nurses and dental hygienists along with other allied healthcare providers, such as diabetes educators, nutritionists, exercise physiologists, sports medicine professionals, pharmacists, and social workers, (among others). Such teams also could function as delegations of educators by presenting panel discussions on prevention and treatment of diabetes and periodontal disease. Target audiences could include citizen groups, PTAs, self-help/support groups, pre-kindergarten, elementary, middle, high schools, colleges and universities, hospitals, specialty care facilities, churches, nonprofit groups involved with health and human welfare, chambers of commerce, Rotary clubs, and the like. The same teams also could function as "swat teams" for conducting large-scale screenings for diabetes and periodontal disease at malls, transportation hubs, grocery stores, and community fairs. For an excellent template for organizing community-based initiatives that target obesity, readers should contact the National Heart, Lung, and Blood Institute to request We Can! Ways to Enhance Children's Activity and Nutrition; Energize our Community: Toolkit for Action, online at <http://email.nhlbihin.net> or by phoning (301) 592-8573.

These kinds of intervention strategies take root in healthcare communities where the philosophy of care is grounded in wellness over repair. Putting this collaborative model of care into practice will require "thought leaders" in dentistry and medicine who are willing to collaborate, and develop a plan for transdisciplinary team training, and assign responsibility for coordination. As momentum builds, other healthcare professionals will become willing partners. Teams can expand their reach by enlisting media support of local newspaper columnists, extending invitations to media representatives to cover an event such as a diabetes and periodontal disease screening day at a mall, or through interviews and discussions on local talk radio. Another valuable collaborative opportunity is to partner with state or local professional organizations, e.g., associations of nurses, diabetes educators, dental hygienists, and dieticians.

On a private practice level, dental professionals who are interested in collaborating with medical providers on diabetes care, building a micro-system of collaboration between a general dental practice and a primary care medical practice will provide the framework for cross referral of patients. To assist dental providers in developing micro-systems of collaboration with primary care medical providers, a questionnaire designed to help identify gaps in knowledge of evidence based research, training, equipment and supplies, and weaknesses in protocols related to prevention and treatment of diabetes in the dental practice is provided. The questionnaire, entitled Needs Assessment for

Implementation of Appropriate Prevention, Screening and Treatment of Diabetes in Dental Practice Settings may be accessed and downloaded from the Clinical Decision-Making Tools section at www.thesystemiclink.com. In addition, the National Diabetes Education Program recently launched an online resource at www.betterdiabetescare.nih.gov to help healthcare professionals better organize their diabetes care and help users design and implement more effective healthcare delivery systems for those with diabetes.²

Dental and Medical Providers

Transdisciplinary Intervention Opportunities for Dental and Medical Providers

Opportunities for transdisciplinary intervention of diabetes for dental and medical providers exist at all levels of prevention (i.e., primordial, primary, and secondary).

Primordial Prevention

Primordial prevention of diabetes includes targeting the prenatal state, childhood, and adolescence to promote healthy lifestyles before risk factors are acquired. Today, it is known that the atherosclerotic process begins in youth, culminating in the risk factor-related development of vascular plaque in the third and fourth decades of life.⁷ Good nutrition, a physically active lifestyle, and absence of tobacco use contribute to lower risk prevalence and either delay or prevent the onset of cardiovascular disease.⁷

Central to these measures is education about the benefits of optimal nutrition and physical activity.⁷ According to the American Heart Association (AHA), "To be sedentary, have a nutritionally adequate diet, and to avoid excessive caloric intake in contemporary society is difficult."⁷ To address the crisis associated with the obesity epidemic, the AHA formulated the concept of energy balance. The concept of energy balance has simplified the science of matching appropriate energy intake to energy expenditure. For example, new dietary guidelines for populations between the ages of 3 and 18 have adjusted daily calorie requirements downward to reflect the prevalence of a sedentary lifestyle. Those children and adolescents who have increased physical activity will require more calories.⁷ Health promotion today that addresses the dangers associated with children's over-consumption of energy-dense, nutrient-poor foods and beverages and physical activity patterns will help reduce the risks for future chronic degenerative diseases such as CVD, type 2 diabetes, cancer, obesity, and osteoporosis.³⁴ Patient education material that helped parents understand the risks of childhood and adolescent obesity and the suspected link to gum disease is located in the Patient Education Material section which can be accessed and downloaded from www.thesystemiclink.com.

Healthcare providers must provide useful advice about diet to parents but are often constrained by time to provide that level of care. However, information on caloric/energy values of food can be provided through literature and referral to the abundance of consumer-oriented websites. Parental participation in plotting a child's BMI percentile followed by clinical assessment of those results against standard growth curves allows parent/clinician coassessment of a child's weight gain in a given time period. Healthcare providers are urged to access the CDC's website at www.cdc.gov/growthcharts (Figure 2), which contains important information and detailed steps to plot BMI-for-age for pediatric patients. Dental providers have a joint responsibility with members of the medical community to develop and implement these types of interventions that begin prevention of chronic diseases early in life. Yet, unless healthcare providers believe that certain dietary practices are harmful and start to understand that inaction may endanger their patients, motivation to change will be very limited.

Primordial prevention of periodontal disease includes targeting women of child-bearing years to ensure periodontal wellness before pregnancy, and education of children and adults regarding the importance of oral health in ensuring systemic health.

Primary Prevention

Primary prevention of diabetes includes aggressive screening and risk-reduction strategies targeting patients with risk factors for diabetes and patients with undetected diabetes. Approximately one-third of all diabetics may be undiagnosed,² and dental providers are uniquely positioned to identify these undetected cases. Insurance utilization patterns indicate that individuals tend to seek routine and preventive oral healthcare on a more frequent and regular basis than routine and preventive medical care,³⁵ placing dentists and dental hygienists at the front line of screening interventions. In the 2006 Standards of Medical Care in Diabetes, the ADA has established criteria for screening for diabetes in asymptomatic adults and children.² ADA Criteria for testing for diabetes in asymptomatic adults and ADA criteria for testing for type 2 diabetes in children may be accessed in the Clinical Decision-Making Tools section at www.thesystemiclink.com. These screening criteria can be easily incorporated into new patient as well as periodic dental examinations.

Besides screening for diabetes utilizing the criteria recommended by the ADA guidelines, astute clinicians also will be aware of any oral conditions that may be a manifestation of diabetes. Some of these include xerostomia, which may be related to thirst (a symptom of diabetes), oral mucosal diseases such as lichen planus, recurrent aphthous stomatitis and oral fungal infections, the presence of opportunistic infections like candidiasis, disturbances in taste, and neurosensory disorders such as burning mouth syndrome.³⁶ Gingivitis is almost twice as prevalent in populations of diabetic children and adolescents as it is in age-matched cohort groups without diabetes.³⁷ For those children who present with gingivitis, looking for less obvious signs of diabetes or unattended risk factors may help identify undetected cases, which can then be referred to a physician for diabetes testing.

Several interventions targeting risk reduction should be noted. Moderate weight loss improves glycemic control, reduces CVD risk, and may prevent the development of type 2 diabetes in pre-diabetic individuals.² There is a significant body of evidence that suggests that being overweight in childhood and adolescence is associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood.³⁸ It is also known that weight loss in obese children and adolescents improves insulin sensitivity. The components of the insulin-

resistance syndrome (obesity, hypertension, dyslipidemia, and hyperinsulinemia) track from childhood to adulthood, supporting the conclusion that the precursors of CVD are present early in life. Lifestyle modification and weight control in overweight children and adolescents reduce the risk of developing insulin resistance, type 2 diabetes, and CVD.³⁸ According to the AHA, once a child or adolescent is identified as obese, vigorous clinical efforts should be directed at treatment.³⁸ Currently, these interventions target behavior modification; however, pharmacological approaches are being considered for the future.³⁸ Clinicians are cautioned to look for subtle signs indicating that children or adolescents are developing insulin resistance. According to the AHA, "The best approach to prevention of future cardiovascular disease in these young patients is early recognition and aggressive therapy."³⁸ Without this, it is likely that this patient population is destined to develop cardiovascular complications and require substantial resources for future management.³⁸

The distribution of fat tissue is an independent predictor of diabetes. Abdominal obesity, defined as waist circumference of > 40 inches in men and > 35 inches in women, increases the risk of developing diabetes by 3.5 fold after adjusting for BMI.³⁹ Identifying individuals at risk for MSyn and modifying their risk factors may prevent the progression to MSyn. (Criteria used to establish the presence of the Metabolic Syndrome may be accessed and downloaded from the Clinical Decision-Making Tools section at www.thesystemiclink.com.) For individuals diagnosed with MSyn, modifications of diet, exercise, and other lifestyle factors may help reduce detrimental health consequences.¹⁰

On the dental side, obesity is a significant predictor of periodontal disease independent of age, gender, race and ethnicity, and smoking.³ Evidence suggests that insulin resistance mediates the relationship between obesity and periodontal disease.³ In addition, BMI is positively and significantly related to the severity of attachment loss after adjusting for age, gender, income, education, race and ethnicity, and smoking.³ This increased risk does not vary after adjusting for cholesterol, triglycerides, and CRP.³ An analysis of NHANES III data indicated that waist-to-hip ratio, BMI, fat-free mass, and subcutaneous fat (central adiposity) were significantly correlated with periodontal disease, suggesting that abnormal fat metabolism plays a role in the pathogenesis of periodontal disease.³ Additional research mirrors these risk relationships. Al-Zahrani⁴ and colleagues found that young individuals (18-34 years old) with abdominal obesity (high waist circumference) had an adjusted odds ratio of 2.27 for having periodontal disease. This suggests that obesity could be a potential risk factor for periodontal disease, especially in younger individuals.⁴ Saito⁴⁰ and colleagues found that individuals with upper body obesity (i.e., high waist-to-hip ratios) are at increased risk for periodontal disease. Clearly, promoting healthy nutrition and appropriate physical activity may prevent or decrease the rate of progression of periodontal disease. Patient education material that alerts patients about the role of obesity in increasing the risk for gum disease may be accessed and downloaded from the Clinical Decision-Making Tools section at www.thesystemiclink.com.

Secondary Prevention

Secondary prevention of diabetes is aimed at minimizing the risk diabetic patients have for macro- and micro-vascular complications. Interventions focus primarily on gaining and sustaining glycemic control to the same level as a healthy, non-diabetic individual.⁴¹ Recognizing the less obvious signs of uncontrolled glucose levels, such as poor healing and unresolved infection, and correlating these findings with classic signs and symptoms of uncontrolled diabetes can enable dental providers to identify patients with previously undetected diabetes.

Metabolic control appears to be an important factor in the development and progression of gingivitis.³⁷ For this reason, it is important that children with diabetes be monitored carefully for glycemic control. In a study group of 182 children and adolescents with diabetes and 160 non-diabetic control subjects, Lalla⁴² and colleagues found that diabetes remained highly correlated with periodontitis, especially in 12- to 18-year-olds, and BMI was significantly correlated with destruction of the periodontium. These observations suggest that periodontal destruction may start very early in life for diabetics and become more advanced as children become adolescents, exposing young patients to greater risk for periodontal disease, which in turn complicates glycemic control and increases risk for systemic injury. Programs to promote periodontal disease prevention and treatment should be provided to young diabetic patients.⁴²

Certain subgroups of diabetic people are at higher risk for developing periodontal disease. These include patients with poor oral hygiene, patients with a long history of diabetes, patients with complications of diabetes (i.e., retinopathy, angiopathy, nephropathy, neuropathy, delayed wound healing), patients with poorly controlled diabetes, teenagers, and pregnant women.³⁷

In diabetic patients, the risk of infection may be directly related to fasting blood glucose levels. One study found that patients with fasting blood glucose levels below 206 mg/dL had no increased risk, and patients above 230 mg/dL had an 80% increased risk of developing infection.⁴³ Intensive glycemic control can prevent or delay the onset and slow the progression of microvascular complications associated with both types 1 and 2 diabetes.⁴⁴ Likewise, good glycemic control is associated with improved periodontal status.¹⁹ Insulin-dependent diabetics may also be genetically predisposed to an exaggerated inflammatory response to gram-negative bacterial infections.¹⁷ Compared with non-diabetic individuals, insulin-dependent diabetic patients exhibit this hyperinflammatory response when challenged with an equivalent bacterial burden.¹⁷ There is also evidence suggesting that chronic periodontal infection contributes to the state of insulin resistance.^{45,46} Accordingly, medical providers need to identify patients at risk for periodontitis and incorporate referral protocols into routine practice. Physician recognition that periodontal disease is a chronic gram-negative infection with a direct impact on glycemic control is the first step in developing important collaboration with dental providers.

To provide a more graphic description of the opportunity for systemic seeding of periodontal bacteria throughout the vasculature, it has been estimated that the epithelial surface area potentially exposed to virulent, gram-negative bacteria associated with chronic periodontitis ranges in size from 8 cm² to 20 cm² (ref 47) roughly the average size of an adult palm. For diabetics with poor glycemic control, exposure to a gram-negative infection of this size would pose an obvious threat to systemic health. For this reason, healthcare providers from both medicine and dentistry must be familiar with the glycemic control (HbA1c) of patients so that they can formulate specific preventive or treatment plans to mitigate diabetic complications. For example, dental providers may prescribe more aggressive treatment of periodontal disease or increased frequency of maintenance care, and medical providers may be more vigilant in identifying patients with poor glycemic control who are at risk

for infection, including periodontal disease. Accordingly, medical providers should update dentists on a patient's glycemic control, and dental providers should apprise physicians of a diabetic patient's oral status to help regulate their blood glucose levels.³⁶

Conclusion

A shift to preventive medicine may very well be on the way. In the past few years, insurers have begun adding preventive-care benefits to many plans, and some insurers are paying for preventive care, regardless of whether deductibles have been satisfied.⁴⁸ Yet, there is still convincing to be done - financial models which demonstrate that expenditures made for prevention and wellness promotion will translate into cost savings in the not-so-distant future. The dream case for demonstrating that investment in prevention reduces morbidity and related costs in the long-term is calculating the return on investment for tobacco-cessation services.⁴⁹ Over the last 10 years, there has been a dramatic increase in benefits for tobacco-cessation interventions. Research has shown that investing \$.18-\$.79 per member per month to offer a tobacco use-treatment program involving the "5 A's" plus "Quitline" support and nicotine-replacement therapy generated a positive net return on investment of over \$1.70-\$2.20 per member per month after 5 years.⁵⁰ Some authorities suggest that the framework now in place for treatment of tobacco use could be adapted to address obesity.⁵⁰

Equally exciting is that some insurers are starting to look at chronic conditions associated with periodontal disease. One recently reported study sought to quantify the effect of periodontal treatment on the reduction of overall risk and medical expenditures for diabetes, coronary artery disease, and cerebrovascular disease (CVD) in a large population of patients with both dental and medical benefits from one company.⁵⁰ The conclusions were that earlier periodontal treatment resulted in lower medical costs for diabetes, CAD, and CVD.⁵⁰

Consider the case of an obese, 57-year-old white male with type 2 diabetes, with his last three HbA1c values over 8.0%, advancing retinopathy, and recently diagnosed periodontal disease. This patient just experienced his first non-fatal myocardial infarction (MI). His familial history of diabetes has been known for over 40 years, and hyperlipidemia and hypertension were diagnosed over 25 years ago. Given what we now know, what interventions could we have employed 40, 30, 20, or even 10 years ago that may have prevented this outcome? Diabetes, heart damage and periodontal disease cannot be reversed to a state of biological health even with the most progressive medical and dental care. At best, our current healthcare system can only offer this man treatment aimed at minimizing the risk for future MIs, and delaying the advance of retinopathy and tooth loss. What can be said about the missed opportunities for prevention earlier in his life? What's more, if this patient does not control his blood sugars, he is at significantly greater risk for a second MI which is likely to be fatal.

It is time to take a fresh look at the pandemic of diabetes, a tidal wave that threatens to engulf our current healthcare system. The responsibility for diabetes prevention, diagnosis, and treatment cannot rest primarily on the shoulders of medical providers. The problem is just too big. Mobilizing the dental profession is critical for large-scale intervention of diabetes. Dental professionals who fully understand the immuno-inflammatory relationship between diabetes and other chronic disease states, and adopt a syndemic orientation, will make the greatest contribution to preventive interventions. Their commitment and cooperation must be enlisted to implement prevention strategies that reinforce and complement the recommendations embodied within the most recent standards of medical care for diabetes (2006).² Ultimately, the medical and dental professions' level of commitment will be decided by individual practitioners. For those who decide to "dig in," rewarding patient interventions are just around the corner, as are new opportunities for collaboration in transdisciplinary care.

Note from Co-Author Doreen Small, RN, MA, CDE: As a clinical nurse specialist in diabetes for more than 31 years, I have had the opportunity to observe the evolution of both the profession of nursing and the management of diabetes. Nursing has evolved into a diversified profession with nurses not only providing bedside but ambulatory care. Nurses in private practice settings, those in education, and those in research are eager to solve the many still-unanswered questions about diabetes and its management. Nurses also have expanded their focus to include prevention. I see the role of the dental hygienist undergoing a similar transformation, with both nurses and hygienists expanding their focus and practicing in a more holistic, syndemic manner.

As a result of research, we know that complications of diabetes can be avoided. Individuals with diabetes no longer have to anticipate experiencing the loss of vision or kidney function experienced by parents, aunts, and uncles. We have blood-glucose monitors to measure control, and patients are taught how to manage their own disease by adjusting exercise and food intake on the basis of blood-glucose results. Likewise, knowledge of the relationship between chronic inflammatory conditions such as diabetes and oral health is evolving. This creates a need to modify the delivery of care in medical and dental settings. Working in a transdisciplinary manner, we can triple our successes in combating the epidemic of diabetes.

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Figure 1 - Syndemic relationships of the interrelated cluster of chronic inflammatory disease states

The blue nodes represent diseases or conditions, and the ties represent forces (environmental and acquired risk factors) that cause the diseases or conditions and bind them together. Healthcare providers have been trained to focus mainly on the nodes, i.e., obesity, diabetes, hypertension, periodontal disease. These forces (ties) are as much of a problem as the diseases themselves, and the prevalence of chronic diseases may persist unless the connecting forces are addressed. To affect change, intervention strategies that disrupt these ties must be developed and implemented.

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PERIODONTAL DISEASE, INSULIN RESISTANCE, AND DIABETES MELLITUS: A REVIEW AND CLINICAL IMPLICATIONS

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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 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 E₂ (PGE₂).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 cm² (approximately 3 in² 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 without 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/m², 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 affect 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 patients 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/m² than in patients with BMI \leq 20 kg/m².^(ref 65) Patients with BMI \leq 30 kg/m² 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 inflammation 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 periodontitis⁸⁵ and 11 times the risk of progressive bone loss⁸⁴ 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-1 β , TNF- α , and PGE₂.^{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 glycosylated 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-1 β 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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Oral Health in Diabetes Care Gaining Traction at the American Diabetes Association

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by Casey Hein, BSDH, MBA

What might the therapeutic potential be if physicians recognized that untreated periodontal disease, like any other chronic infection, increased the systemic inflammatory burden, and posed a threat to the diabetic patient? What if the care of a diabetic patient was no longer fragmented and medical and dental providers collaborated on integrating care and shared joint responsibility for clinical outcomes? What if there were guidelines in place that provided the framework for cross referral of the diabetic patient, i.e., dentists' referral to a physician of a patient suspected to have diabetes which is undiagnosed and physicians' referral of a diabetic patient who is suspected to have periodontal disease which has not yet been diagnosed?

Evidence validating the bi-directional relationship between diabetes and periodontitis has been recognized in dentistry for decades but traditional medical guidelines for diabetes management have failed to factor in the significance of oral infections. Even the most recently updated guidelines, Standards of Medical Care in Diabetes-2006,¹ made little reference to the priority of oral health in diabetic management. Of note, periodontitis was still not included as a complication of diabetes, and dentists were not included among healthcare providers who should be considered for referral of diabetic patients. Many within the dental profession thought the role of oral diseases and conditions in increasing the risk for diabetic complications would go largely unrecognized by the medical community. That might be starting to change.

With the updated standards for medical care in diabetes published only 4 months ago, it seems the American Diabetes Association (ADA) is already rethinking the importance of oral health. Indeed, the perception of the medical community regarding oral infection as simply a localized threat might be starting to change. According to Nathaniel G. Clark, MD, MS, RD, Vice President of Clinical Affairs for the ADA, the issue of the relationship between diabetes and oral diseases and conditions has risen to the surface and there is now momentum within the ADA to address this practice gap (N. Clark, oral communication, March 2006).

In discussing what prompted the ADA to revisit the importance of oral health in diabetic management, Clark compared the ADA's new interest in developing oral care protocols to the evolution the ADA went through in revising guidelines that recognized certain risks associated with anti-psychotic drugs. Although psychiatrists had long witnessed the therapeutic challenges associated with placing patients on anti-psychotic drugs (weight gain, development of diabetes), few outside the psychiatry community were as astutely aware of the potential deleterious effects of these drugs in their patients. Similarly, reasoned Clark, although dental providers have long been aware of the bi-directional relationship between diabetes and oral infections, the medical profession may not have understood this as well. The increased risk diabetic patients have for periodontal disease and the effect of periodontal infection on glycemic control with the potential for ratcheting up the risk for diabetic complications, has not been readily apparent to most within the medical community until recently. Clark cited the growing body of related literature in both dental and medical journals as significant in bringing about this increased level of awareness of the ADA. In his own diabetes practice, Clark noted, "As long as [diabetic patients] have ongoing infections in their mouths, their diabetes is very difficult to manage often leading to the need for more and more insulin."

Clark reported that the Professional Practice Committee of the ADA will soon be looking at what reasonable conclusions may be drawn from the scientific evidence that currently exists to support the bi-directional relationship between diabetes and periodontal disease. Their scientific inquiry will also include looking at other oral complications of diabetes such as xerostomia, dental caries, candida infection, burning mouth syndrome, and lichen planus. According to Clark, plans to develop a consensus statement and care management guidelines may soon be underway.

On the dental side of the collaboration equation, getting involved with the active management of diabetic patients may be a stretch for some within dentistry.² A study designed to investigate general dentists' and periodontists' willingness toward assessment and management of the patient with diabetes was conducted and recently reported by researchers from Columbia University.² Analysis of the data from the small sample of practitioners who were surveyed found that there is a need to increase periodontists' and general dentists' involvement in the active management of the diabetic patient.²

The commitment of the American Diabetes Association in drafting more progressive protocols related to oral health in diabetes management is unprecedented. Undertaking this level of progressive disease management has the greatest potential to succeed in a delivery system that is integrated and coordinated. We can only hope those on the dental side will also embrace this as a valuable opportunity for collaboration.

References

1. American Diabetes Association. Standards of Medical Care in Diabetes-2006. Diabetes Care 2006;29 (Suppl 1):S4-33.

2. Kunzel C, Lalla E, Lamster IB. Management of the patient who smokes and the diabetic patient in the dental office. J Periodontol 2006;77:331-340.

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Tools for Implementation

As a courtesy to the professions, Grand Rounds in Oral-Systemic Medicine™ has designed patient education materials, information for clinical decision-making, and templates of letters to assist dentists in developing collaborative relationships with the medical community. Readers are invited to reproduce these copyrighted materials by accessing and downloading (for free) this information from the Grand Rounds website at www.thesystemiclink.com. Collateral case study information may also be accessed and viewed/downloaded from this website.

Listing of the materials available through www.thesystemiclink.com:

Patient Education Materials

- Alerting patients about the role of obesity in increasing risk for gum disease
- Helping parents understand the risks of childhood and adolescent obesity and the suspected link to gum disease
- Helping patients with diabetes understand the 2-way relationship between diabetes and gum disease

Clinical Decision-Making Tools

- ADA criteria for testing for diabetes in asymptomatic adults
- ADA criteria for testing for type 2 diabetes in children
- Criteria used to establish the presence of the Metabolic Syndrome
- Needs assessment for implementation of appropriate prevention, screening and treatment of diabetes in dental practice settings

Templates of Letters for Dentist-Physician Communications

- Template for dentist's referral to a physician for evaluation of a periodontal patient who is at risk for diabetes or suspected to have undiagnosed diabetes
- Template for dentist's request to a physician for a complete physical evaluation and analysis of blood chemistries on a diabetic patient who has been stable in periodontal maintenance until recent changes in periodontal disease activity

Collateral Case Study Information (Ryan, Carnu, Tenzler)

- Case Study 2: Intraoral images and panorex radiographs
- Case Study 3: Radiographs and periodontal chartings
- Case Study 4: Radiographs, periodontal chartings and intraoral images

To assist dentists in developing collaborative relationships with the medical community, Grand Rounds in Oral-Systemic Medicine™ has provided templates for dentists working in collaboration with physicians of at-risk patients.

These letters may be customized for individual patients by editing the fields (which appear in red typeface) as they are related to the unique risk profile and periodontal treatment plan of a specific patient.

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