Original Article

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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*(A complimentary copy of this article may be downloaded at **www.thesystemiclink.com**.)*

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 1920s[1] 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 nephropathy[3] 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 Löe, 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

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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, dieticians, 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).

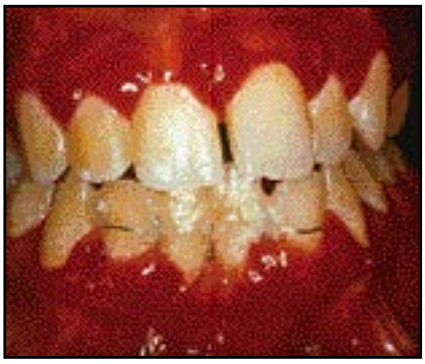

Figure 1

Case 1. Clinical presentation of severe periodontitis in an adolescent girl with type 1 diabetes and poor glycemic control.

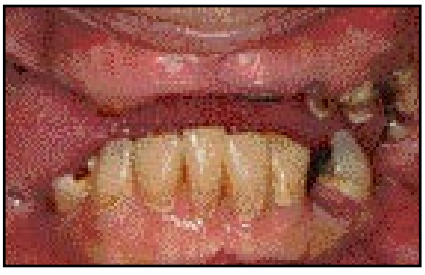

Figure 2

Case 2. Clinical presentation of severe periodontal disease and generalized caries in a 46-year-old female with type 2 diabetes.

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 prostanoids, all known to have a profound effect on diabetic patients, leading to insulin resistance, and resulting in difficulties in achieving glycemic 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 us-

[i] Lantus®, Sanofi Aventis, Bridgewater, NJ
[ii] Synthroid®, Abbott Laboratories, Abbott Park, IL
[iii] Altace®, King Pharmaceuticals, Bristol, TN

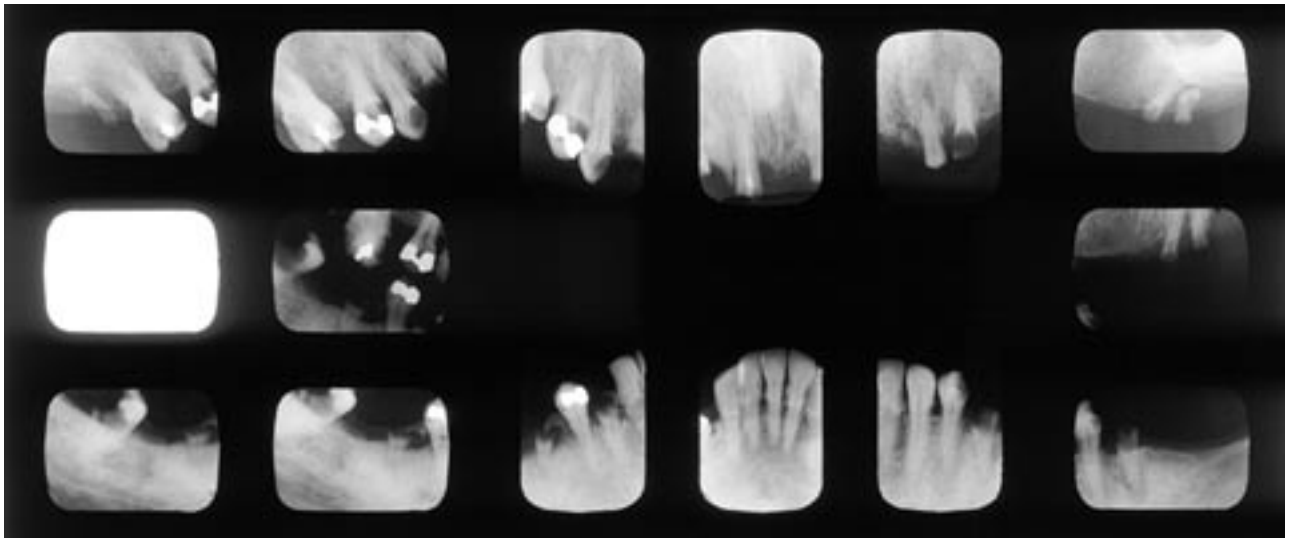

Figure 3

Case 2. Radiographic presentation of severe periodontal disease, generalized caries and abscesses in a 46-year-old female with type 2 diabetes.

ing 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 patients average glycemia over the past 2 to 3 months[37] (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 diabetes[10] 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 reinstituted. 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 results[38] of periodontal treatment with simultaneous improvements in the glycemic control of diabetic patients, as assessed by significant

[iv] Arestin®, OraPharma, Inc., Warminster, PA
[v] Atridox®, CollaGenex Pharmaceuticals, Newtown, PA
[vi] Periochip™, Dexcel Pharma, Jerusalem
[vii] Periostat®, CollaGenex Pharmaceuticals, Newtown, PA

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/copolymer[viii] 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.

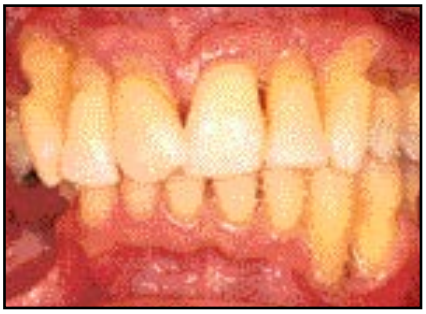

Figure 4

Case 3. Cinical presentation of severe periodontal disease in a 66-year-old male with poorly controlled type 2 diabetes.

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 sam-

Table 1
Case 3. Blood chemistries of a 66-year-old type 2 diabetic male

Blood Levels	Baseline	4 mo. post therapy
Serum Glucose (mg/dL)	288	237
Glycated Hemoglobin (%)	9.1	9.5
Serum TNF-α (pg/ml)	1793.3	400.0
Serum IL-6 (pg/ml)	6.8	4.7
Culture IL-1β (pg/ml)	(-)LPS/(+)LPS 262.4/898.4	(-)LPS/(+)LPS 64.0/382.0

[viii] Colgate® Total® Toothpaste, Colgate-Palmolive, Piscataway, NJ
[ix] Cleocin®, Pfizer, New York, NY
[x] Vasotec®, Merck Worldwide

ples 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-1β, 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.

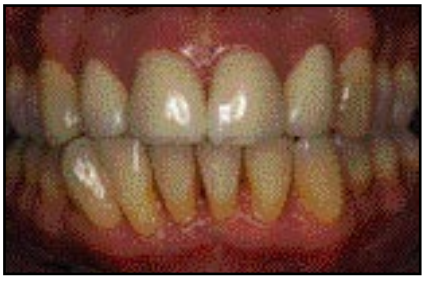

Figure 5

Case 4. Clinical presentation of severe periodontal disease of a 34-year-old, type 1 diabetic female.

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 study[49] 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

Table 2
Case 4. Blood, urine, and GCF analyses from baseline to 6 months after therapy

Serum

	HGB A1C (%)	HS CRP (mg/L)
Normal Range	4.1 - 6.5%	*<1.0
Baseline	10.5	3.9
6 Months	9.5	.7

GFC

	IL-1β (pg/ml)	IL-8 (pg/ml)	VEGF (pg/ml)
Normal Range	—	—	—
Baseline	176.43	513.45	9.96
6 Months	1.75	24.58	undetectable

Urine

	Random urine Microalbuminuria (MG/DL)	Albumin/ Creatinine Ratio (MG/G)	Random Urine Protein (MG/DL	IL-1β (pg/ml)	IL-8 (pg/ml)	VEGF (pg/ml)
Normal Range	<1.9	0 - 25	—	—	—	—
Baseline	273	3995	375.1	1.16	26.51	7.78
6 Months	58	2180.5	84.2	undetectable	2.98	2.01

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

[xi] Humalog®, Eli Lilly, Indianapolis, IN
[xii] Lasix®, Sanofi Aventis, Bridgewater, NJ
[xiii] Zoloft®, Pfizer, New York, NY

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-1β, 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 it's 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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Dr. Ryan is a consultant, serves on a number of advisory boards and is named on patents as an inventor of therapeutic applications of tetracyclines discussed in this article. These patents have been fully assigned to the research foundation of Stony Brook University, State University of New York, Stony Brook, NY, and have been exclusively licensed to CollaGenex Pharmaceuticals, Newtown, PA.

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