Diabetes mellitus and inflammatory periodontal diseases

Brian L. Mealey[a] and Louis F. Rose[b]

[a]Department of Periodontics, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA and [b]University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania, New York University School of Dentistry, New York, New York, and Drexel University College of Medicine, Philadelphia, Pennsylvania, USA

Correspondence to Louis F. Rose, DDS, MD, Clinical Professor of Periodontics at the University of Pennsylvania School of Dental Medicine, 100 South Broad St, Suite 2020, Philadelphia, PA 19110-1009, USA
Tel: +1 215 563 7688; e-mail: lfrddsmd@verizon.net

Current Opinion in Endocrinology, Diabetes & Obesity 2008, 15:135–141

Purpose of review

Periodontal diseases are inflammatory conditions that were once thought to have manifestations localized to the oral cavity alone, and were therefore considered the concern of only dentists and other oral health professionals. Emerging evidence has changed this view and now suggests that periodontal diseases may play a role in numerous conditions that impact systemic well being, including diabetes mellitus. This review examines the relationships that exist between periodontal diseases and diabetes mellitus, with a focus on potential common pathophysiologic pathways including those associated with inflammation, altered host responses, and insulin resistance.

Recent findings

Periodontal inflammation is associated with an elevated systemic inflammatory state and an increased risk of major cardiovascular events such as myocardial infarction and stroke, adverse pregnancy outcomes such as preeclampsia, low birth weight and preterm birth, and altered glycemic control in people with diabetes. Intervention trials suggest that periodontal therapy, which decreases the intraoral bacterial bioburden and reduces periodontal inflammation, can have a significant impact on systemic inflammatory status. Evidence suggests that periodontal therapy is associated with improved glycemic control in many patients with both diabetes and periodontal diseases.

Summary

Recognition of the bilateral relationships between oral and systemic health will challenge physicians and dentists to work together closely in the future when managing patients with diabetes and periodontal disease.

Keywords

diabetes mellitus, inflammation, insulin resistance, periodontal diseases

Curr Opin Endocrinol Diabetes Obes 15:135–141.

1752-296X

Introduction

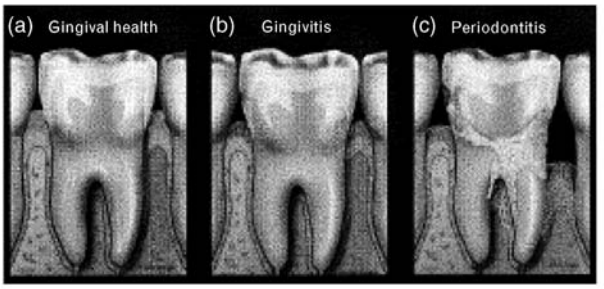
Diabetes mellitus and periodontal diseases are both chronic inflammatory disorders that have a major impact on the health and well being of millions of individuals worldwide. Periodontal diseases are among the most common diseases in humans; therefore, if the presence of periodontal diseases plays any role in overall systemic health, the public health impact may be substantial. Evidence consistently reveals that diabetes is a risk factor for increased severity of gingivitis and periodontitis [1••]. Conversely, periodontitis is a risk factor for worsening glycemic control in patients with diabetes, and may increase the risk for diabetic complications [1••,2]. While associations between periodontal diseases and several chronic systemic diseases have been demonstrated in recent years, the most consistently supported interaction has been that between periodontal disease and diabetes [1••,3•].

Inflammatory periodontal diseases and overall systemic effects

Approximately 75% of adults in the United States have gingivitis (inflammation of the gingival tissues surrounding the teeth), while about 35% have periodontitis (inflammation involving the supporting structures of the teeth including the periodontal ligament and alveolar bone) [4]. Severe periodontitis resulting in loss of alveolar bone, destruction of the connective tissue attachment between the bone and the root surface of the tooth, and formation of deep pockets around the teeth is seen in about 13% of Americans (Fig. 1).

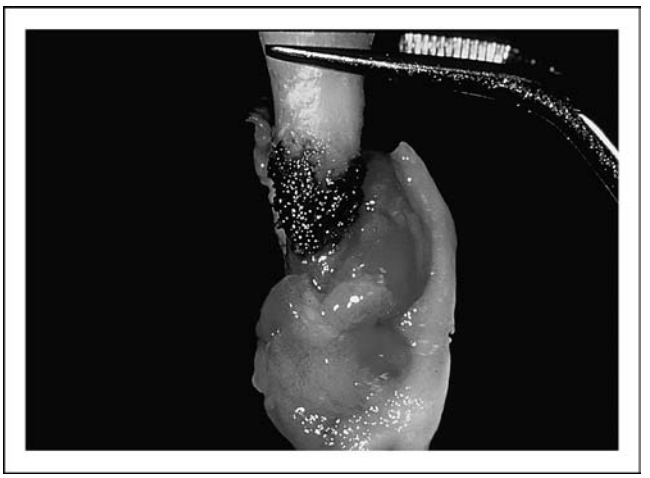
The periodontium is a unique ecological niche in the human body. In people without teeth, the mucosal lining of the oral cavity is intact and is inhabited by a commensal bacterial microbiota that provides little challenge to the host, similar to that seen on an intact skin surface. The

Figure 1 Transition from gingival health to periodontal disease



(a) Gingival health occurs in subjects with impeccable oral hygiene, minimal plaque biofilm, and the absence of clinical inflammation. (b) In gingivitis, ineffective plaque biofilm control results in clinical signs of soft tissue inflammation (gingival erythema, edema and bleeding). (c) Patients with periodontitis exhibit significant deep inflammatory changes, including tissue destruction (periodontal pocket formation, clinical attachment loss, and alveolar bone resporption). Adapted with permission from F.A. Scannapieco, *Compendium of Continuing Education in Dentistry*; Published by Dental Learning Systems Co., 2004.

Figure 2 An extracted tooth with the gingival tissue attached



The soft tissue was reflected from the tooth allowing for the visualization of the subgingival calculus and plaque, as well as the chronic granulation tissue lining the internal aspect of the periodontal pocket. Photograph taken by Dr Bobby Roman, Jacksonville, Florida, USA.

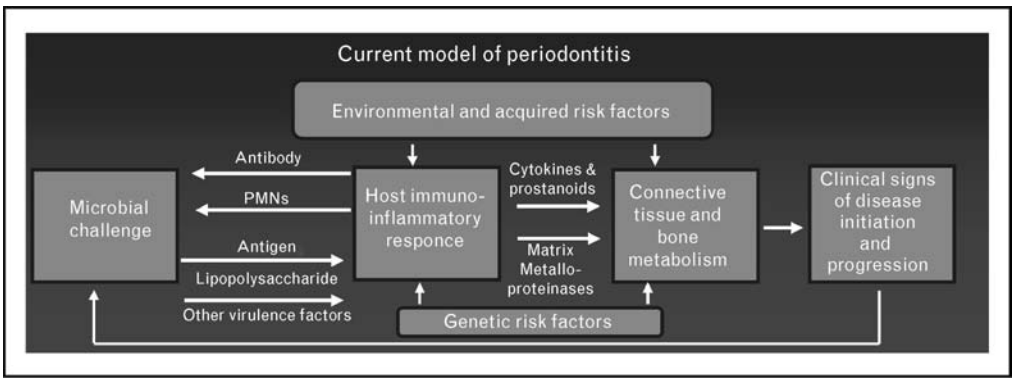
presence of teeth changes this ecological niche because the teeth project through the mucosal surface. An analogous situation would be a skin surface into which an intravenous catheter or an ostomy is placed. The formerly intact skin surface is now interrupted and the junction between the skin surface and the ostomy or catheter becomes a site of persistent microbial challenge. At the junction between the gingiva and the tooth, there is a space known as the 'gingival sulcus' in health and the 'periodontal pocket' in disease. In the sulcus or pocket there exists a delicate balance between microbial colonization and host defense. Periodontal diseases are initiated by bacteria residing in biofilms along the tooth surface at this interface of the gingival tissues and the tooth, many of which are Gram-negative and anaerobic [5]. There is a persistent microbial wound present at this site, a wound contaminated by any of the more than 400 bacterial species present in the mouth. An intact wound healing response is necessary to prevent local tissue destruction or systemic dissemination of bacterial products (Fig. 2).

Biofilm-related products released into the periodontal pocket include bacterial endotoxins, chemotactic peptides and organic acids [6••]. Inflammation results in ulceration of the epithelial pocket lining, providing ready access of these compounds into the gingival tissues. This results in further stimulation of the host response, activation of host enzymes including matrix metalloproteinases, and release of pro-inflammatory cytokines such as IL-1, TNF-α, IL-6, IL-17, and prostaglandin E_2 (PGE_2), among others [1••]. This cascade of events leads to eventual destruction of periodontal tissues (Fig. 3).

In untreated severe periodontal disease, the cumulative surface area of ulcerated pocket epithelium has been estimated to range from 8 to 20 cm^2, which approximates the size of the palm of an adult hand [7]. Thus, the potential for bacterial products and resultant inflammatory mediators to reach the systemic circulation is significant. Bacteremia and endotoxemia can be induced by dental procedures as well as by normal daily activities like chewing and tooth brushing [8,9]. In one study [10], chewing induced systemic endotoxemia in 40% of patients with periodontitis compared to only 12% of periodontally healthy patients; furthermore, the concentration of endotoxin was five-fold greater in the bloodstream of subjects with periodontitis. This study clearly demonstrates that periodontitis can result in systemic dissemination of bacterial products during daily function.

There is a large body of evidence demonstrating elevated serum markers and mediators of inflammation in individuals with periodontitis, particularly if the periodontal destruction is severe or affects numerous teeth [11,12]. Periodontal therapy has been associated with a subsequent decrease in these serum inflammatory markers, such as IL-6, TNF-α, and C-reactive protein (CRP) [13]. Periodontitis is also associated with endothelial dysfunction and elevated serum levels of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. Periodontal therapy results in improved endothelial function and reduction in these cell adhesion molecules [14••]. Periodontitis has also been shown to induce a prothrombotic state, with elevations in serum von Willebrand factor and plasminogen activator inhibitor-1 (PAI-1) [15]. It is thus clear that the presence of periodontal inflammation has effects that range well

Figure 3 Bacteria are necessary agents in the pathogenesis of periodontitis



Bacteria and their antigens stimulate a host immunoinflammatory response, which serves to destroy the pathogenic organisms. The response can also result in tissue destruction, however, through the production of proinflammatory cytokines and mediators. Production of certain proteases enhances tissue destruction. Variability in this immunoinflammatory response between individuals may alter the protective versus destructive nature of the response. This variability may be due to a variety of genetic and environmental factors that increase or decrease the risk for disease expression, such as diabetes.

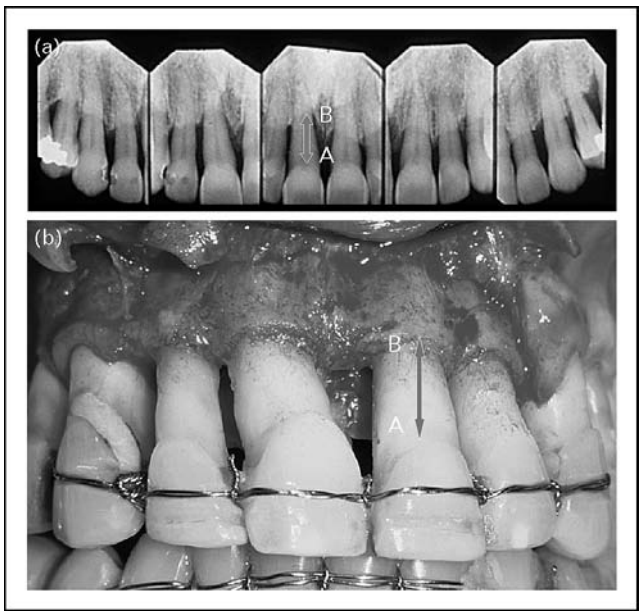
beyond the oral cavity. In a striking demonstration of this fact, a recent study [16•] examined 67 individuals with severe periodontitis requiring extraction of all remaining teeth. Serum levels of CRP, PAI-1, and fibrinogen were all significantly reduced 12 weeks following extraction. Similarly, total white blood cell count and the number of neutrophils and lymphocytes decreased significantly following treatment. Tooth extraction results in elimination of the periodontal pocket and eradication of the ecological niche in which the local and systemic challenge to the host is instigated by the presence of biofilm. While nobody would suggest wholesale extraction of all teeth in all patients with periodontitis, this study and others in which periodontal therapy was performed to improve the health of the existing dentition demonstrate that inflammatory periodontitis poses a challenge to the host, and that reduction of periodontal inflammation has potential positive systemic benefits to the host as well.

Impact of diabetes on the periodontium

There is strong evidence that diabetes is a risk factor for gingivitis and periodontitis, and the level of glycemic control appears to be an important determinant in this relationship [1••,17•,18,19]. Diabetes patients with poor glycemic control are at greater risk for progression of periodontal destruction over time, and are more likely to have severe periodontitis than those with well controlled diabetes [20,21]. There are a wide range of mechanisms by which diabetes adversely affects the periodontium [1••,3•]. In general, the mechanisms that explain the classic microvascular and macrovascular complications of diabetes are also operant in the periodontium. The periodontium is a richly vascularized end organ, similar in many respects to the retina and the glomerulus. Thus, accumulation of advanced glycation end products and their effects on cell-to-matrix and matrix-to-matrix interactions, increased tissue oxidant stress, altered endothelial cell function, elevated activity of matrix metalloproteinases, and similar changes seen in the tissues affected by the classic diabetic complications also occur in the periodontal tissues [1••,18].

The periodontium is different from other tissues and organs, as previously mentioned, in that the periodontium undergoes constant wounding from the bacterial biofilm. The immunoinflammatory response, so critical to maintaining periodontal health, is markedly altered in many people with diabetes. Diabetes results in changes in the function of immune cells including neutrophils, monocytes and macrophages. Neutrophil adherence, chemotaxis and phagocytosis are often impaired, enabling bacteria to persist in the periodontal pocket and to significantly increase periodontal destruction [18]. Conversely, the monocyte–macrophage cell line may be hyperresponsive to bacterial antigens in people with diabetes, resulting in significantly increased production of pro-inflammatory cytokines and mediators [22•]. For example, peripheral blood monocytes from individuals with diabetes demonstrate upregulated production of TNF-α in response to antigens from the Gram-negative, anaerobic periodontal pathogen *Porphyromonas gingivalis*, when compared to monocytes from people without diabetes [23]. This hyperinflammatory monocyte/macrophage response results in elevated levels of pro-inflammatory cytokines in the gingival crevicular fluid that is present in the periodontal pocket adjacent to the teeth. Furthermore, poorly controlled diabetes is associated with a two-fold elevation in crevicular fluid IL-1β levels compared to well controlled diabetes [24]. These host defense alterations in diabetes result in increased periodontal inflammation and destruction of the supporting structures of the teeth (Fig. 4).

Figure 4 Periapical radiographs and clinical photographs demonstrating 70–80% bone loss in a patient with diabetes



(a) The radiographs demonstrate extensive bone loss due to the periodontal infection. In the absence of periodontal infection, one would expect the bone levels to be at position A. (b) Photograph taken during periodontal surgery, after flap reflection, reveals the extent of bone loss B. In the absence of periodontal infection, one would expect the bone levels to be at position A.

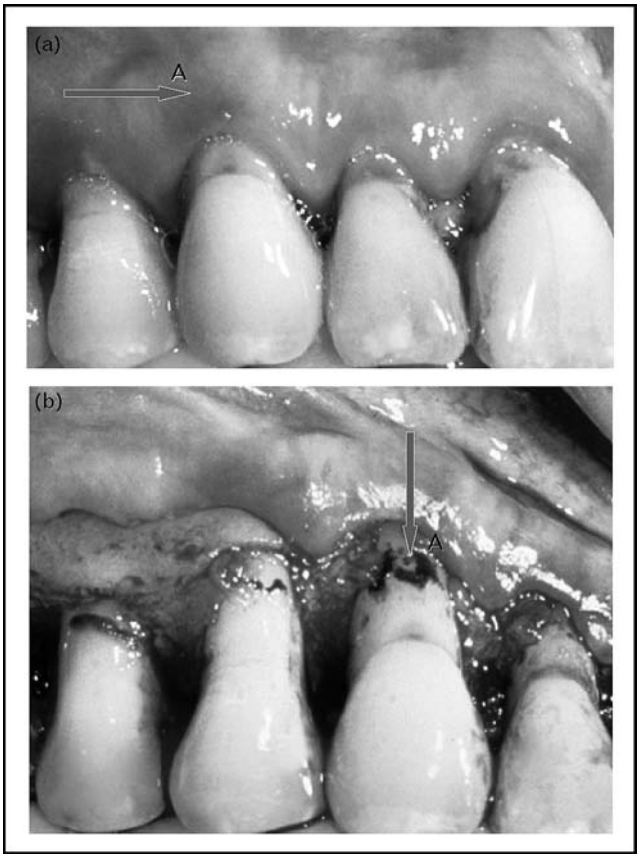
Impact of inflammatory periodontal diseases on diabetes

The presence of periodontal diseases can have a significant impact on the metabolic state in diabetes. Diabetic subjects with periodontitis have a six-fold higher risk for worsening of glycemic control over time compared to diabetic subjects without periodontitis [25]. Periodontitis is also associated with an increased risk for diabetic complications. In one study [2], 82% of diabetic patients with periodontitis experienced one or more major cardiovascular, cerebrovascular or peripheral vascular events during the study period of 1–11 years, compared to only 21% of diabetic subjects without periodontitis. A longitudinal trial [26] examined the effect of periodontal disease on mortality in over 600 subjects with type 2 diabetes. After accounting for other known risk factors, the death rate from ischemic heart disease was 2.3 times higher in people with severe periodontitis than in subjects without periodontitis or with only mild periodontitis, while the death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis. In people with type 2 diabetes, moderate to severe periodontitis was associated with an increased risk of macroalbuminuria and end-stage renal disease by two to three-fold over a follow-up period of up to 22 years, compared to those with little or no periodontitis [27•]. Thus, the presence of periodontal disease is associated with cardiovascular and renal complications in people with diabetes, independent of other risk factors for these conditions.

One of the most important means of determining the impact of periodontal diseases on diabetes is through intervention trials. Periodontal treatment usually consists of the debridement of root surfaces to remove bacterial plaque biofilms and mineralized accretions (calculus). Such debridement, called scaling and root planing, can be done using a nonsurgical approach or following surgical reflection of soft tissue flaps to allow visual and physical access to the root surfaces and alveolar bone. (Fig. 5)

In some cases, systemic antibiotics are used as an adjunct to therapy. In people with diabetes, the tetracycline class of antibiotics has most frequently been used since the tetracyclines are known to decrease production of matrix metalloproteinases such as collagenase, in addition to their antimicrobial effects [28].

Figure 5 Calculus can be seen on the root of the tooth, both before and after reflection of the soft tissue



(a) A patient with periodontitis. Recession is due to loss of underlying bone support. The arrow is identifying subgingival calculus that is visible under the gingival tissue. (b) A flap is reflected to directly visualize and gain access in order to definitively remove the plaque and calculus.

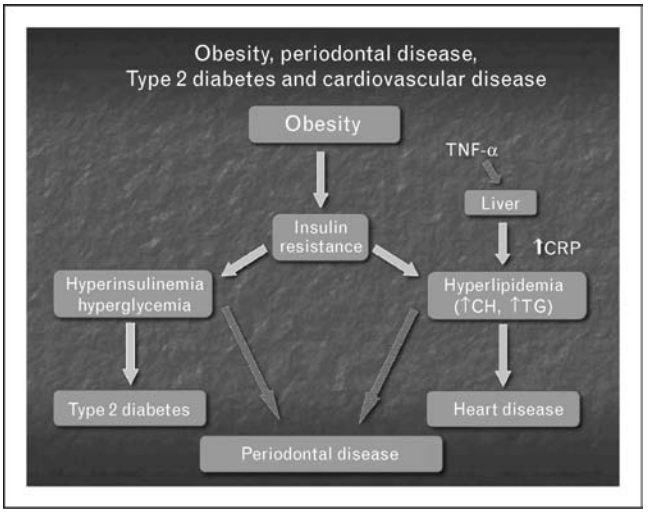
Clinical intervention trials suggest a significant metabolic benefit of periodontal therapy in people with diabetes. Several studies of diabetic subjects with severe periodontitis have shown improvements in glycemic control following scaling and root planing combined with adjunctive systemic doxycycline therapy [29–31]. In these studies, patients demonstrated an approximate 10% reduction in HbA1c levels 2–3 months after periodontal therapy, with no concomitant changes in medical management regimens (an absolute decrease in HbA1c of about 1%). Other studies show that scaling and root planing without adjunctive antibiotics results in improved periodontal health as well as reductions in HbA1c values [32,33]. Not all studies, however, show the same degree of effect. In some, periodontal treatment resulted in improved periodontal health but no significant change in glycemic control [34•]. These conflicting results are difficult to interpret, especially given the wide range of medical treatment regimens used by study populations, which may confound changes related to resolution of periodontal inflammation. In most studies, there is significant heterogeneity in glycemic control changes after periodontal treatment. For example, reductions of one to two absolute HbA1c percentage points may be seen in some subjects after treatment, while other subjects receiving the same therapy may show little change in HbA1c values. In a meta-analysis of 10 intervention trials including 456 patients, the weighted average decrease in absolute HbA1c values was approximately 0.7% following periodontal treatment consisting of debridement and systemic antibiotic therapy, but this reduction was not found to be statistically significant [35]. Heterogeneity in study populations, inadequate sample sizes, and confounding effects of smoking, body mass index, and medications, makes the results of this meta-analysis difficult to generalize.

The impact of periodontal therapy on glycemic control is often related to changes in periodontal health after treatment [29]. That is, HbA1c values are decreased more in subjects who demonstrate greater reduction in periodontal inflammation after treatment than in those who still have considerable inflammation despite therapy. For example, in a study of patients with well controlled type 2 diabetes some subjects received a thorough debridement of the teeth, while control subjects received no treatment [33]. Debridement resulted in a 50% reduction in gingival bleeding and a reduction in mean HbA1c from 7.3% to 6.5%. The control group had no change in gingival bleeding and no improvement in HbA1c (baseline mean 7.0%; follow-up mean 7.3%). Thus, changes in glycemic control may reflect changes in the level of gingival inflammation.

Extensive research has examined the mechanisms by which periodontal diseases might impact glycemic control in diabetes [1••,3•]. From the discussion above, it is clear that inflammatory periodontal diseases may have significant effects on systemic health. Elevations in serum inflammatory and thrombotic mediators such as TNF-α, IL-6, fibrinogen and CRP in individuals with periodontitis may have a major impact on glycemic control, especially through their effect on insulin resistance [36•,37]. These mediators are significantly elevated in the presence of obesity, insulin resistance, hyperglycemia and diabetes [3•]. Obesity and insulin resistance are linked to the actions of IL-6 and TNF-α, and their resultant stimulation of acute phase reactant production in the liver [38]. In individuals with type 2 diabetes and periodontitis, elevated serum inflammatory mediators resulting from the periodontal disease may add to existing insulin resistance, worsening glycemic control (Fig. 6).

A recent study of individuals with type 2 diabetes and periodontitis [39•] demonstrated that serum levels of TNF-α were significantly correlated to the severity of periodontal destruction, but not to the body mass index. Furthermore, a dose–response relationship was seen between the severity of periodontitis and serum TNF-α levels, suggesting that periodontal disease may play a major role in elevating this pro-inflammatory cytokine closely linked to insulin resistance. Animal studies support this concept. For example, in a study of prediabetic Zucker fatty rats (ZFRs) and nondiabetic control rats, periodontitis

Figure 6 Model to describe insulin resistance as a possible mechanism common to periodontal infection and systemic complications such as type 2 diabetes and cardiovascular disease



Insulin resistance (often initiated or exacerbated by obesity) results in hyperinsulinemia and hyperglycemia, which worsens glycemic control. Hyperglycemia may then increase the risk for periodontal disease. Insulin resistance is also associated with hyperlipidemia (CH, cholesterol; TG, triglycerides). Increased TNF-α levels associated with obesity may result in increased C-reactive protein (CRP) production by the liver, further exacerbating hyperlipidemia, Increased lipid levels, particularly low density lipoprotein and triglyceride, increase the risk for heart disease and may play a role in the pathogenesis of periodontal disease.

was induced with placement of ligatures around the teeth in test animals [40]. This resulted in increased glucose intolerance in the ZFRs with periodontitis compared to ZFRs without periodontitis. Most interestingly, periodontitis in lean control rats resulted in increased fasting glucose, insulinemia, and insulin resistance. Therefore, periodontitis affected glucose metabolic regulation in both lean and prediabetic rats.

Periodontal treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control [37,41]. Intervention studies showing improved glycemic control following periodontal therapy would support such a hypothesis. In a pilot study of subjects with type 2 diabetes and periodontitis [41], periodontal treatment resulted in a significant reduction in serum TNF-α levels, which was accompanied by a significant decrease in mean HbA1c levels from 8.0% to 7.1%. The decrease in HbA1c values was strongly correlated with the reductions in serum TNF-α levels following treatment. Thus, periodontal treatment may reduce inflammation not only locally, but also can decrease serum levels of the inflammatory mediators that cause insulin resistance; thereby positively affecting glycemic control.

Conclusion

Strong evidence demonstrates that diabetes increases the risk for and severity of inflammatory periodontal diseases. Furthermore, the presence of periodontal disease may adversely affect glycemic control in diabetes, and may increase the risk for other diabetic complications. Because periodontal diseases are 'silent' in nature, most patients do not realize they have such conditions until significant destruction has occurred. Likewise, physicians may not know that their patients have a condition that could alter glycemic control and make diabetes management more difficult. It is important for clinicians to discuss with their diabetic patients the increased risk for periodontal diseases. This is especially true for patients who have poor glycemic control, since they are at even greater risk. Patients should be asked whether or not they have seen a dentist in the past 6–12 months. If not, physicians should recommend that patients with diabetes seek a thorough periodontal evaluation by a periodontist or general dentist. Following periodontal therapy, most dentists reevaluate the effects of that therapy several weeks to months after treatment. Many periodontists now request a new HbA1c be performed a few months following periodontal therapy, since they have treated an infection and wish to determine any systemic effects of that therapy. Physicians should expect increased interaction with oral health professionals in the future, as evidence continues to accumulate that inflammatory periodontal diseases and diabetes are closely linked with one another.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 200–201).

1 •• Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. J Periodontol 2006; 77:1289–1303.
This is a broad and detailed review commissioned by the American Academy of Periodontology. It covers scope of bilateral interrelationships between diabetes and inflammatory periodontal diseases.

2 Thorstensson H, Kuylensteirna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol 1996; 23:194–202.

3 • Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontology 2000 2007; 44:127–153.
This is a review of diabetes and periodontitis as individual chronic conditions and as diseases impacting one another.

4 Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States. J Periodontol 1999; 70:13–29.

5 Paster BJ, Bloches SK, Galvin JL, *et al.* Bacterial diversity in human subgingival plaque. J Bacteriol 2001; 183:3770–3783.

6 •• Kinane DF, Bartold PM. Clinical relevance of the host responses of periodontitis. Periodontology 2000 2007; 43:178–193.
This up-to-date review of pathogenesis of periodontal diseases focuses on clinical relevance of evidence for disease susceptibility, risk factors for disease, and immunoinflammatory processes.

7 Hujoel PP, White BA, Garcia RI, Listgarten MA. The dentogingival epithelial surface area revisited. J Periodontal Res 2001; 36:48–55.

8 Daly CG, Mitchell DH, Highfield JE, *et al.* Bacteremia due to periodontal probing: a clinical and microbiological investigation. J Periodontol 2001; 72:210–214.

9 Forner L, Larseon T, Kilian M, Holmstrup P. Incidence of bactermia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol 2006; 33:401–407.

10 Geerts SO, Nys M, De Mol P, *et al.* Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. J Periodontol 2002; 73:73–78.

11 Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005; 76:2106–2115.

12 Loos BG, Craandijk J, Hoek FJ, *et al.* Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol 2000; 71:1528–1534.

13 D'Aiuto F, Parkar M, Andreou G, *et al.* Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res 2004; 83:156–160.

14 •• Tonetti MS, D'Aiuto F, Nibali L, *et al.* Treatment of periodontitis and endothelial function. New Engl J Med 2007; 356:911–920.
This landmark study demonstrated improved flow-mediated dilatation and reduced serum E-selectin levels following periodontal treatment.

15 Bizzarro S, van der Velden U, ten Heggler JMAG, *et al.* Periodontitis is characterized by elevated PAI-1 activity. J Clin Periodontol 2007; 34:574–580.

16 • Taylor BA, Tofler GH, Carey HMR, *et al.* Full-mouth tooth extraction lowers systemic inflammatory and thrombotic markers of cardiovascular risk. J Dent Res 2006; 85:74–78.
Elimination of periodontal inflammation by removing all remaining teeth resulted in reduction in serum markers of inflammation and thrombosis.

17 • Lalla E, Cheng B, Lal S, *et al.* Periodontal changes in children and adolescents with diabetes. Diabetes Care 2006; 29:295–299.
This describes the largest study of periodontal conditions in children and adolescents with type 1 diabetes. It showed significantly greater gingival inflammation and more teeth with periodontitis in children with diabetes than in those without diabetes.

18 Mealey BL. Periodontal disease and diabetes: A two-way street. J Am Dent Assoc 2006; 137 (10 suppl):26s–31s.

19 Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in noninsulin-dependent diabetes mellitus. J Periodontol 1991; 62:123–130.

20 Campus G, Salem A, Uzzau S, *et al.* Diabetes and periodontal disease: a case-control study. J Periodontol 2005; 76:418–425.

21 Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol 2002; 30:182–192.

22 Nassar H, Kantarci A, Van Dyke TE. Diabetic periodontitis: a model for • activated innate immunity and impaired resolution of inflammation. Periodontol 2000 2007; 43:233–244.
This is an excellent review of diabetes and innate immunity, as they relate to periodontitis.

23 Salvi GE, Collins JG, Yalda B, *et al.* Monocytic TNF-α secretion patterns in IDDM patients with periodontal diseases. J Clin Periodontol 1997; 24:8–16.

24 Engebretson SP, Hey-Hadavi J, Ehrhardt FJ, *et al.* Gingival crevicular fluid levels of interleukin-1β and glycemic control in patients with chronic periodontitis and type 2 diabetes. J Periodontol 2004; 75:1203–1208.

25 Taylor GW, Burt BA, Becker MP, *et al.* Severe periodontitis and risk for poor glycemic control in patients with noninsulin-dependent diabetes mellitus. J Periodontol 1996; 67:1085–1093.

26 Saremi A, Nelson RG, Tulloch-Reid M, *et al.* Periodontal disease and mortality in type 2 diabetes. Diabetes Care 2005; 28:27–32.

27 Shultis WA, Weil EJ, Looker HC, *et al.* Effect of periodontitis on overt • nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care 2007; 30:306–311.
In people with type 2 diabetes, the presence of moderate to severe periodontitis was associated with a two-fold increased incidence of macroalbuminuria and a three-fold increased incidence of ESRD compared to those without periodontitis.

28 Golub LM, Lee H-M, Ryan ME. Tetracyclines inhibit connective tissue breakdown by multiple nonantimicrobial mechanisms. Adv Dent Res 1998; 12:12–26.

29 Miller LS, Manwell MA, Newbold D, *et al.* The relationship between reduction in periodontal inflammation and diabetes control: a report of 9 cases. J Periodontol 1992; 63:843–848.

30 Grossi SG, Skrepcinski FB, DeCaro T, *et al.* Response to periodontal therapy in diabetics and smokers. J Periodontol 1996; 67:1094–1102.

31 Grossi SG, Skrepcinski FB, DeCaro T, *et al.* Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol 1997; 68:713–719.

32 Stewart JE, Pager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. J Clin Periodontol 2001; 28:306–310.

33 Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. J Clin Periodontol 2005; 32:266–272.

34 Jones JA, Miller DR, Wehler CJ, *et al.* Does periodontal care improve glycemic • control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontol 2007; 34:46–52.
The most recently published intervention trial showed trends toward improved HbA1c in subjects with poorly controlled diabetes, but not statistically significant. This report is of short-term 4-month results in a longitudinal trial. Results are confounded by altered medical intervention (increased insulin dosages), especially in control group.

35 Janket S-J, Wightman A, Baird AE, *et al.* Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. J Dent Res 2005; 84:1154–1159.

36 Nishimura F, Iwamoto Y, Soga Y. The periodontal host response with • diabetes. Periodontology 2000 2007; 43:245–253.
The article reviews impact of periodontal diseases on insulin resistance, renal function and lipid metabolism.

37 Genco RJ, Grossi SG, Ho A, *et al.* A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontol 2005; 76:2075–2084.

38 Pickup JC, Crook MA. Is type 2 diabetes mellitus a disease of the innate immune system? Diabetologia 1998; 41:1241–1248.

39 Engebretson S, Chertog R, Nichols A, *et al.* Plasma levels of tumour necrosis • factor-α in patients with chronic periodontitis and type 2 diabetes. J Clin Periodontol 2007; 34:18–24.
Serum levels of TNF-α were correlated with severity of periodontal destruction but not to BMI; a dose–response relationship was found between severity of periodontitis and TNF-α levels.

40 Pontes Anderson CC, Flyvbjerg A, Buschard K, Holmstrup P. Periodontitis is associated with aggravation of prediabetes in Zucker fattys rats. J Periodontol 2007; 78:559–565.

41 Iwamoto Y, Nishimura F, Nakagawa M, *et al.* The effects of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontol 2001; 72:774–778.