Data from the Centers for Disease Control and Prevention indicate that more than 20 million people (approximately 7% of the population) in the United States have diabetes mellitus. Physicians often fail to examine the mouths and teeth of their patients, even though the condition of the mouth and teeth have clinical relevance for the treatment of patients with diabetes mellitus. The authors examine the current state of knowledge regarding periodontal disease and the effect of periodontal disease on worsening of glycemic control. They review several studies investigating how the management of periodontal disease affects the ability of patients to control symptoms of diabetes mellitus. The authors conclude with several recommendations for the treatment of patients with periodontal disease to improve glycemic control.

A physician’s examination of the mouth usually involves a “Say ‘Ahh...’” and a quick look at the pharynx. Unfortunately, this brief examination is likely to miss important, clinically relevant information. For example, periodontal disease has the potential to have an adverse impact on glycemic control in patients with diabetes mellitus. Data from the Centers for Disease Control and Prevention (CDC) indicate that more than 20 million people (approximately 7% of the population) in the United States have diabetes mellitus. Diabetes mellitus remains undiagnosed in more than 6 million of these individuals, according to CDC estimates. Figure 1 lists a number of medical conditions, including periodontitis, gingivitis, lesions, and pigmentation changes, that can be revealed with a thorough examination of the mouth. Family physicians need to recognize how such conditions can affect various disease processes, including that of diabetes mellitus, and refer their patients to dentists for evaluation and treatment when necessary.

Periodontal disease involves an inflammatory process that develops in the gingiva (gums) in response to bacterial antigens in tooth plaque (a coating on teeth composed of various kinds of bacteria, salivary proteins, and shed epithelial cells). Diabetes mellitus has long been considered a risk factor for the development of periodontal disease. However, there is also evidence that periodontal disease can worsen a patient’s control of diabetes mellitus and that proper management of periodontal disease can improve control of diabetes mellitus. The present report reviews current knowledge about periodontal disease, including the physiologic mechanisms and clinical studies linking periodontal disease with worsening glycemic control.

Methods
The National Library of Medicine’s MEDLINE database was searched for studies on periodontal disease and diabetes mellitus. Terms used in the literature search, which was performed in early 2005, included diabetes mellitus, glycemic control, periodontal disease, and treatment. No publication date limits were placed on the literature search.

Anatomy of the Tooth
The tooth is embedded in and attached to the alveolar process of the mandible or maxilla (Figure 2). The visible portion of the tooth is the crown, and the embedded portion is the root. The innermost layer of the tooth is the pulp, which contains the nerves and blood supply of the tooth. The next layer of the tooth is the dentin, which is a mineralized connective tissue containing tubules that house the cellular processes, or extensions, of the odontoblasts, connective tissue cells whose cell bodies are located in the pulp cavity. The odontoblasts produce and deposit new dentin. The crown is covered by enamel, which is a mineralized, acellular, connective tissue that is the hardest substance in the body. The root of the tooth is covered by cementum, bone-like connective tissue. The tooth is attached to the alveolar process by periodontal ligaments.

The gingiva covers the alveolar process and part of the tooth. The space between the gingival epithelium and the tooth is the gingival sulcus. The depth of the sulcus is determined by periodontal ligaments. The normal depth of the gingival sulcus is about 2 mm to 3 mm. However, with destruct-
action of proteolytic enzymes produced by neutrophils. In addition, reactive oxygen species (eg, free radicals, oxygen ions, peroxides) form as a result of the inflammation, prompting the activation of metalloproteinases in the connective tissue matrix of the periodontal ligaments. At this point, the disease state has progressed to periodontitis. It is important to realize that periodontal disease involves a shift in the oral/dental flora from the normal, gram-positive anaerobic bacteria (eg, Lactobacillus, Peptostreptococcus, Streptococcus), to predominantly gram-negative anaerobic bacteria. Some of the bacteria believed to be involved in periodontal disease are Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola. The host responds to this shift in bacterial flora by developing an inflammatory response, with the generation of such cytokines as tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1). A major concern with periodontal disease is that, in some patients, the immune system does not effectively eliminate the source of the inflammation (ie, the gram-negative anaerobes). If these bacteria are not eliminated, the patient’s immune system is continuously activated, and a chronic inflammatory process results. This chronic inflammation leads to production of reactive oxygen species, which, in turn, activate matrix metalloproteinases. These enzymes degrade the collagen in the periodontal ligaments, leading to decreased attachment of the tooth to the alveolar process (which presents clinically as a loose tooth) and deepening of the gingival sulcus.

Gingival pockets are spaces in which bacteria can potentially proliferate, resulting in worsening of infection and/or inflammation. The oxygen pressure (P<sub>O2</sub>) in gingival pockets is low, fostering the growth of anaerobic bacteria. For the most part, these bacteria do not invade the periodontal tissue because...
The pathogenesis of periodontal disease involves mechanical methods—professional cleaning and mechanical débridement of the plaque or calculus, including both the supragingival and infragingival plaque. The infragingival plaque is the plaque that forms inside the gingival pockets. If the gingival pockets are deep enough, surgery may be required to reduce pocket depth, thereby helping to limit the buildup of bacteria.

In addition to mechanical treatment, the use of antimicrobial agents, both systemic and topical, has been increasing because of the realization that periodontal disease is not merely an overgrowth of bacteria, but also a shift in bacterial species.6,8 Topical treatment with either antibiotics or antiseptics has the advantage of delivering the antibacterial agent directly to where it is needed. Topical antibiotics include medications in the tetracycline family (eg, doxycycline, metronidazole, minocycline, and ofloxacin). Topical antiseptics include chlorhexidine-containing formulations, povidone-iodine, and sodium hypochlorite.

Systemic antibiotics reach the gingival pockets through the gingival crevice fluid, which is a type of transudate. Adding systemic treatment to topical treatment also addresses the problem of bacteria on the tongue and oral mucosa, thereby reducing potential sources of recolonization of the gingival pockets. Furthermore, when bacteria invade periodontal tissue, systemic antibiotics will destroy the microorganisms deep in the crevices, in areas that may be missed in the application of topical treatments. Common systemic antibiotics include clindamycin, metronidazole, penicillins, and tetracyclines. Most of the studies discussed in the present review involved the use of antibiotics in the tetracycline family, which are the most commonly used systemic antibiotics for these patients.

Although research has shown that tetracycline concentration in the gingival crevice fluid varies substantially from patient to patient,3 an advantage of using antibiotics in the tetracycline family is that, in addition to their antimicrobial action, they also inhibit the activity of metalloproteinases. Metalloproteinases are zinc-dependent enzymes. Tetracyclines cause chelation of zinc (as well as calcium), which inhibits the activity of the enzymes. Tetracyclines may also decrease intracellular expression of metalloproteinases.9 Doxycycline has been shown to be the most effective of the tetracyclines at inhibiting metalloproteinases.9 This inhibitory action prevents the degradation of collagen in the periodontal ligaments and the resulting formation of gingival pockets and loss of tooth attachment.6

Physiologic Mechanisms Involved in Periodontal Disease and Diabetes Mellitus

Periodontal disease is an inflammatory process. Nishimura et al10 presented a hypothesis that the inflammatory process in periodontal disease leads to increased levels of TNF-α, which is known to foster insulin resistance. Tumor necrosis factor α is a cytokine that is released by adipocytes (fat cells), among other cells. It is believed to play a role in the insulin resistance associated with obesity.4

Several actions of TNF-α have been identified.4 Tumor necrosis factor α is believed to impair the tyrosine phosphorylation of insulin receptor substrate molecules, an essential step in the signal transduction pathway for insulin.4 This action thereby impairs the messenger RNA (mRNA) transcription process needed for synthesis of the insulin-responsive glucose transporter protein (GLUT-4) receptor. In addition, TNF-α causes adipocytes to release free fatty acids, which contribute to insulin resistance by impairing insulin signaling.4

Experimental evidence reported by Keskin et al10 suggests that medical treatment of patients with periodontal disease decreases their levels of TNF-α, thereby improving periodontal control. In this study,10 obese patients with diabetes...
mellitus and periodontal disease were treated with mechanical débridement of the plaque and topical minocycline. Follow-up evaluations of these patients demonstrated significant decreases in hemoglobin A1c (HbA1c), TNF-α, and insulin resistance ($P<.05$), as measured with the homeostasis model assessment insulin resistance (HOMA-IR) index. This index is a method of calculating insulin resistance using the product of fasting glucose and insulin levels, divided by a constant.

In a noncontrolled study by Iwamoto et al, there was a strong correlation between improved HbA1c levels and decreases in TNF-α levels in patients with type 2 diabetes mellitus. The results led the authors to conclude that treatment with antibiotics is effective in improving metabolic control in patients with diabetes mellitus.

According to Noma et al, there is evidence that periodontal disease may be related to diabetic retinopathy. Interleukin 6, an inflammatory cytokine that is produced in response to periodontal inflammation, is believed to be involved in the pathogenesis of diabetic retinopathy. A cross-sectional study by Noma et al demonstrated a correlation between the severity of periodontal disease, IL-6 levels in the vitreous humor, and the severity of diabetic retinopathy.

Studies Evaluating Treatment

At least two longitudinal studies have shown that patients with severe periodontitis are more likely to develop impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes mellitus than patients with moderate periodontitis. Taylor et al observed 80 American Indians living in the Gila River Indian Community in Arizona (age range, 18–67 y). The researchers found that at the 2-year follow-up, patients with severe periodontal disease were 1.5 to 3.4 times more likely to have IGT and/or diabetes than patients without severe periodontal disease. In a study of 961 adults in Japan, Saito et al showed that patients with gingival pockets greater than 2 mm in depth were significantly more likely to have IGT than patients with pockets less than 1.3 mm ($P=.001$).

Because each of these studies was longitudinal in design, it was unclear if periodontal disease was the cause of the impaired glucose tolerance observed in the patients. There may have been some other factor causing both the periodontal disease and diabetes mellitus in the patients. For example, obesity leads to insulin resistance and diabetes mellitus as a result of TNF-α being released from adipocytes. In addition, TNF-α released from adipocytes may contribute to periodontal disease by stimulating the production of matrix metalloproteinases by fibroblasts and by stimulating bone resorption.

Although periodontal disease is not the singular causative agent of diabetes mellitus, several studies using various interventions have demonstrated improved glucose tolerance with the use of tetracycline analogues in the treatment of patients with periodontal disease.

Mechanical/Nonsurgical Treatment

A retrospective controlled trial by Stewart et al demonstrated that mechanical treatment (eg, ultrasonic scaling and root planing) led to significantly reduced HbA1c levels in patients with periodontitis and type 2 diabetes mellitus (n=36), compared with an equal number of individuals who received no periodontal treatment. Patients in the treatment group had, on average, a 17.1% reduction in HbA1c levels at 10 months follow-up, while those in the control group had a reduction of 6.7%, a statistically significant difference ($P=.02$). Stewart et al stated that during the 10-month period, physicians began using HbA1c levels as guides for treatment, which may have been the reason for the improvement in the control group. However, because the treatment group’s improvement was greater than that experienced by the control group, the authors concluded that the reduction in HbA1c levels in patients who received treatment was probably the result of not only improved diabetes control but also periodontal disease treatment.

A randomized controlled trial by Kiran et al of 44 patients with type 2 diabetes mellitus demonstrated that patients who received mechanical treatment for periodontal disease had, on average, a 10.94% reduction in HbA1c levels at 3 months follow-up. This reduction compared with a 4.42% increase in HbA1c levels in the control group. The difference between the two groups was significant ($P=.033$).

In contrast to these studies, some studies have shown no significant improvement in glycemic control with periodontal treatment. A randomized controlled trial by al-Mubarak et al of 52 patients who had either type 1 or type 2 diabetes mellitus compared the use of ultrasonic scaling and root planing alone with the use of subgingival water irrigation added to these mechanical treatment methods. The authors did not find a significant decrease in HbA1c levels in either group, though there was significant improvement in periodontal status in both groups ($P<.02$).

Chrisigau et al conducted a nonrandomized trial of nonsurgical treatment for periodontal disease in 20 patients with type 1 and type 2 diabetes mellitus, revealing no change in metabolic parameters at 4 months, compared with baseline. The patients were treated in two phases: the first phase involved instruction in oral hygiene and routine dental care. The second phase involved subgingival scaling and root planing combined with administration of chlorhexidine.

Tetracycline Family of Antibiotics

A noncontrolled pilot study by Miller et al of nine cases investigated the usefulness of mechanical débridement, chlorhexidine rinse (30 seconds twice daily), and doxycycline (100 mg twice daily for 1 day, once daily for 13 days). Five patients showed improved periodontal status as manifested by reduced bleeding during probing of the gingival sulcus, and they had a significant decrease in HbA1c levels, from 8.7% to 7.8% ($P<.01$). The other four patients had no improvement in...
periodontal status and did not have an overall improvement in HbA1c levels.  

A controlled trial by Grossi et al\(^{21}\) involving 113 Pima Indians revealed that patients with periodontal disease and diabetes mellitus who were treated with mechanical débridement and systemic doxycycline had significant decreases in HbA1c levels at 3 months follow-up (\(P<.04\)), compared with patients who received oral rinses of water (ie, placebo), chlorhexidine, or iodine. Although improvement in periodontal status was maintained or even increased at 6 months’ follow-up, the decreased HbA1c levels did not persist for this length of time. Grossi et al\(^{20}\) concluded that the doxycycline probably caused a reduction in the periodontal infection and inflammation, leading to decreased TNF-\(\alpha\) levels. However, the authors noted that doxycycline has also been shown to reduce nonenzymatic glycation—a reduction that is probably a factor in decreased HbA1c levels.\(^{20}\)  

Iwamoto et al\(^{11}\) demonstrated that treatment with local minocycline was associated with significantly decreased serum TNF-\(\alpha\) levels (\(P<.015\)), as well as decreased insulin resistance as manifested by the HOMA-\(\beta\) index (\(P<.03\)). In addition, the authors found a strong correlation between the decreased TNF-\(\alpha\) levels and the HbA1c levels,\(^{11}\) supporting the idea that the reduction of insulin resistance is at least part of the effect of the tetracycline family of antibiotics.

At least one study of patients with periodontal disease has found contrasting results to reports of significant benefits in glycemic control. In a randomized controlled trial that included 52 patients with periodontal disease, Promsudthi et al\(^{21}\) compared mechanical treatment and systemic doxycycline (100 mg/d for 14 days) with no periodontal treatment. Although the authors found some reduction in HbA1c levels in the treatment group, these reductions were not significant.\(^{21}\)

**Treatment Using Other Antibiotics**

A randomized controlled trial by Rodrigues et al\(^{22}\) compared mechanical treatment of patients with periodontal disease (\(n=15\)) with mechanical treatment combined with amoxicillin and clavunate combination therapy (\(n=15\)). The authors reported that the patients who received mechanical débridement alone had a significant reduction in HbA1c levels (\(P<.05\)), but the patients who received amoxicillin and clavunate combination therapy in addition to débridement did not have significantly reduced levels.\(^{22}\) This result occurred despite the fact that both groups showed significant improvements in probing depth (\(P<.05\)), a main measurement of severity of periodontal disease.

**Patients With Type 1 Diabetes Mellitus**

More than 90% of patients with diabetes have type 2 diabetes mellitus,\(^3\) and most studies examined in the present review focused on the relationship between that form of diabetes mellitus and periodontal disease. The role of periodontal disease in patients with type 1 diabetes mellitus is unclear. Type 1 diabetes mellitus is characterized primarily by absolute insulin deficiency rather than insulin resistance. Therefore, it makes intuitive sense that periodontal disease would not be as important in exacerbating type 1 diabetes mellitus as it is in type 2 diabetes mellitus. Nevertheless, it has been shown that patients with type 1 diabetes mellitus are at risk for developing periodontal disease and that this risk is related to the duration of their disease and their glycemic control.\(^{23-25}\)

Is it possible that subtle changes in insulin resistance resulting from periodontal disease may worsen glycemic control even in patients with type 1 diabetes mellitus? In studies of patients with insulin-dependent diabetes mellitus, neither Smith et al\(^{23}\) nor Aldridge et al\(^{24}\) found a significant difference in patients’ HbA1c levels before and after treatment with débridement. A study by Skaleric et al\(^{25}\)—which made a comparison between patients treated with scaling, root planing, and minocycline microspheres and patients treated with only scaling and root planing—noted reductions in HbA1c in both groups. However, these reductions did not reach levels of significance.\(^{25}\)

**Comment**

The experimental results reported in the present review are encouraging. There is some evidence that both nonsurgical, mechanical treatment and treatment with the tetracycline family of antibiotics in patients with periodontal disease are useful in optimizing the patients’ control of diabetes mellitus. However, as indicated by the studies that failed to show such a benefit,\(^{17,18,21,23-25}\) this evidence is not conclusive.

Even in those studies that involved the tetracycline family of antibiotics, such as Grossi et al,\(^{20}\) the improvements in HbA1c did not persist at 6 months’ follow-up, though periodontal health was maintained at that point. Grossi et al\(^{20}\) noted that tetracyclines can produce various effects, including the inhibition of glycosylation reactions. Such studies may cause one to wonder whether the antibiotics administered to patients for periodontal disease lead to improved glucose control and, thus, decreased HbA1c levels—or whether tetracycline merely decreases glycosylation of hemoglobin, leading to decreased HbA1c levels despite no improvement in glucose control. Might tetracyclines alleviate symptoms of periodontal disease and decrease glycosylation of hemoglobin via mechanisms that have nothing to do with each other? Even if that is the case, inhibition of glycosylation of proteins by tetracycline may help prevent some of the complications of diabetes mellitus, which are, in part, caused by glycosylation of such proteins as the collagen in vessel walls.

**Conclusions**

In general, the evidence described in the present review supports a potential role for careful management of periodontal disease and glycemic control. Further studies are needed to delineate the mechanism(s) by which tetracyclines can improve the glycemic control in patients with type 1 diabetes mellitus.
disease in patients with diabetes mellitus as an adjunctive treatment to help improve glycemic control. However, larger randomized controlled trials are necessary to provide conclusive evidence.

Physicians need to be mindful of poor periodontal health as one of the possible reasons for a patient’s poor control of diabetes mellitus. Thorough examination by physicians of the mouth and teeth is important for all patients—especially those diagnosed as having diabetes mellitus. It is also appropriate for physicians to recommend that patients avoid concentrated sweets, brush and floss after meals, and use topical antiseptics as an oral rinse or a pulsed irrigation. Physicians should consider prescribing doxycycline to patients with diabetes mellitus who have signs of periodontal disease. Physicians should also strongly consider referring such patients to dentists for mechanical treatment.

Before undergoing periodontal procedures, such as root planing and scaling, patients with valvular disease and/or cardiovascular stents must receive an additional antibiotic for endocarditis prophylaxis. Doxycycline is not an appropriate antibiotic for prophylaxis because it does not adequately eliminate the bacteria responsible for endocarditis. Alternative antibiotic prophylaxis may also be indicated for patients who have had joint replacements within the previous 2 years or who are immunosuppressed, as in cases of diabetes mellitus.

References