STATE OF THE SCIENCE: CHRONIC PERIODONTITIS AND SYSTEMIC HEALTH

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ABSTRACT

Context: Inflammatory periodontal diseases exhibit an association with multiple systemic conditions. Currently, there is a lack of consensus among experts on the nature of these associations and confusion among health care providers and the public on how to interpret this rapidly growing body of science. This article overviews the current evidence linking periodontal diseases to diabetes, cardiovascular disease, osteoporosis, preterm low birth weight babies, respiratory diseases, and rheumatoid arthritis.

Evidence Acquisition: Evidence was taken from systematic reviews, clinical trials, and mechanistic studies retrieved in searches of the PubMed electronic database. The available data provide the basis for applied practical clinical recommendations.

Evidence Synthesis: Evidence is summarized and critically reviewed from systematic reviews, primary clinical trials, and mechanistic studies.

Conclusions: Surrogate markers for chronic periodontitis, such as tooth loss, show relatively consistent but weak associations with multiple systemic conditions. Despite biological plausibility, shorter-term interventional trials have generally not supported unambiguous cause-and-effect relationships. Nevertheless, the effective treatment of periodontal infections is important to achieve oral health goals, as well as to reduce the systemic risks of chronic local inflammation and bacteremias.

Inflammatory periodontal diseases exhibit an association with multiple systemic conditions. With pregnancy as a possible exception, the local and systemic effects of periodontal infections and inflammation are usually exerted for many years, typically among those who are middle-aged or older. It follows that numerous epidemiological associations linking chronic periodontitis to age-associated and biologically complex conditions such as diabetes, cardiovascular disease, osteoporosis, respiratory diseases, rheumatoid arthritis, certain cancers, erectile dysfunction, kidney disease and dementia, have been reported. In the coming years, it seems likely that additional associations will be reported, despite adjustments for known genetic, behavioral and environmental confounders. Determining cause-and-effect mechanisms is more complicated, especially in circumstances where systemic effects may be subtle. Currently, however, there is a lack of consensus among experts on the nature of these associations and confusion among health care providers and the public on how to interpret this rapidly growing body of science. This article overviews the current evidence linking periodontal diseases to diabetes,
cardiovascular disease, osteoporosis, preterm/low birth weight babies, respiratory diseases, and rheumatoid arthritis.

**DIABETES**

Diabetes mellitus (DM), a metabolic disease resulting in high levels of blood glucose from defects in insulin production, insulin activity, or both, can lead to micro- and macrovascular complications. The classic 5 complications associated with diabetes are retinopathy, neuropathy, nephropathy, cardiovascular complications, and delayed wound healing. With mounting evidence and observations of the frequent presence of periodontitis in patients with diabetes, in 1993 Loe suggested that periodontal disease represents the sixth complication of DM. Since then, a great amount of research has been directed toward the links between these 2 diseases.

It is estimated that there are approximately 25.8 million diabetic individuals in the United States, or 8.3% of the population. Type 1 and type 2 are the most common forms of DM. Type 1 diabetes is an autoimmune disorder affecting the pancreatic B cells and currently represents 90% to 95% of the cases in children. It comprises, however, only approximately 5% to 10% of diabetes cases. Type 2 diabetes mostly affects older patients, but is increasingly seen in younger age groups. In type 2 diabetes, insulin resistance develops as cells lose their ability to respond to insulin. The demand for insulin increases and may eventually lead to the pancreas losing its ability to produce any insulin. A third form of DM, gestational diabetes, comprises 1% to 5% of the cases. Insulin resistance is influenced by diet, genetics, decreased physical activity, poor nutrition, obesity, and infection.

Diabetic individuals are prone to macrovascular and microvascular complications. Two mechanisms have been suggested to explain these complications: (1) the polyol pathway and (2) production of advanced glycosylation end products (AGEs). The binding of AGEs to mononuclear and polymorphonuclear cells decreases chemotaxis and phagocytosis in these cells. In addition, there is a hyperresponse to bacteria releasing larger amounts of cytokines and mediators of inflammation. Fibroblasts are also affected, resulting in impaired wound healing in diabetic patients and increased collagenase production with increased tissue destruction. Binding of AGEs to other cells in the body produces the complications related to DM.

Physicians attempt to optimize metabolic control of their patients to control the progression of these complications. Glycemic control is frequently assessed using measurements of glycated hemoglobin Alc (HbA1c) that reflects blood glucose levels in the preceding several weeks. There is a direct correlation with elevated HbA1c levels and diabetic complications.

As bacterial plaque matures on subgingival tooth surfaces, the bacterial flora becomes increasingly populated by gram-negative anaerobic species. In a susceptible patient, this increasingly pathogenic flora may lead to periodontitis. Approximately 35% of American adults have some form of periodontitis; 13% are said to have severe periodontitis. As the inflammatory process proceeds, the epithelial lining of the gingival sulcus becomes ulcerated and the specialized periodontal tissues are destroyed, including the periodontal ligament and nearby alveolar bone. In severe periodontitis, the total surface of ulcerated sulcular epithelium has been estimated to approximate the surface area of the palm of an adult hand (8-20 cm²). Bacteremia and endotoxemia may occur. Proinflammatory mediators interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-α), and prostaglandin E₂ (PGE₂) can enter the bloodstream and have systemic effects. Serum antibodies and mediators of inflammation (eg, C-reactive protein [CRP]) are increased in people with untreated periodontitis. Periodontal treatment decreases these inflammatory mediators in the blood.

Poorly controlled diabetic patients appear more susceptible to infectious diseases, including periodontitis. Khader et al conducted a meta-analysis to examine the extent and severity of periodontal disease in persons with and without DM. Results provided evidence to support an association between the 2 diseases. Diabetic individuals had poorer oral hygiene, more severe gingival disease, and more severe periodontal disease. A systematic review and meta-analysis of 57 peer-reviewed investigations led to the conclusion that type 2 DM is a risk factor for periodontitis. The authors also concluded that the analysis of the association between type 1 diabetes and periodontitis remains insufficient, because of the inadequate representation of subjects 25 years and older with type 1 DM.

Poorly controlled diabetic individuals present with an exaggerated inflammatory response to the bacterial challenge of periodontitis. This response to the bacterial challenge in periodontitis, with impaired tissue repair, is partly mediated by the receptor for AGEs and its ligands. The hyperinflammatory response and impaired wound healing and repair may enhance the inflammatory reaction and periodontal tissue destruction explaining the severe disease seen in these patients.

Evidence also suggests that periodontal disease severity has an effect on glycemic control with more severe periodontal disease having a greater negative impact on HbA1c levels. Thus, untreated periodontitis poses an inflammatory challenge to the patient and the reduction of periodontal inflammation has potential positive benefits to the patient both locally and systemically. Chronic inflammation from untreated periodontitis with resultant release of inflammatory mediators can increase insulin resistance.
Diabetic individuals in a chronic inflammatory state induced by untreated periodontitis may have elevated levels of inflammatory mediators in the circulation. The release of inflammatory mediators into the circulation may contribute to insulin resistance, worsening glycemic control. It has been shown that periodontitis can contribute to worsening glycemic control. Conversely, will treatment of periodontal disease improve glycemic control in diabetic patients with periodontal disease? Results of trials have been equivocal, with some subjects having a significant reduction in HbA1c levels, whereas others have had little change. Heterogeneity of the study population, inadequate sample sizes, and the confounding effects of smoking, body mass index, and medications make the results of meta-analysis difficult to generalize.

A Cochrane systematic review looked at improvement of the HbA1c (7 studies, 3 were included in a meta-analysis). Most subjects in the studies had poorly controlled type 2 diabetes. Initial periodontal therapy with or without antibiotics led to a mean reduction in the HbA1c of 0.4% after 3 to 4 months relative to no treatment. Meta-analysis of types 1 and 2 diabetic individuals (10 interventional trials) resulted in a decrease in the HbA1c levels an average of 0.38% and with antibiotics by 0.71%. A systematic review and meta-analysis of 5 studies suggested a decrease in the HbA1c of 0.40% in type 2 diabetic patients compared with those without periodontal therapy.

Although the latter results were not statistically significant, the variability in treatment response might reflect important differences in selected patient populations. The mean reduction in HbA1c levels after initial periodontal therapy is similar to estimated reductions achieved with less potent oral agents, such as α-glucosidase inhibitors, which reduce HbA1c levels by 0.5%. Initial periodontal treatment may be an alternative or adjunct therapy to improving glycemic control. It is estimated there is a 35% reduction in complications for every 1% point decrease in A1c levels. It has also been suggested that a 0.2% reduction in HbA1c is associated with a 10% reduction in mortality. Therefore, studies finding improvement in glycemic control after periodontal treatment support significant associations between periodontitis and diabetes, in particular type 2 diabetes.

Diabetes is a risk factor for periodontal disease and periodontal disease severity may influence glycemic control as well as contribute to complications in these patients. Treatment of periodontal disease has shown to have beneficial effects on glycemic control in type 2 diabetic individuals in which the inflammatory process has shown to be an important factor in disease progression. As evidence mounts supporting the link between diabetes and periodontitis, closer collaboration between physicians and oral health care professionals to improve the glycemic control of their patients is warranted.

**CARDIOVASCULAR DISEASES**

Cardiovascular diseases (ischemic heart disease, cerebrovascular diseases, and peripheral vascular disease) are progressive, chronic problems that are the leading cause of death and disability worldwide. Periodontal diseases are also progressive and chronic. Both periodontal diseases and atherosclerotic heart diseases are multifactorial, of high prevalence, and share multiple risk factors.

Systemic inflammation has markers associated with cardiovascular disease that include lipoprotein-associated phospholipase A2, matrix metalloproteinases, tissue inhibitors of metalloproteinase, myeloperoxidase, fibrinogen, IL-6, soluble intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, soluble CD40 ligand, and CRP. CRP has been shown to be a predictor of future cardiovascular events. Inflammation associated with periodontal diseases has similar markers (CRP, IL-1, IL-6, IL-8, TNF-α) that have been implicated in contributing to atherogenesis or atheromatous plaque rupture in patients with periodontal disease. Also, bacteraemias containing periodontal pathogens may be deposited in an atheromatous plaques, induce a procoagulant response, or invade vascular cells. Periodontitis has also been studied because of a possible association with endothelial dysfunction. Endothelial dysfunction may be the earliest manifestation of atherosclerotic vascular disease (ASVD). Finally, increased carotid intima-media thickness (c-IMT) has also been correlated with severe periodontal disease.

Meta-analysis of studies published between 2003 and 2009 showed a weak but statistically significant association between cardiovascular disease and periodontal disease. On the basis of these meta-analyses, it can be concluded that an individual with periodontitis is at greater risk of either having or developing cardiovascular disease. Therefore, to date, we can state that periodontal disease is associated with ASVD independent of known confounders. This means that common risk factors (smoking, obesity, diabetes, and heredity) do not completely explain the association between the 2 conditions and that periodontal disease itself contributes to the risk for ASVD. Whether or not periodontal therapy alters the risk for ASVD, however, has not been established. Studies still need to answer a vital question: “Do subclinical findings translate in clinical events?”

A recent statement of the American Heart Association concluded with the following:

“This review highlights significant gaps in our scientific understanding of the interaction of oral health and ASVD. Identification of clinically relevant aspects of their association or therapeutic strategies that might improve the recognition or therapy of ASVD in patients with periodontal disease would require further study in well-designed controlled interventional studies. Such investigations should reflect the
Osteoporosis and periodontitis have confounding factors that play a significant role owing to the chronicity of both problems. Studies on tooth loss, alveolar crestal height, and clinical attachment loss have been performed; however, problems in extrapolation and application of data arise because of small sample sizes, study design, inadequately controlled confounders, and limited understanding of the relationship between the 2 diseases.  

The bone mineral densities (BMDs) of the spine, trochanter, and other skeletal bones with the maxilla and mandible have been evaluated. There is evidence indicating an association between systemic measures of osteoporosis and oral BMD. Animal models indicated fragility of the trabecular structure of molar alveolar bone as well as increased vertical loss mandibular alveolar bone. Radiologic examination of the facial skeleton may be an area where first detection of osteoporosis may be a cost-effective adjunct to complement the early diagnosis, treatment, and follow-up. Teeth, no teeth, anatomical structures, access, angulation, standardized roentgen dose, regenerative interventions, and infection alter outcomes for interpretation of BMD. Standardization with any radiographic method is needed for application to chairside planning and determining BMD levels. Today, computed tomography scanners can provide the percentage of calcification in localized sites. This may be applied to enhance clinical treatment planning and possibly predict periodontal disease progression before clinical attachment loss and enhance dental implant therapy.

Current knowledge regarding the effects of osteoporosis/osteopenia on periodontal diseases and alveolar bone loss is a work in progress. Associations of decreasing systemic BMD in postmenopausal women with periodontitis, attachment loss, and gingival recession have been found; however, others have found weak or no significant association. Recent studies provide stronger evidence of an association between osteoporosis and clinical attachment loss in humans. Interventions to alter BMD assess their effects on periodontal disease or periodontal therapy. Jabbar et al investigated the relationship between periodontal disease and plasma cytokines, vitamin D, and BMD in postmenopausal women with and without osteoporosis. They found periodontal disease was more common in women with osteoporosis and was associated with lower vitamin D and higher concentrations of RANKL and osteoprotegerin (OPG). Subantimicrobial doses of doxycycline in postmenopausal women have shown a possible benefit in reducing progressive attachment loss with an effect on serum biomarkers of systemic bone loss. Increased alveolar bone mass with associated improved alveolar crestal height, reduced clinical attachment loss, or reduced periodontal inflammation have been reported with patients on hormone therapy. The effect of daily administration of teriparatide versus a placebo medication was studied in conjunction with periodontal regeneration in patients with severe periodontal disease. Radiographic linear resolution of osseous defects was significantly greater after teriparatide therapy than after placebo beginning at 6 months, with a mean linear gain in bone at 1 year of 29% as compared with 3% (P < .001). Also, patients with normal serum vitamin D3 levels before osseous regeneration therapy had significantly greater amounts of periodontal defect regeneration. A recent review suggested that reduced BMD is a shared risk factor for periodontitis rather than a causal factor; but more prospective studies are required to fully determine what, if any, relationship truly exists between periodontal disease and reduced BMD. Further clinical trials with greater numbers of study subjects, longer observation periods, and male patients, and trials that account for confounding variables need to be performed.
Clinical periodontal and implant therapies are affected by medications that reduce or enhance BMD (Table 1). Decisions regarding periodontal/implant patients on bisphosphonates will depend on a host of variables: length of time on the drug, patient age, type of drug, dosing (continuous or intermittent), drug compliance, oral versus intravenous delivery, dental/periodontal status, satisfactory clinical end points, and overall systemic health (Table 2). Patients on oral bisphosphonates for longer than 3 years should have a medical consult before extensive periodontal and/or implant therapy, as should patients who have been recently prescribed immunosuppressants, are post-cancer chemotherapy, elderly, or are at higher risk for problems such as osteonecrosis of the jaw (ONJ). Patients with active periodontal disease have also been reported to be at higher risk. Each patient should be evaluated for his or her individual risks.

### PREGNANCY: PRETERM/LOW BIRTH WEIGHT BABIES

The American Academy of Periodontology “Guidelines for Treating the Pregnant Patient” remain applicable. Research indicates that the presence of acute infection, chronic abscesses, or other disseminating sources of sepsis may harm fetal health. Therefore, prompt and thorough periodontal intervention is indicated irrespective of the stage of pregnancy.\(^{35}\)

The occurrence of pregnancy gingivitis is extremely common, occurring in 30% to 100% of all pregnant women. The condition is characterized by erythema, edema, hyperplasia, and increased bleeding. Histologically, the description is the same as for gingivitis; however, the etiologic factors are different despite clinical and histologic similarities. The pregnant patient is considered to be in an immunocompromised state. Periodontal tissues may reflect systemically as pregnancy granulomas or severe erythema and HIV periodontitis or which can progress to severe hyperplasia, pain, and bleeding. Other growths that resemble pregnancy granulomas must be ruled out, such as central giant cell granulomas or underlying systemic diseases. The periodontal status before pregnancy may influence the progression or severity as the circulating hormones fluctuate.

The current opinion is that periodontal disease increases the relative risk for adverse pregnancy outcomes. The Oral Conditions in Pregnancy (OCAP) study also stated periodontal disease progression during pregnancy was a predictor of the more severe adverse pregnancy outcomes of very preterm birth, independent of traditional obstetric, periodontal, and social domain risk factors.\(^{36}\) However, there are inconsistent results relating to the efficacy of periodontal treatment on birth outcomes.\(^{37}\) Preterm/low birth weight births may occur as a result of infection and is mediated indirectly, principally by the translocation of bacterial products, such as endotoxin (lipopolysaccharide), and the action of maternally produced inflammatory mediators. Jared et al\(^{38}\) noted in utero fetal exposure to oral pathogens increases the risk of neonatal intensive care unit admission and length of stay. Biologically active molecules such as PGE2 and TNF-\(\alpha\), which are normally involved in normal parturition, are raised to artificially high levels by the infection process, which may foster premature labor. Gram-negative bacteria in periodontal diseases, therefore, may permit selective overgrowth or invasion of gram-negative bacteria within the genitourinary tract.

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**TABLE 2. Dosage and FDA approval rates of bisphosphonates**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage forms</th>
<th>Approved</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate (Didronel)</td>
<td>200/400-mg tabs</td>
<td>9/1/1977</td>
<td>1×</td>
</tr>
<tr>
<td>Clodronate (Bonefos)</td>
<td>400/800-mg tabs, 60-mg/mL ampule</td>
<td>Not approved</td>
<td>10×</td>
</tr>
<tr>
<td>Clodronate (Bonefos)</td>
<td>20-mg tabs</td>
<td>3/7/1977</td>
<td>10×</td>
</tr>
<tr>
<td>Pamidronate (Aredia)</td>
<td>20/60/90-mg vials</td>
<td>10/31/1991</td>
<td>100×</td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>5/10/35/40/70-mg tabs, 70-mg/75-mL oral solution</td>
<td>9/29/1995</td>
<td>100×</td>
</tr>
<tr>
<td>Alendronate + D</td>
<td>70-mg and 2800-U cholecalciferol tab</td>
<td>4/7/2005</td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>2.5-mg tab, 150-mg tab, 3-mg/3-mL vials</td>
<td>5/16/2003</td>
<td>500×</td>
</tr>
<tr>
<td>Risendronate + (Actonel + calcium)</td>
<td>35-mg/1250-mg calcium carbonate</td>
<td>8/12/2005</td>
<td></td>
</tr>
<tr>
<td>Aoledronate Zometa</td>
<td>4-mg vials, 5-mg vial</td>
<td>8/20/2001</td>
<td>10,000×</td>
</tr>
<tr>
<td>Reclast</td>
<td></td>
<td>8/17/2007</td>
<td></td>
</tr>
</tbody>
</table>
The pregnant patient also possesses a suppressed immune system. Maternal immune-responsiveness suggests an increased susceptibility to developing gingival inflammation, noted by changes in increase of monocytes (in which large numbers inhibit in vitro proliferative responses to mitogens, allogeneic cells, and soluble antigen), decrease in the ratio of peripheral T-helper cells to T-suppressor cells (CD4/CD8), decreased polymorphonuclear leukocyte chemotaxis, decreased levels of immunoglobulin G to periodontal pathogens during the second trimester; ovarian hormone stimulation of prostaglandins (PGE 1 and PGE 2), and influence of plasminogen activator inhibitor type 2 (PAI-2) disrupting the balance of the fibrinolytic system.

The rise in sex hormones directly affects gingival tissues. Estrogen may regulate cellular proliferation, differentiation, and keratinization, whereas progesterone influences the permeability of the microvasculature, alters the rate and pattern of collagen production, and increases the metabolic breakdown of folate (necessary for tissue maintenance). High concentrations of sex hormones in gingival tissues, saliva, serum, and gingival crevicular fluid (GCF) also may exaggerate the response. Periodontal therapy and prevention of periodontal inflammation should begin when women become of childbearing age. Explanation of the effect of hormones on supporting periodontal tissues with early preventive measures should be part of a maintenance program. If a patient is trying to become pregnant or is pregnant, a thorough medical history is an imperative component of the periodontal examination, especially in the pregnant patient. Because of immunologic alterations, increased blood volume (ruling out mitral valve prolapse and heart murmurs), and fetal interactions, the clinician must diligently and consistently monitor the patient’s medical and periodontal stability. Medical history dialog should include pregnancy complications, previous miscarriages, and recent history of cramping, spotting, or pernicious vomiting. The patient’s obstetrician should be contacted to discuss her medical status, periodontal or dental needs, and the proposed treatment plan.

Quick reference guidelines have been developed by the California Dental Association Foundation in collaboration with state and national medical, dental, and public health experts and organizational representatives (American College of Obstetrics and Gynecology district IX) to assist health care professionals at the chair. The summary guidelines are the in-depth science reviews and supporting evidence for each of the protocols. Finally, recommendations for system improvements and public policy changes that support expanded oral health care for pregnant women accompany the clinical guidelines. Available evidence indicates there is a possible correlation between periodontitis and preterm and/or low birth weight deliveries; however, periodontal therapy to reduce adverse pregnancy outcomes is inconclusive.

**RESPIRATORY DISEASES**

Microbes from the oral cavity can be aspirated into the respiratory tract and may affect the initiation or progression of respiratory maladies, especially nosocomial pneumonia in high-risk patients. Improved oral hygiene has been shown to reduce the incidence of nosocomial pneumonia in ventilated inpatients as well as nonventilated nursing home residents.

Bacterial pneumonia is an inflammation of the lungs caused by viral, fungal, or bacterial infections. Normal lung defenses usually successfully eliminate microbes from the lower airways, but these may be impaired by a variety of circumstances, including smoking, malnutrition, chronic obstructive pulmonary disease (COPD), diabetes, intubation, and corticosteroid use.

Community-acquired bacterial pneumonia is usually caused by microbes that are normal residents of the oropharynx. In contrast, among intensive care units (ICUs) and nursing homes, opportunistic nonoral bacteria that colonize the oropharynx from the environment are more likely to cause nosocomial pneumonia. This may be because patients in ICUs and in nursing homes have more dental plaque and worse oral hygiene than do their community-dwelling counterparts and because respiratory pathogens are much more commonly found in the dental plaque of intubated or institutionalized patients. Fortunately, improved oral hygiene can reduce the incidence of nosocomial pneumonia in high-risk patients.

Poor oral hygiene or periodontitis has also been associated with a group of maladies termed COPD. It is not clear that there is a cause-and-effect relationship, but in light of the success of improved oral hygiene in reducing the incidence of nosocomial pneumonia, it appears likely.

Optimal or improved periodontal health would likely decrease the incidence of pneumonia and may also decrease the intensity or incidence of COPD. Because both pneumonia and COPD are such highly morbid maladies and efforts to improve oral hygiene are low cost and have minimal adverse side effects, improved periodontal health makes good sense in the context of decreasing the incidence or the intensity of serious respiratory infections.

**RHEUMATOID ARTHRITIS**

Rheumatoid arthritis (RA) is a systemic inflammatory, autoimmune disorder characterized by synovial inflammation leading to joint swelling, stiffness, and tenderness, eventually culminating in cartilage damage, bone erosions, and joint destruction. RA can result in significant limitations in activity and disability and increases risk of mortality. The Centers for Disease Control and Prevention estimates that 1.5 million adults have been diagnosed with RA in the United States, which represents a significant public health problem.
The concept that oral infection may cause or underlie exacerbations in RA was introduced in the medical literature nearly 200 years ago. The natural history of RA is generally categorized as monocyclic, polycyclic, or progressive. The monocyclic course of RA is characterized by a single episode of disease that typically ends within 2 to 5 years of initial diagnosis, with remission presumably resulting from early diagnosis and/or aggressive treatment. In polycyclic progression, which is the most common, RA manifests as a progressive condition that includes periods of acute activity (“flare-ups”) and remission. In progressive RA, the most aggressive clinical course, the disorder progression is constant and destructive, with significant deformity and disfigurement. Comparisons can be made between the natural history of RA and periodontitis, which has been categorized as well-maintained, downhill, or extreme downhill following therapy.

Multiple biologically plausible mechanisms may account for the association between RA and periodontitis, with activation of underlying and overlapping inflammatory pathways as a common feature. The observation that obesity and metabolic syndrome, which share systemic inflammation as a prominent feature, are associated with increased risk of developing RA, increased severity of RA, and reduced responsiveness of RA to anti-TNF therapy.

RA is characterized by the production of 2 characterized antibodies, rheumatoid factor and anti-citrullinated peptide antibody, against common autoantigens expressed within and outside joints. More than 30 confirmed genetic markers have been identified that predispose to RA. Antibodies to gram-negative, anaerobic periodontal pathogens, such as Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythia, have been detected in the serum and synovial fluid of patients with RA. These pathogens also have been identified in the synovial fluid of patients with active RA. Immunity to P gingivalis has been shown to be significantly associated with the presence of RA-related autoantibodies in individuals at risk for RA. Patients diagnosed with new-onset, untreated RA have been found to exhibit a high prevalence of periodontal disease, despite their young age and paucity of smoking history; however, no consistent differences have been found in periodontal parameters and inflammatory biomarkers between subjects with RA and adults with periodontitis.

Early medical treatment of RA often included full-mouth extraction of teeth; however, this practice waned as evidence increasingly failed to document clinical benefits. Current evidence does not support a positive effect of periodontal treatment on RA disease activity. In a recent prospective study of RA, the effectiveness of anti-TNF-α therapy in reducing measures of disease activity was examined in relation to presence of periodontal disease. Improvements in disease activity score (28 joints), erythrocyte sedimentation rate, and CRP were limited to those patients without probing pockets. The results of this study are consistent with the hypothesis that periodontal infection and inflammation may hamper the effectiveness of anti-TNF therapy in patients with RA. These findings may provide a basis for the inconsistent results in studies evaluating the effect of anti–TNF-α therapy in subjects with RA and periodontitis.

SUMMARY
Surrogate markers for chronic periodontitis, such as tooth loss, show relatively consistent but weak associations with multiple systemic conditions. Despite biological plausibility, shorter-term interventional trials have generally not supported unambiguous cause-and-effect relationships. Nevertheless, the effective treatment of periodontal infections is important to achieve oral health goals, as well as to reduce the systemic risks of chronic local inflammation and bacteremias.

REFERENCES


