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Systemic Effects of Periodontal Diseases

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The possibility that a localized oral condition such as periodontal disease (PD) may have systemic effects seems to be of interest to the average person. The notion that a condition that is often ignored (or dealt with only when causing pain) may have long-term systemic consequences gets people's attention. To some constituencies of the dental profession, this attention is a good thing; perhaps some of those who have ignored their oral health will now pay attention to their mouth and seek regular dental care. This notion has considerable public health significance because if it is true, then treatment of periodontal inflammation would contribute to reduction in the risk of many prevalent, often fatal chronic diseases.

To what extent are the putative associations between PD and systemic conditions such as atherosclerosis, myocardial infarction, stroke, pneumonia, diabetes mellitus, and adverse pregnancy outcomes based on proven fact? To what extent can these potential associations be explained by a plausible pathogenic mechanism? Will provision of periodontal therapy reduce the risk of these systemic diseases? The goal of this article is to briefly review the history of this concept, describe the biologically plausible circumstances that may underlie these potential associations, and provide a summary of the published literature that supports or refutes them.

History of the focal infection hypothesis

The concept that oral infection may contribute to various systemic diseases is not new. Indeed, the possibility that a localized, or focal, infection such as PD could have systemic effects was a popular idea at the turn of the twentieth century [1,2]. A focal infection is a chronic, localized infection that can disseminate microorganisms or toxic microbial products to contiguous or

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distant tissues. In addition to the teeth and jaws, other common sites of focal infection were considered to be tonsils, sinuses, fingers and toes, bronchi, the gastrointestinal tract including appendicitis and ulcers, the urinary tract, and lymph nodes. It was thought that many focal infections led to indolent systemic diseases such as arthritis, nephritis, conjunctivitis and iritis, otitis media, endocarditis, and anemia. As a result of this theory, many physicians of the era often recommended preventive full-mouth extractions in subjects suspected of having a focal infection causing systemic diseases.

Over time, a variety of arguments developed against the focal infection theory. In many patients, extraction of the teeth did not reverse the course of the systemic disease. Most of these early ideas were based on anecdotal evidence, not on evidence obtained from carefully designed epidemiologic studies or controlled trials (to be fair, such studies were rarely if ever performed in those days). Thus, by the 1950s, the focal infection hypothesis fell from favor.

In recent years, evidence has come forth supporting the notion that localized infectious diseases such as PD may indeed influence a number of systemic diseases (Fig. 1). This view holds that bacteria from dental plaque enter the blood stream through discontinuities of the oral tissues (ulcerated sulcular epithelium; infected root canals) and travel through the blood to cause infection at a distant site. It may also be possible that PD bacteria

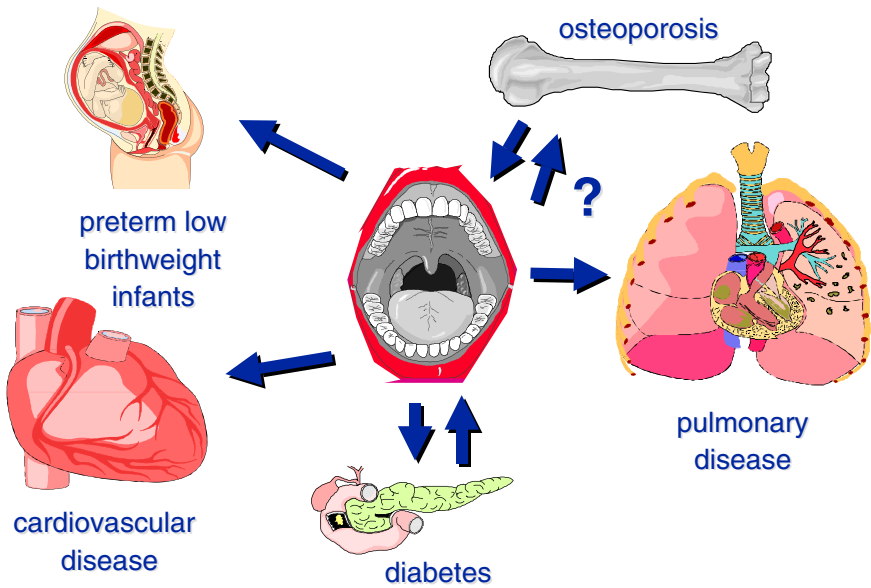

Fig. 1. Recent evidence suggests the possibility that poor oral health, particularly PD, may influence the initiation or the progression of several important and prevalent systemic diseases and conditions.

stimulate the release of pro-inflammatory cytokines or acute-phase proteins at a distant site (eg, liver, pancreas, skeleton, arteries). These products may initiate or intensify a disease process (eg, atherosclerosis, diabetes). Bacteria may also travel from oral sites to other mucosal surfaces (lung, gut) to cause inflammation and infection (pneumonia, gastric ulcers). This article reviews recent studies that address the association of oral infection with systemic conditions such as atherosclerosis, pulmonary disease, and pregnancy complications.

Association of periodontal disease with atherosclerosis, cardiovascular disease, and stroke

Most cases of coronary heart disease and cerebrovascular disease (stroke) result from atherosclerosis, an aberrant biologic process that causes narrowing of arteries due to deposition of cholesterol and cholesterol esters on the surface of blood vessel walls. The cholesterol-rich plaques also contain cells, including fibroblasts and immune cells [3]. Not all individuals suffer atherosclerosis equally; some individuals have higher risk for this disease process than others. Well-recognized risk factors for atherosclerosis include chronically elevated blood levels of cholesterol and triglyceride, hypertension, diabetes mellitus, and cigarette smoking.

Cholesterol, a lipid necessary for normal cell function, is synthesized in the liver and absorbed through the gut from dietary sources and transported in the blood bound to low-density lipoproteins. These low-density lipoproteins bind to specific transmembrane receptor proteins for transport into the cell through receptor-mediated endocytosis. Cholesterol uptake is reduced in some people and excess cholesterol accumulates in the blood to eventually form atherosclerotic plaques. If these plaques occlude blood flow in brain arteries, the result can be stroke; if they occur in coronary arteries, it can lead to myocardial infarction.

A recent and growing literature implicates chronic inflammation, infection, and possibly autoimmunity in the pathogenesis of atherosclerosis [4]. Arterial inflammation may be locally increased by lipid imbalances, hemodynamic stress, and immune reactions directed against the vascular wall, eventually leading to the formation of complicated atherosclerotic lesions [5]. This inflammation-mediated damage may initiate or contribute to the progression of the atherosclerotic plaque. A number of infectious agents appear to be associated with atherosclerosis, and alterations in the immune response may compromise clearance of such agents from these plaques. One of the best studied of these association's involves *Chlamydia pneumoniae,* an intracellular bacterium that commonly causes pneumonia and milder respiratory tract infections. *C pneumoniae* DNA and proteins have been detected in arteries of patients with giant cell arteritis [6] and in endarterectomy samples [7]. Elevated levels of antibody against *C pneumoniae* are found in patients with coronary heart disease compared with controls [8].

Other chronic infections such as PD have also been implicated as inciting agents for cardiovascular inflammation and disease. The first article of the recent era to report a relationship between PD and cardiovascular disease was a case-control study published by Simonka et al [9] in 1988. These researchers age matched 211 men with previous heart attack to 336 patients without heart attack. They found significantly more evidence of PD and need for periodontal surgery in patients over 50 years old with heart attack compared with those without heart attack. Since then, several additional case-control studies on this subject have been published [10–13]. Of these, all except one [12] reported a positive association between indicators of poor dental health and outcomes of atherosclerosis (cerebrovascular disease). The one study reporting the absence of a positive association was of very elderly subjects. It is possible that the cumulative effects of various disease processes that contribute to atherosclerosis in the elderly could have obscured the effect of oral disease on these processes. Another recent study determined whether a combination of clinical variables in a functional risk diagram enhanced the ability to differentiate between subjects with or without an immediate history of acute myocardial infarction [14]. Eighty-eight subjects with recent acute myocardial infarction and 80 matched control subjects with no history of acute myocardial infarction were compared. It was found that alveolar bone loss $\geq$4.0 mm was significantly greater in subjects with acute myocardial infarction. Taken together, these studies support a positive association between PD and the prevalence of cardiovascular events.

Stimulated by the early case-control studies, a number of cross-sectional studies provided further evidence in support of the association between PD with cerebrovascular disease, after controlling for other cardiovascular risk factors, particularly smoking [15–23]. As an example, Table 1 demonstrates the moderate risk for a history of heart attack in subjects with periodontal attachment loss [20]. In addition, several other studies have shown a positive association between PD and stroke [18,24–26], and one study associated PD with peripheral vascular disease, another sequela of atherosclerosis [27].

It has been suggested that the association observed between atherosclerosis-induced disease and PD may be the result of etiologic factors common

Table 1
Risk of heart attack in subjects with various levels of periodontal attachment loss

Sites with periodontal attachment loss $\geq$3 mm (%)	Odds ratio (95% confidence interval) for yes versus no: "Has your doctor ever told you that you had a heart attack?"
0	1.00 (reference)
>0–33	1.38 (0.75–2.254)
>33–67	2.28 (1.18–4.39)
>67–100	3.77 (1.46–9.74)

Data from Arbes SJ Jr, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. J Dent Res 1999;78(12):1779.

to both disease processes, such as lifestyle practices like cigarette smoking, and therefore coincidental [28–31]. Determining the role of lifestyle factors independent from the effect of PD on atherosclerosis requires the conduct of large prospective longitudinal epidemiologic studies of never smokers in addition to large randomized controlled clinical trials to determine whether periodontal intervention prevents the initiation or progression of atherosclerosis-induced diseases.

Because of the great heterogeneity in methodologies used between studies in assessment of oral disease, it is difficult to directly compare the results of one study to others. Nevertheless, the available data suggest that PD is modestly associated with atherosclerosis-induced diseases such as cardiovascular disease, stroke, and peripheral vascular disease.

Association of periodontal disease with pneumonia

Pneumonia is defined as an inflammation of the lungs caused by fungal, viral, parasitic, or bacterial infection. Bacterial pneumonia, the most common and treatable form of the disease, is initiated following colonization of the oral cavity and pharyngeal mucosa by potential respiratory pathogens, aspiration of the colonized pathogens into the lower airway, and failure of defense mechanisms to eliminate the bacteria from the airway mucosa [32]. Aspiration of oral secretions, a somewhat frequent event even in normal, healthy individuals who may aspirate small quantities of secretions during sleep, is more frequent in patients with altered consciousness [33]. Other conditions predisposing to aberrant aspiration include stroke, Parkinson's disease, alcohol abuse, and sedative use [34]. Multiple defense mechanisms operate within the healthy respiratory tract to eliminate aspirated material from the lower airway, but their effectiveness can be impaired by a variety of conditions such as malnutrition, smoking, chronic obstructive pulmonary disease (COPD), diabetes, corticosteroid use, and endotracheal or nasogastric intubation.

Bacterial pneumonia can be classified as either community-acquired pneumonia or hospital-acquired (nosocomial) pneumonia. Up to 5.6 million cases of community-acquired pneumonia occur annually in the United States [35] and the overall mortality rate is <5%. Among the community-acquired pneumonia cases that require hospitalization, the mortality rate can be as high as 40% in those admitted to ICUs. Community-acquired pneumonia is typically caused by aspiration of bacteria that normally reside in the oropharynx, such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Mycoplasma pneumoniae*.

Nosocomial pneumonia occurs in institutionalized subjects such as hospitalized patients admitted to ICUs and nursing home patients. Nosocomial pneumonia accounts for 10% to 15% of all hospital-acquired infections, with a mortality rate as high as 25%. In contrast to community-acquired pneumonia, a different set of bacteria causes nosocomial pneumonia,

including species such as *Staphylococcus aureus* and gram-negative bacteria such as *Pseudomonas aeruginosa* and the enteric species *Klebsiella pneumoniae, Escherichia coli*, and *Enterobacter* spp.

Several studies have demonstrated that the oral cavity may serve as a reservoir for respiratory pathogen colonization and infection. One of the first studies to document this finding [36] compared oral hygiene and the rate of dental plaque or buccal mucosal colonization by potential respiratory pathogens in ICU subjects with age- and gender-matched outpatients at their initial visit to a dental school clinic. The ICU patients demonstrated significantly more plaque than the control subjects. Colonization of dental plaque or oral mucosa by potential respiratory pathogens was found in 65% of the ICU patients but in only 16% of the preventive dentistry clinic patients. The potential respiratory pathogens identified in the ICU patients included *Staphylococcus aureus, Pseudomonas aeruginosa,* and a number of different enteric gram-negative bacteria. Several patients had oropharyngeal colonization by two or more potential pathogens. Oral colonization by respiratory pathogens was associated with antibiotic usage.

This observation was also noted in a subsequent study [37] in which an association was noted between poor oral health status (including dental caries, dental plaque, and colonization of dental plaque by respiratory pathogens) and onset on pneumonia in 57 ICU patients. The relative risk for pneumonia was increased 9.6-fold when the dental plaque was colonized by a pathogen between days 0 and 5 following ICU admission. Furthermore, the pathogen causing pneumonia was noted to first colonize the dental plaque.

Recent studies have also assessed the relationship between oral health, respiratory pathogen oral colonization, and pneumonia in nursing home populations. For example, 134 geriatric patients (34 inpatients, 53 long-term care patients, and 47 outpatients) were assessed for oral conditions such as xerostomia, caries, PD, and salivary IgA levels [38]. These subjects were also assessed for a diagnosis of aspiration pneumonia based on body temperature $>2^{\circ}$C above baseline, clinical deterioration, elevated white blood cell count, and infiltrates on chest radiograph. They noted that 27% of dentate inpatients and 19% of dentate long-term care patients developed aspiration pneumonia, whereas only 5% edentulous patients developed pneumonia, suggesting that teeth may serve as a reservoir of respiratory pathogen colonization in these subjects. A study of the relationship of oral health status and lung infection in 302 nursing home residents was reported by Mojon et al [39] who found an increased risk of respiratory tract infection in subjects with teeth in comparison to edentulous subjects. Another study [40] of 189 elderly male outpatients, hospital inpatients, and nursing-home patients over 60 years of age found significant associations between pneumonia and the number of decayed teeth, the frequency of brushing teeth, and being dependent for oral care. A subsequent study found the dental plaque of 12 of 28 (43%) elderly patients recently admitted to a hospital were colonized by gram-negative bacillary pathogens, suggesting the possibility that dental plaque may serve as

a reservoir for lung infections [41]. When 28 chronic-care nursing home residents were compared with 30 dental clinic outpatients over 65 years of age, matched for gender and race, it was found that the dental plaque scores were significantly higher in the nursing home residents than in the outpatient controls (Fig. 2). In addition, 14.3% of chronic-care subjects showed dental plaque colonization with respiratory pathogens compared with 0% of the control dental outpatients [42].

Finally, 358 veterans aged 55 years and older were found to have an elevated risk of aspiration pneumonia if they had teeth and (1) if their teeth were carious, (2) when the periodontopathogen *Porphyromonas gingivalis* was detected in dental plaque, and (3) when the respiratory pathogen *Staphylococcus aureus* was detected in saliva [43].

Oral intervention trials to prevent pneumonia

The findings reviewed in the previous section suggest that the oral cavity may serve as a reservoir for lower airway infection, especially in institutionalized subjects. This observation further suggests that improved oral hygiene could reduce or eliminate respiratory pathogens from the mouth

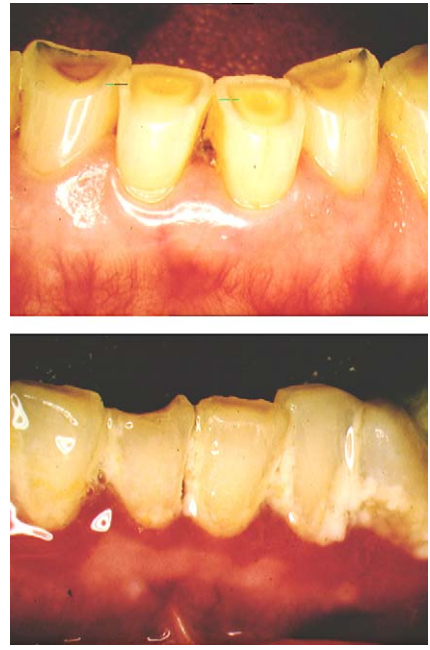

Fig. 2. (*Upper panel*) Example of oral hygiene status of elderly subject presenting for the first time to a dental school clinic. (*Lower panel*) Example of oral hygiene status of elderly nursing home resident. Subjects enrolled in the study are described in Russell et al [42]. (Courtesy of S. Russell, DDS, MPH, New York, NY.)

and thus prevent the onset of serious respiratory infection in vulnerable subjects. Although oral hygiene measures are a component of nursing care, implementation of such measures is difficult in some patients such as those who are orally intubated. Several intervention studies show, however, that improved oral hygiene measures can reduce the incidence of ventilator-associated pneumonia (VAP).

Several approaches have been taken to reduce the numbers of bacterial pathogens in the oral cavity of subjects with high risk of pneumonia. One approach uses topical nonabsorbable antibiotics (eg, 150 mg polymyxin B sulfate, 1 g neomycin sulfate, 1 g vancomycin hydrochloride in 60 mL of 5% dextrose) [44]. The 25 ICU test patients had the antibiotic mixture applied to the retropharynx every 24 hours and then swallowed. These patients were compared with 27 in a placebo group who received topical 5% dextrose. Application of the antibiotic paste reduced tracheobronchial colonization by gram-negative respiratory pathogens and *Staphylococcus aureus* and reduced the rate of pneumonia fivefold compared with the control treatment.

The effectiveness of oral topical chlorhexidine gluconate to reduce pneumonia was examined in mechanically ventilated patients following cardiac surgery [45]. Patients were randomly assigned to two groups: one group received 0.12% chlorhexidine gluconate (treatment) applied twice daily to buccal, pharyngeal, gingival, tongue, and tooth surfaces. The second group received the vehicle alone (placebo) applied in a similar fashion. Patients in both groups also received standard oral care according to the ICU's protocol. The topical chlorhexidine gluconate treatment reduced the incidence of total respiratory tract infections by 69% ($P < 0.05$) compared with placebo (Table 2). This intervention also significantly reduced total mortality (1.16% versus 5.56%) and the need for systemic antibiotics.

In another study, a test group of 30 patients received 0.2% chlorhexidine gel three times a day [46], whereas a similar-sized control group received an oral rinse with bicarbonate isotonic serum and oropharyngeal aspiration four times a day. The results showed that oral antiseptic decontamination

Table 2
Reduction of nosocomial respiratory infection by the use of oral 0.12% chlorhexidine gluconate

	Experimental group	Placebo control group
No. of patients	173	180
No. of respiratory infections	5	17*
No. of cases in which gram-negative bacteria was cause of pneumonia	8	20

*$P < 0.05$.

Data from DeRiso AJ II, Ladowski JS, Dillon TA, et al. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996;109(6):1558.

with 0.2% chlorhexidine gel significantly reduced the incidence of nosocomial pneumonia.

A subsequent prospective study [47] provides additional evidence that oral topical antimicrobial agents reduce the risk of pneumonia. Three groups of patients admitted to three ICUs over a 2-year period were enrolled in this study. The test group of 87 patients received a 2% gentamycin/colostin/vancomycin paste every 6 hours. A placebo group of 78 patients received Orabase without antibiotics. A control group of 61 patients received no treatment. The topical antibiotic treatment prevented acquired oropharyngeal colonization (10% versus 59% in the placebo group and 63% in the control group, $P<0.0001$ and $P<0.00001$, respectively) and the incidence of VAP (10% versus 31% in the placebo group and 23% in the control group, $P=0.001$ and $P=0.04$, respectively).

There have also been several preliminary trials testing oral hygiene interventions to reduce the incidence of pneumonia in nursing home subjects [48,49]. For example, 366 elderly residents from 11 nursing homes were studied; a test group of 184 subjects received supervised toothbrushing after each meal, and topical povidone iodine 1% once a day; the control group of 182 subjects received no intervention. A 2-year follow-up found that the relative risk of pneumonia in the group with no active oral care was 67% greater compared with the oral care group ($P=0.04$).

Association of periodontal disease with chronic obstructive pulmonary disease

Poor oral hygiene and PD also may be associated with other respiratory diseases such as COPD, a very prevalent chronic disease [35]. COPD is defined as a spectrum of conditions characterized by chronic obstruction to airflow due to emphysema and/or chronic bronchitis. Although no study has established that PD influences the pathophysiology of COPD, several studies have demonstrated a statistical association between the two conditions. For example, an analysis of 23,808 community-dwelling individuals enrolled in the First National Health and Nutrition Examination Survey data [50] found 365 individuals reporting a respiratory condition confirmed by a study physician. These subjects were categorized as having a confirmed chronic respiratory disease (chronic bronchitis or emphysema), acute respiratory disease (influenza, pneumonia, acute bronchitis), or not having a respiratory disease. Logistic regression analysis revealed that poor oral hygiene and smoking status were statistically associated with chronic respiratory disease. Additional data in support of this concept found that PD (measured as alveolar bone loss assessed from periapical radiographs) was an independent risk factor for COPD in adult men enrolled in the VA Normative Aging study [51].

To verify these results, a cross-sectional, retrospective analysis of data from the Third National Health and Nutrition Examination Survey

(NHANES III) was performed. The NHANES III documented the general health and nutritional status of randomly selected United States subjects from 1988 to 1994 [52]. Of 13,792 subjects $\geq$20 years of age having at least six natural teeth, those with a history of bronchitis or emphysema were considered together as having COPD. Subjects with COPD had, on average, more periodontal attachment loss (mean clinical attachment level [CAL] 1.48 $\pm$ 1.35) than those without COPD (mean CAL 1.17 $\pm$ 1.09). Taking into account a variety of risk factors common to COPD and PD (eg, gender, age, race, education, income, dental treatment history, alcohol consumption, diabetes status, smoking status), logistic regression analysis found risk of COPD to be significantly elevated when the mean attachment loss was $\geq$2.0 mm compared with periodontally healthy individuals (mean attachment loss $<$2.0 mm; odds ratio 1.35; 95% confidence interval [CI]: 1.07–1.71). In addition, the trend was noted that lung function appeared to diminish as the amount of attachment loss increased. No such trend was apparent when gingival bleeding was considered.

A more recent study evaluated the role of smoking in a possible relationship between PD and COPD [53]. The authors re-evaluated 7625 NHANES III participants $\geq$30 years of age who received a spirometric examination. After adjustment for potential confounders, no statistically significant association between PD and COPD was found among former smokers or nonsmokers. Current smokers with $\geq$4 mm mean loss of attachment, however, had an odds ratio of 3.71 (95% CI: 1.74, 7.89) for COPD. The investigators concluded that cigarette smoking is a cofactor in the relationship between PD and COPD. Because smoking is important in the etiology of PD and COPD, it is difficult to separate the contribution of PD and smoking to the etiology of COPD. It is likely that smoking is the major initiator and contributor to COPD and may contribute to disease progression by way of several pathways [32].

In summary, oral colonization by respiratory pathogens appears to be a risk factor for lung infection in high-risk subjects. Oral interventions that improve oral hygiene and possibly reduce oral inflammation may prove to be a simple, inexpensive, and effective means to lower risk of pneumonia in institutionalized populations. Further studies are required to verify the apparent association between PD and COPD.

Adverse pregnancy outcomes and periodontal disease

Preterm low birth weight (PTLBW) continues to be a significant cause of infant morbidity and mortality. PTLBW is associated with elevated risk for mortality in the first year of life, for developmental problems in childhood, and for several diseases in adulthood. Most perinatal deaths occur in infants born prematurely, especially in infants delivered before 32 weeks' gestation [54]. The prevalence of preterm birth varies from 6% to 15% of all deliveries

depending on the population studied in developed countries, and the prevalence has risen in recent years. Risk factors that appear to contribute to adverse pregnancy outcomes include low socioeconomic status, race, multiple births, the mother's age, history of a preterm birth or delivery of a low birth weight infant, parity, past reproductive history, drug and alcohol abuse, and systemic maternal infection. Bacterial vaginosis is a clinical condition caused by overgrowth of the vaginal mucosa by certain aerobic and anaerobic bacteria. Several studies have shown that the onset of bacterial vaginosis during pregnancy is associated with spontaneous abortion, preterm labor, premature birth, premature rupture of the membranes, amniotic fluid infection, postpartum endometriosis, and postcesarean wound infections.

It is also possible that infectious processes occurring elsewhere in the body may contribute to neonatal morbidity and mortality. It has been suggested that PD may be one such infection. The first report of a possible association between PTLBW and PD examined 93 mothers who gave birth to preterm or low birth weight children [55]. These mothers were matched with 31 control mothers who gave birth to children of normal term and birth weight. PTLBW was defined as birth weight less than 2500 g, spontaneous abortion before 12 weeks gestation, preterm labor requiring medical intervention, or premature rupture of the membranes before 36 weeks of gestational age of birth, with gestational age less than 36 weeks. It was found that the risk of PTLBW was 7.5-fold greater if the mother had evidence of PD (diagnosed as having clinical attachment loss) compared with mothers without evidence of PD. Several additional studies have since been published that provide evidence supporting the contention that women with PD have a greater risk of having preterm or low birth weight children [56–60].

In contrast, a case-control study of 236 mothers with PTLBW and 507 normal-birth controls [61] found no association between maternal PD and increased risk of PTLBW. In fact, these investigators found that increasing mean pocket depth at the time of delivery was associated with a reduction in the risk of PTLBW. Other studies since published have not supported this association [62–64].

These conflicting results demonstrate the need for large-scale, multicenter randomized trials of PD treatment to establish causal relationships between periodontal status and PTLBW. Recently, several studies have been published that have tested the effect of periodontal intervention to reduce adverse pregnancy outcomes [65,66]. One study examined 200 pregnant women who received periodontal treatment before 28 weeks of gestation. These women were compared with 200 mothers who received periodontal treatment after delivery (Table 3). Although this trial was randomized, it was not double blinded. Oral intervention included plaque control instruction, scaling, and root planing, with oral rinsing once a day. It was found that periodontal therapy before 28 weeks' gestation significantly reduced the rate of PTLBW in women with PD. Another study [67] compared 74 subjects who

Table 3
Incidence of preterm births, low birth weight, and preterm/low birth weight in treatment and control groups

	Treatment group (N = 163)		Control group (N = 188)		
	n	%	n	%	*P*
Preterm birth	2	1.10	12	6.38	0.017
Low birth weight	1	0.55	7	3.72	0.083
Preterm/low birth weight	3	1.63	19	10.11	0.001

Treatment consisted of plaque control instructions, rinse once a day with 0.12% chlorhexidine, scaling, and root planing performed under local anesthesia. The control group subjects received no intervention.

Modified from Lopez NJ, Smith PC, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol 2002;73(8):916.

received mechanical dental plaque control instructions and scaling and root planing of all teeth compared with 90 control subjects who did not receive periodontal intervention. Significant reduction in the incidence of PTLBW was found in women who received periodontal therapy during pregnancy. These preliminary intervention studies provide provocative evidence that periodontal therapy before 28 weeks of gestation may significantly reduce the incidence of PTLBW children.

Diabetes mellitus

Diabetes mellitus (diabetes) is a metabolic derangement characterized by impairment in glucose use. Diabetes occurs in two major forms: type 1 diabetes is the result of a reduction in or the elimination of insulin production by beta cells in the pancreas. Insulin functions through interaction with muscle and liver cells to regulate glucose metabolism. Reduced insulin production is most often the result of destruction of the beta cells, probably due to autoimmune or viral disease. Individuals with type 1 diabetes require daily insulin supplementation to properly regulate glucose use. Insulin delivery is usually by injection, although progress has been made with the use of insulin pumps and pancreatic transplantation that provides an endogenous source of insulin.

Type 2 diabetes is characterized by a deficient response to insulin by target cells, although insulin production is typically normal or even enhanced in these individuals. This impairment may be due to changes in the structure or number of the cell receptors for insulin. This form of diabetes is by far the most common (estimated to be 85%–90% of all diabetes). Taken together, type 1 and 2 diabetes now appear to occur in epidemic proportions, with 5% to 10% of all Americans having some form of the disease. Recent studies suggest that the number of cases of diabetes is increasing each year, probably related to the concomitant increase in obesity in the population.

Diabetes is a serious medical condition, with numerous acute and chronic complications. The complications of diabetes are related to chronic elevation of blood glucose levels in peripheral blood (hyperglycemia). One effect of hyperglycemia is the formation of advanced glycation end products (AGEs), the products of nonenzymatic glycation/oxidation of proteins/lipids that accumulate in the blood vessel wall [68]. These AGEs are monitored as the concentration of glycated hemoglobin (HbA1c) in the blood. These molecules bind to the receptor for AGE (RAGE). This interaction leads to recruitment of inflammatory cells and their activation to stimulate inflammatory pathways that exacerbate atherosclerosis and other untoward effects.

Over time, several serious side effects can occur as the result of AGE–RAGE interactions, including so-called "macrovascular" complications such as coronary artery disease, cerebrovascular disease (stroke), and peripheral vascular disease. Microvascular complications include retinopathy, nephropathy, and neuropathy. Detailed descriptions of the clinical signs and symptoms, complications, and treatment are beyond the scope of the present discussion.

Diabetes also seems to impact fibroblast and collagen metabolism. Hyperglycemia has been associated with reduced cellular proliferation and reduced collagen synthesis [69,70]. Hyperglycemia could have untoward effects on wound healing, which is essential in the response to periodontal therapy.

It has been known for several decades that persons with diabetes tend to have more serious PD than nondiabetics. Numerous studies have documented that diabetics show more severe pocket depths, alveolar bone loss, frequent abscess formation, and poor healing following therapy than nondiabetics [71]. Studies of Pima Native Americans, who have a very high rate of diabetes [72], show a higher prevalence and incidence of periodontal attachment loss and alveolar bone loss than control populations [73].

A recent study found a relationship between periodontitis and glucose tolerance status [74]. Patients with deep periodontal pockets (defined as having a mean pocket depth >2.0 mm) were significantly associated with having impaired glucose tolerance and diabetes compared with subjects with shallow pockets (<1.3 mm). Subjects with normal glucose tolerance at baseline and who subsequently developed impaired glucose tolerance were significantly more likely to have deep pockets.

The mechanisms responsible for more aggressive periodontitis in diabetics may involve the same mechanisms involved in chronic complications of diabetes. For example, diabetic mice infected with the human periodontal pathogen *Porphyromonas gingivalis* were treated with soluble RAGE [75]. Soluble RAGE binds ligand and blocks interaction with and activation of cell-surface RAGE. Blockade of RAGE diminished alveolar bone loss, with decreased generation of tumor necrosis factor α and interleukin 6 in gingival tissue and decreased levels of matrix metalloproteinases.

In addition to the finding that individuals with diabetes have a greater risk of PD, recent studies have also suggested that subjects with PD are more likely to have poor glycemic control than diabetics without PD. Infections such as periodontitis may stimulate proinflammatory cytokine synthesis to amplify the production of AGEs in diabetics [76]. Thus, control of chronic periodontal infection may contribute to long-term glycemic control. For example, in one study, 113 Native Americans (81 female and 32 male subjects) with PD and type 2 diabetes were randomized into five treatment groups [77]. Periodontal treatment included ultrasonic scaling and curettage combined with one of the following antimicrobial regimens: (1) topical water and systemic doxycycline, 100 mg, for 2 weeks; (2) topical 0.12% chlorhexidine and systemic doxycycline, 100 mg, for 2 weeks; (3) topical povidone-iodine and systemic doxycycline, 100 mg, for 2 weeks; (4) topical 0.12% chlorhexidine and placebo; and (5) topical water and placebo (control group). The doxycycline-treated groups showed the greatest reduction in probing depth and subgingival *Porphyromonas gingivalis* compared with the control group. In addition, all three groups receiving systemic doxycycline showed significant reductions ($P \leq 0.04$) in mean HbA1c at 3 months, reaching nearly 10% from the pretreatment value. It was unclear from this study what role scaling alone would play in reducing HbA1c in diabetics. In a more recent study, subjects with type 2 diabetes with periodontitis were randomly divided into two groups [78]. Group 1 (15 subjects) received full-mouth scaling and root planing plus amoxicillin/clavulanic acid, 875 mg. The second group (15 patients) received only full-mouth scaling and root planing. Following therapy, both groups showed reduction in probing depths and reduced levels of HbA1c values after the 3 months; however, the reduction in HbA1c values was statistically significant only for group 2.

Summary

A number of studies suggest that PD is associated with diseases resulting from atherosclerosis, lung diseases such as pneumonia and COPD, and adverse pregnancy outcomes. Presently, the data must be regarded as preliminary. Additional large-scale longitudinal epidemiologic and interventional studies are necessary to validate these associations and to determine whether the associations are causal.

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