Review Article

The impact of periodontal infections on systemic diseases

An update for medical practitioners

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ABSTRACT

Oral health status is an integral component of a general health and well-being of an individual. Knowledge about the link between periodontal disease and systemic diseases are growing rapidly. Increasing evidence is available from many investigators to indicate periodontitis as a risk factor for cardiovascular diseases, diabetes mellitus, low birth weight infants and pulmonary diseases. Both epidemiologists and researchers in oral microbiology have contributed significantly to the new paradigm of periodontal disease. Although additional studies are needed to determine the mechanisms by which such associations exist; available research clearly demonstrates that oral diseases and conditions are not only markers for underlying health problems, but also important determinants influencing the development and management of adverse chronic health conditions. Physicians and dentists should be aware of this link and provide treatment that will greatly benefit the patients. A review of the relationship between periodontal infections and its possible impact on systemic diseases is discussed.

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Periodontal diseases comprise group of infections involving the supporting tissues of the teeth. These range in severity from mild and reversible inflammation of the gingiva (gum) to chronic destruction of periodontal tissues (gingiva, periodontal ligament, and alveolar bone) with eventual exfoliation of teeth. The destructive process of the periodontal tissues begins with the accumulation of biofilms on the tooth surface that contains bacterial masses at or below the gingival margin (**Figure 1**). The destruction continues with the release of toxic products from the pathogenic plaque bacteria and is compounded by the host response elicited against these bacteria and their products.[1] Some periodontopathic bacteria such as *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* (*P. gingivalis*) are unique to the oral cavity, where they can cause chronic periodontal infections and disseminate into the systemic circulation and affect other organs.[2] The concept of oral infections as a risk for systemic disease has been suggested at various eras throughout the centuries. The emergence of oral sepsis as a cause for systemic disease began sometime before the turn of the nineteenth century but was disregarded in the 1940s. However, it resurfaced again in the 1990.[3] Since then much research have been conducted and gathered findings to suggest the possible association with oral disease, such as periodontitis, with systemic diseases.[4,5] A large extent of the periodontal tissue destruction observed in periodontitis is caused by

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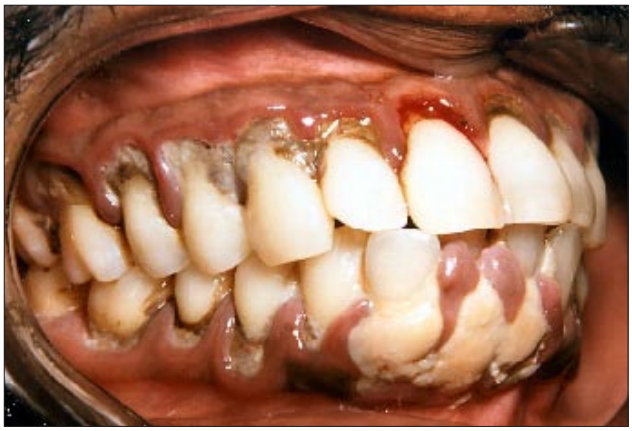

Figure 1 - A case of periodontitis. Note the calculus and plaque accumulation and destruction of the supporting tooth structures.

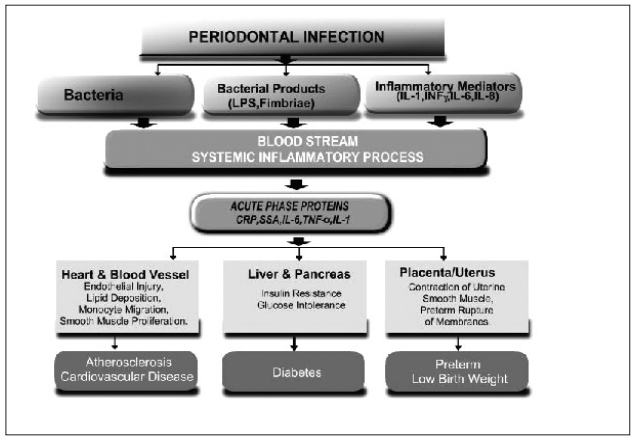

Figure 2 - Periodontal infection and systemic conditions - potential linkage and possible pathogenic mechanisms. CRP-C-reactive protein, LPS- lipopolysaccharide, IL-1- interleukin-1, IL-6 - interleukin-6, IL-8 - interleukin-8, SSA - Sjogren's antibodies, INF-g-Interferon-gamma, TNF-a Tumor necrosis factor-alpha.

host-mediated release of pro-inflammatory cytokines, such as Interlukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), by local tissue and immune cells in response to the bacteria flora and its metabolites.[6] Periodontal infections might pose additional risks for susceptible people, contributing to serious diseases such as coronary heart disease and stroke;[7] increasing pregnant women's risks of having a preterm, low birth weight (LBW) baby;[8] and posing a threat to people whose health is compromised by uncontrolled diabetes[9] or respiratory diseases.[10] The association between periodontitis and chronic disorders such as diabetes and coronary artery disease (CAD) may also be mediated by either non-specific or specific mechanisms, in addition to being linked to immunologic components. Therefore, evidence for potential associations between dental infections and systemic diseases must be carefully reexamined to distinguish potential confounding factors from other risk factors.

Pathways linking periodontal infection to systemic disease. The biological basis and potential mechanisms by which periodontal diseases might influence these conditions have been proposed. Periodontitis may affect the host's susceptibility to systemic disease in 3 distinct pathways: by shared risk factors, by subgingival biofilms acting as reservoirs of gram-negative bacteria, and through the periodontium acting as a reservoir of inflammatory mediators[4] (**Figure 2**).

Shared risk factors. Periodontal diseases certain systemic diseases and conditions may share common risk factors.[11] Among these are tobacco smoking, stress, aging, race or ethnicity, and cardiovascular disease and periodontitis gender are common in female.[12] The possible role of genetic factors shared by periodontitis, cardiovascular disease, preterm labor, and osteoporosis are under investigation.

Subgingival biofilms. Subgingival biofilms constitute an enormous and continuing bacterial load.[13] They present continually renewing reservoirs of lipopolysaccharides (LPS) and other gram-negative bacteria with ready access to the periodontal tissues and the circulation. The systemic challenge with gram-negative bacteria or LPS induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration, and intravascular coagulation.[14] Lipopolysaccharides upregulates expression of endothelial cell adhesion molecules and secretion of IL-1, TNF-α and thromboxane, which results in platelet aggregation and adhesion, formation of lipid-laden foam cells, and deposits of cholesterol and cholesterol esters.[15]

Periodontium as cytokine reservoir. The serum pro-inflammatory cytokines TNF-α, IL-1ß and gamma interferon as well as prostaglandin E2 (PGE2) reach high tissue concentrations in Periodontitis.[4] The periodontium can therefore serve as a renewing reservoir for the overflow of several of these mediators, which can enter the circulation and induce and perpetuate systemic effects. Interlukin-1ß favors coagulation and thrombosis and retards fibrinolysis.[15] Interlukin-1, TNF-α, and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells, and deposition of cholesterol. These same mediators originating from the diseased periodontium may also account for preterm labor and low birth weight infants.[4]

Periodontal disease and diabetes mellitus. The association between diabetes mellitus (DM) and periodontitis have long been discussed.[16,17] Both diseases have a relatively high incidence in the general population and are polygenic disorders featuring some degree of immune system dysfunction.[18,19] Most of the early studies tended to consider the relationship between the 2 diseases as unidirectional, with a higher incidence and severity of periodontitis in patients with diabetes. Recent studies have suggested evidence for a bidirectional adverse interrelationship between DM and periodontal diseases.[20] In particular, individuals susceptible to diabetes and those with poor metabolic control may experience one or more complications in multiple organs and tissues. The evidence for a bidirectional relationship between the 2 conditions comes from studies conducted in distinctly different settings worldwide.[21-23]

The presence of periodontal disease has been shown to aggravate the glycemic state.[24] Type 2 DM individuals with severe periodontal disease demonstrated significantly worse glycemic control than diabetic individuals with mild periodontal disease.[25,26] The severe periodontal infection may increase the risk for microvascular and macrovascular diabetic complications. Control of infection through periodontal therapy has been shown to improve glycemic control with reduced insulin requirements in both type 1 and type 2 diabetics.[27,28] Studies have also shown that diabetics with severe periodontitis exhibit more complications and poor metabolic control compared to diabetics without periodontitis.[29-31] Taylor et al[25] showed that type 2 diabetes subjects with severe periodontitis at baseline were approximately 6 times more likely to have poor glycemic control during 2 years of follow-up than those without severe periodontitis at baseline. Another study among elderly patients also reported an association between advanced periodontitis and impaired glycemic control.[32] It is suggested that type 2 diabetes may be a disorder of the innate immune system and results from a chronic, low-level inflammatory process.[33] The triggers of inflammation are many and potentially include oral infection, which may lead to a cascade of events, including increased cytokine production,[34] activation of acute-phase protein synthesis,[35] and consequent insulin resistance that produces pathogenic changes resulting in type 2 diabetes.[36] Periodontal pathogens have been shown to invade deep vascular endothelium associated with the periodontium, and can be found within vascular pathological plaques.[37,38] *Porphyromonas gingivalis*, one of the most potent periodontal pathogens, is able to invade endothelial cells and can provide a compelling signal for monocyte and macrophage activation.[39] Thus, once established in the diabetic host, this chronic infection may complicate diabetes control and increase the occurrence and severity of microvascular and macrovascular complications.[1]

It is further proposed that an infection mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from LPS and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end (AGE) product mediated cytokine response that is operative in DM.[40-42] The combination of these 2 pathways, infection and AGE-mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a 2-way relationship between DM and periodontal disease or infection. Overall, the evidence supports the view that the relationship between diabetes and periodontal diseases is bidirectional. Further, rigorous systematic study is warranted to firmly establish that treating periodontal infections can contribute to glycemic management and possibly to a reduction in the complications of DM. However, there is already sufficient evidence to recommend incorporating thorough oral examination and necessary periodontal care in the management regimens of diabetic patients.

Periodontal disease and cardiovascular disease. Coronary artery disease remains the principal cause of death in most developed countries, despite significant preventive and therapeutic advances. Recent studies have shown that people with periodontitis are more likely to develop cardiovascular disease (CVD) specifically atherosclerosis.[43] Oral pathogens from periodontal lesions intermittently reach the bloodstream, inducing systemic inflammatory reactants and immune effectors against these periodontal bacteria. In addition, the chronic and intense local inflammatory response accompanying periodontitis has been proposed to spill beyond the oral cavity, resulting in circulating mediators of inflammation that could initiate or exacerbate the inflammatory components of atherosclerosis.[44,45] Studies have suggested that the presence of periodontitis is at least a moderate risk factor for the development of CVD.[46] Evidence linking periodontal disease with an increased risk of CVD has shown that patients with periodontal disease have 1.5 to 2.0 greater risk of incurring fatal CVD compared to patients without periodontal disease.[47] Men with periodontal disease <50 years seem to have a greater propensity for CVD. The incidence of stroke is also higher. It has been proposed that the chronic

periodontitis might increase the systemic bacterial load, bacterial antigens, endotoxins and inflammatory cytokines, which in turn contribute to the progress of atherogenic and thromboembolic events.[48] It is now becoming clear that chronic inflammation and infection such as periodontitis may influence the atherosclerotic process.[49] Severe, chronic periodontal disease provides a rich source of subgingival microbial and host response products and may exert its effect over a long period. The periodontal infection can induce changes in immune functions that result in metabolic dysregulation of serum lipid metabolism through proinflammatory cytokines. Thus, these locally produced proinflammatory cytokines IL-1ß and TNF-α may exert systemic effects by predisposing the patient to a systemic disorder such as atherosclerosis. This hypothesis is further supported by recent findings that total cholesterol, low-density lipoprotein and triglycerides are significantly higher in subjects with periodontitis than in controls.[50] However, it is not clear whether periodontitis causes an increase in hyperlipidemia or whether periodontitis and cardiovascular disease share hyperlipidemia as a common risk factor.[50] Periodontitis and CVD potentially share many risk factors, the most significant of which may be smoking status. Significant similarities also exist in the pathogenetic processes of CVD and periodontitis, including monocyte hyper-responsiveness,[51] elevations in systemic levels of C-reactive protein (CRP),[52,53] serum amyloid A (SAA)[54] and fibrinogen.[55] The question is whether periodontitis, a chronic inflammation initiated by microbial plaque, can predispose once to atherosclerosis. Studies on human atheromas obtained during endoarterectomy have found multiple periodontal pathogens in the atheromas, including *P. gingivalis, Prevotella intermedia, Bacteroides forsythus* and *A. actinomycetemcomitans*.[56] Since certain bacteria from dental plaque can cause infective endocarditis and disseminated intravascular coagulation, these pathogens may promote development of atherosclerosis and trigger coronary thrombosis.[57] In particular, studies have suggested that *P. gingivalis* exhibits several properties that could contribute to CVD as potential mediator of atherosclerosis. *Porphyromonas gingivalis* infection can induce platelet activation and aggregation, increase serum lipid levels, and induce pro-inflammatory mediators such as IL-1, TNF-α and IL-6.[58] Compared with *Escherichia coli* LPS, *P. gingivalis* LPS induced significantly higher level of TNF-α and IL-1 production by the monocytes,[59] providing evidence for the potential of this bacterial component to play a critical role in the chronic inflammatory response associated with periodontitis. Results from other studies have not found evidence to support an association between periodontitis and coronary heart disease (CHD).[60,61] It remains controversial whether or not eliminating periodontal infections would contribute to the prevention of CHD.[62,63] However, the studies that focused on stroke appear to demonstrate stronger relationships with periodontal disease than those studies that used CHD as an outcome.[64] An increasing number of studies implicate periodontal pathogenic organisms in atherogenesis. Potential mechanisms include blood platelet aggregation, elevated lipid levels, activation of the acute-phase response, and systemic production of proinflammatory mediators. Periodontal disease may trigger certain events leading to CVD through direct and indirect effects of oral bacteria on the heart. During episodes of bacteremia originating from the oral flora such as *Streptococcus sanguis* and *P. gingivalis* triggers thrombosis by inducing platelet aggregation which leads to thrombus formation. Indirect effects from bacterial products such as endotoxins and LPS could set up inflammatory reactions, which lead to vascular and coagulation complications. Inflammatory mediators could cause an acute phase response leading to heart tissue destruction. It has been shown that the level of C-reactive proteins is elevated in individuals with periodontal disease.[53] Current evidence is insufficient to unequivocally support the premise that periodontal infections constitute an independent risk factor for CAD. Further studies and meta-analyses will be required to evaluate the epidemiologic relationships of periodontitis to cardiovascular diseases.[65]

Periodontal infection and respiratory disorders. The oral cavity plays an important role in infections acquired in hospitals and nursing homes, especially infections of the respiratory tract.[66] Several studies have demonstrated that the teeth of patients in the intensive care unit (ICU) became colonized by respiratory pathogens such as *Pseudomonas aeruginosa, Enteric species* and *Staphylococcus aureus*. Similar studies have shown that the teeth of nursing home residents can also serve as reservoirs for respiratory infection.[67] An association between oral conditions such as periodontal infections and respiratory conditions such as pneumonias and chronic obstructive pulmonary disease has been found.[66,68] Evidence has suggested the oropharyngeal region as a likely source of bacteria implicated in respiratory infection. Oral periodontopathic bacteria can be aspirated into the lung to cause aspiration pneumonia.[69] Respiratory pathogens have been shown to colonize the dental plaque of hospitalized intensive

care and nursing home patients. Once established in the mouth, these pathogens can be aspirated into the lung to cause infection. Cytokines originating from periodontal tissues may change respiratory epithelium to promote infection by respiratory pathogens.[69] A systematic review of the epidemiologic and clinical evidence found that poor periodontal health increases the risk of developing chronic obstructive pulmonary disease (COPD).[70] A trend was noted in these cross-sectional, retrospective studies that lung function appeared to diminish with increasing periodontal attachment loss.[70] In addition, results from preliminary intervention trials demonstrated that attention to oral hygiene, either by the use of mechanical cleansing or oral antiseptic rinses, significantly reduced the rate of lower respiratory infection in patients under intensive care.[71] This suggests that the mouth may serve as an important reservoir for lower respiratory tract infection in these high-risk subjects.

It is also possible that oral bacteria, especially anaerobic species, release biologically active products such as LPS and specific bacterial enzymes, which may modify the airway mucosa to stimulate inflammatory cytokine release from epithelial cells. Exacerbation is also associated with elevated levels of monocyte chemoattractant protein-1 (MCP-1), TNF-α, IL-6 and IL-8 in the sputum.[72,73] Several studies have noted that oral bacteria and their products are potent stimulators of cytokine production from oral epithelial cells.[74,75] Oral bacteria may alter environmental conditions to permit mucosal colonization and infection by respiratory pathogens, and both oral and respiratory bacteria appear to induce the release of proinflammatory cytokines from oral and respiratory epithelial cells.[76] The release of cytokines from mucosal surfaces in response to oral bacterial interactions may change the local micro-environment, promoting the adhesion of microbes to both oral and respiratory epithelial cells, thus facilitating the onset or progression of respiratory diseases in susceptible individuals. The possibility that bacteria in oral biofilms influence respiratory infection suggests that good oral hygiene may prevent the aspiration of large numbers of oral bacteria into the lower airway and thus prevent initiation or progression of respiratory infection in susceptible individuals.

Periodontal disease and adverse pregnancy outcomes. Preterm delivery of low birth weight infants (PLBW) remains a significant public health issue and it is the leading cause of neonatal death and other health problems including neurodevelopmental disturbances.[77,78] Oral infections also seem to increase the risk for or contribute to LBW in newborns.[79] Identified risk factors for PLBW include maternal age; African-American ancestry; low socio-economic status; inadequate prenatal care; drug, alcohol and tobacco abuse; hypertension; genitourinary tract infection; DM; and multiple pregnancies. Smoking during pregnancy has been linked to 20-30% of LBW births and 10% of fetal and infant deaths.[80] Infection is now considered as one of the major causes of PLBW deliveries, responsible for somewhere between 30% and 50% of all cases.[5,81] Bacterial infection of the chorioamnionic, or extraplacental membrane, may lead to chorioamnionitis, a condition strongly associated with a premature membrane rupture and preterm delivery.[5,82] This suggests that distant sites of infection or sepsis may be targeting the placental membranes. The biological mechanisms involve bacterially induced activation of cell-mediated immunity leading to cytokine production and the ensuing synthesis and release of prostaglandin, which appear to trigger preterm labor.[83] Elevated levels of cytokines (IL-1, IL-6, and TNF-α) have been found in the amniotic fluid of patients in preterm labor with amniotic fluid infection.[81] These cytokines are all potent inducers of both prostaglandin synthesis and labor. Intra-amnionic levels of PGE2 and TNF-α rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery.[8] As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome. During pregnancy, the ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaque in the second trimester.[84] The gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that can directly affect the host. One microbial component, LPS, can activate macrophages and other cells to synthesize and secrete a wide array of molecules, including the cytokines IL-1ß, TNF-α, IL-6, and PGE2 and matrix metalloproteinases.[5,85] If they escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of PGE2 and TNF-α in the amniotic fluid and induce premature labor.

Studies have demonstrated that women who have LBW infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severely periodontal disease than mothers with normal-birth-weight infants.[5] A case-control study of 124 pregnant or postpartum mothers was performed, using mothers with normal-birth-weight babies as controls.[8] Multivariate logistic regression models, controlling for other risk factors and co-variates, demonstrated that periodontal disease is a statistically significant risk factor for PLBW, with

adjusted odds ratios of 7.9 and 7.5 for all PLBW cases and primiparous PLBW cases, respectively. These data indicate that periodontal disease represents a previously unrecognized and clinically significant risk factor for PLBW as a consequence of either preterm labor or premature rupture of membranes.

In a study, relating the poor oral health of the pregnant woman to LBW, it was concluded that poor periodontal health of the mother is a potential independent risk factor for LBW.[86] The gingival crevicular fluid (GCF) levels of PGE2 and IL-1ß measured to determine whether mediator levels are related to current pregnancy outcome.[79] In addition, the levels of 4 periodontal pathogens were measured by using microbe specific DNA probes. These data suggest a dose-response relationship for increased GCF, PGE2 as a marker of current periodontal disease activity and decreasing birth weight. Four organisms associated with mature plaque, and progressing periodontitis are *Tannerella forsythia, P. gingivalis, A. actinomycetemcomitans,* and *Treponema denticola*, and are detected at higher levels in mothers of PLBW infants than in controls.[87] Offenbacher et al,[8] concluded that 18.2% of PLBW babies may result from the previously unrecognized periodontal infection in mothers. However, it should be noted that periodontal disease pathogens are necessary but may not sufficient for periodontal disease expression. The role of the host's inflammatory response appears to be the critical determinant of susceptibility and severity.[88] Collectively, these animal and clinical studies clearly indicate an association between periodontal infection and adverse pregnancy outcomes. Although no definitive relationship has been established or a model can nevertheless be envisaged wherein chronic periodontal infection could mediate this systemic effect through one or more of the following mechanisms: (i) Translocation of periodontal pathogens to the fetoplacental unit, (ii) Action of a periodontal reservoir of LPS on the fetoplacental unit, or (iii) Action of a periodontal reservoir of inflammatory mediators (IL-1, IL-6, TNF-α, PGE2) on the fetoplacental unit. The association between periodontal disease and LBW may reflect the patient's altered immune-inflammatory trait that places the patient at risk for both conditions. Thus, periodontitis may be a marker for preterm delivery susceptibility as well as a potential risk factor.

Periodontal infection and gastrointestinal diseases. The oral cavity provides a gateway between the external environment and the gastrointestinal tract, and it facilitates both food ingestion and digestion. Oral hygiene and tooth loss can potentially affect gastrointestinal flora and nutritional status, and thus, they have implications for the development of chronic diseases.[89] Poor dental health, tooth loss, or both have been associated with increased risk for gastrointestinal malignancies, including oral esophageal and gastric cancers.[90-94] Dental plaque has been suggested a reservoir for *Helicobacter pylori (H. pylori*).[95-98] The presence of *H. pylori* has been universally associated with chronic gastritis, and strongly with duodenal ulcer. Previous studies have also identified the microorganism in dental plaque and saliva, which would implicate the oral cavity as a potential reservoir for *H. pylori* or as a possible route of transmission to other sites. Presently, it is not clear whether the oral cavity permanently harbors viable *H. pylori* or merely serves as the route of transmission to other sites.[98] In a survey of Dye et al[99] showed that periodontal disease, specifically periodontal pocket depth, was associated with seroprevalence of *H. pylori*. Furthermore, gastric carriage of *H. pylori* is a known risk factor for gastric cancer, with the cytotoxin-associated gene-A-positive (CagA+) strain having a greater propensity for inflammation, ulceration, and malignancy.[100,101] Tooth loss also reduces masticatory ability and hence may lead to the consumption of a less healthy diet which could be associated with disease.[102,103]

The question as to whether the oral cavities, in general, and dental plaque, specifically, are reservoir of *H. pylori*, has been controversial. Desai et al[104] suggested that the dental plaque as a permanent reservoir of *H. pylori*. Other investigators, however, would argue against the notion that the oral cavity and dental plaque are permanent reservoirs for *H. pylori*.[105] The detection of *H. pylori* by polymerase chain reaction in dental plaque, however, would indicate that the oral cavity may act as a reservoir or sanctuary for the organism.[106,107]

Periodontal infection and osteoporosis. Osteoporosis and osteopenia are characterized by reductions in bone mass and may lead to fragility and fracture. There may be an association between osteoporosis and alveolar bone loss around a tooth.[108] Women with osteoporosis have reductions in bone mineral content, which increases the risk for fracture.[109] The majority of the literature has investigated the role of osteoporosis in the onset and progression of periodontitis and tooth loss.[110-112] However, chronic infection around multiple teeth could contribute significantly to elevations in circulating IL-6 levels, a predictor of bone loss.[113] In an animal study, elevated levels of IL-6 were found in the serum and gingival tissue adjacent to deep periodontal pockets.[114] Therefore, it is at least theoretically possible that chronic periodontitis

may contribute to the development or progression of osteoporosis. Whether individuals with oral osteopenia are at risk for systemic osteopenia and osteoporosis remains to be determined. Medication used for the treatment and prevention of osteoporosis has the potential to reduce alveolar bone loss.[115,116] It has been shown that estrogen used in hormone replacement therapy of postmenopausal women is associated with reduced gingival inflammation and a reduced frequency of gingival attachment loss in osteoporotic women in early menopause.[117] The use of bisphosphonate alendronate, an antiresorptive drug has been shown to lower the risk of bone loss in adults with periodontal disease.[118] There is a possible relationship between osteoporosis and periodontitis which need further investigations.[119]

In conclusions, emerging research is beginning to establish distinct associations between periodontal diseases and adverse chronic health conditions. Epidemiologic evidence suggests that the oral infections may have an association with the occurrence and severity of a wide variety of systemic conditions and diseases such as heart disease, PLBW babies, respiratory disease, and DM. The association is not indicated simply by clinical signs of periodontal disease, but by molecular criteria, such as immune and inflammatory mediators. The early identification of oral disease may contribute to the early diagnosis and treatment for a number of systemic diseases. A need for additional knowledge is required to link the inter-relationships between dentistry and medicine to further improve the management of overall health of patients. New studies are under way, and the results generated will be useful for the better understanding of the mechanisms and interactions between oral infections and systemic diseases, which will further strengthen the partnership between dental and medical communities.

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