Review Article

Periodontal infections: A risk factor for various systemic diseases

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ABSTRACT

A healthy periodontium is vital for the general well-being of an individual. However, periodontal diseases are common and periodontal infections are increasingly associated with systemic diseases. We aimed to critically evaluate the literature on the association between periodontal infections and systemic diseases. We searched the PubMed database over a 20-year period for literature on periodontal diseases and their links to various systemic diseases, and examined the strength of association between periodontal disease and each systemic disease, the dose–response relationship, and the biological plausibility. We found that individuals with periodontal disease may be at higher risk for adverse medical outcomes including cardiovascular diseases, respiratory infections, adverse pregnancy outcomes, rheumatoid arthritis and diabetes mellitus. Many cohort, *in vitro* and animal studies suggest that systemic inflammation due to pathogens associated with periodontal disease may play a role in the initiation and progression of some systemic diseases. Periodontal infections should therefore be considered as a risk factor for various systemic diseases.

Natl Med J India 2011;24:214–19

INTRODUCTION

The oral cavity is a mirror of the body and reflects the general health and well-being of an individual.[1] Humans have been afflicted by major oral diseases such as dental caries and periodontal diseases since time immemorial.[2] Periodontal infections have many causes, often modified by underlying systemic conditions.[3] In recent years, there has been a shift in interest from understanding periodontal manifestations of systemic diseases to linking the role of periodontal infections with various systemic diseases. Associations have been reported between periodontal disease and cardiovascular disease (CVD), stroke, diabetes, preterm low birth-weight babies, respiratory infections and rheumatoid arthritis (RA).[4]

Periodontal disease is the result of host inflammatory reaction to bacterial infection. The focus of infection in the oral cavity can lead to systemic inflammation resulting in adverse medical outcomes. There is a need to educate both dentists as well as general healthcare practitioners about this important aspect of oral health. It is also necessary to coordinate with medical institutions where the results of emerging research are translated into practice guidelines. As the prevalence of CVD, cerebrovascular accidents, respiratory infections and diabetes is increasing globally, identifying risk factors other than the traditionally recognized ones may help in effectively preventing and managing these diseases.

We have summarized the available evidence on the possible mechanisms by which periodontal infections may be responsible for the initiation and progression of systemic diseases. We hope this will increase awareness of the importance of oral health, which is often neglected in India.

METHODS

We searched the PubMed database from 1990 through 2010 (both years included) for English language articles using the following search terms: 'Periodontal disease and systemic diseases', 'periodontal disease and atherosclerosis', '*P. gingivalis* and cardiovascular diseases', 'periodontal disease and stroke', 'periodontitis and respiratory infections', 'periodontal disease and diabetes mellitus', 'periodontal infections and rheumatoid arthritis' and 'periodontal infections and preterm low birth weight babies'. We selected and reviewed cross-sectional, longitudinal, cohort, *in vitro* and animal studies that provided information related to periodontal infection and systemic diseases.

WHAT ARE PERIODONTAL DISEASES?

Periodontal diseases are a group of diseases that cause inflammation and destruction of the investing and supporting structures of the teeth (such as the gingiva, periodontal ligament, alveolar bone and cementum of the tooth), as well as the periodontal tissues. This leads to apical migration of the junctional epithelium, resulting in the formation of periodontal pockets.[5,6] Periodontal diseases occur due to a complex interplay of bacterial infection and host response,

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often modified by behavioural factors and various systemic conditions such as metabolic disorders (diabetes mellitus, female hormonal imbalance), drug-induced disorders, haematological disorders such as leukaemia, and immune system disorders. These systemic disorders have been shown to affect the periodontium and/or influence the treatment of periodontal disease.[5]

Periodontal disease is caused by bacteria found in dental plaque, and about 10 species have been identified as putative pathogens in periodontal disease. Pathogens frequently associated with periodontal disease include *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), *Capnocytophaga*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* and *Treponema denticola*.[6]

PERIODONTAL INFECTIONS AND CARDIOVASCULAR DISEASES

Both periodontal diseases and CVD are chronic, whose causes are multifactorial. Risk factors common to both include older age, male gender and smoking, and psychosocial factors such as stress. A number of epidemiological studies in the 1990s suggested a relationship between CVD and periodontal diseases.[7–9] However, these observational studies did not provide a rationale for periodontal infections leading to systemic complications.

There is now epidemiological evidence to support the concept that poor oral health, especially extensive and severe periodontal disease, may put patients at risk for a variety of systemic conditions such as CVD.[10] This association highlights the importance of good oral health. Poor dental health has been associated with an increased risk of fatal coronary heart disease (CHD).[11] Thus, maintenance of good oral hygiene is important. A study by de Oliveira *et al*.[12] showed that infrequent brushing of the teeth was associated with increased concentrations of C-reactive protein (CRP) and fibrinogen; both are associated with coronary arterial plaque formation.

Strength of association

The evidence for a link between periodontal disease and cardiovascular risk has been reviewed by several groups. In a meta-analysis of published studies, Humphrey *et al*.[13] found a higher risk for CVD in those with periodontal disease, with a summary relative risk (RR) estimate ranging from 1.24 (95% CI 1.01–1.51) to 1.34 (95% CI 1.10–1.63). Cronin[14] has provided an insightful commentary on this study. In a similar review, Janket *et al*.[15] concluded that in patients with periodontal disease, the RR of future cardiovascular events was 1.19 (95% CI 1.08–1.32). In another meta-analysis by Khader *et al*.,[16] the adjusted risk of CHD in those with periodontitis was 1.15 (95% CI 1.06–1.25) and the overall adjusted RR of CVD was 1.13 (95% CI 1.01–1.27). However, in a consensus review from the UK and Ireland, Williams *et al*.[17] have stressed the need for further prospective research before a causal relationship can be established between periodontal disease, CVD and diabetes. Similar views have been expressed in a systematic review by Scannapieco *et al*.,[18] who found a modest association between periodontal disease and atherosclerosis, myocardial infarction and CVD.

Dose–response relationship

The systemic inflammatory burden varies according to the stage of periodontal infection. A study of patients with acute ischaemic heart disease showed that triglyceride and low density lipoprotein (LDL) levels were raised in patients with severe chronic periodontitis compared with those who had mild chronic periodontitis, while high density lipoprotein (HDL) levels were low in those with severe chronic periodontitis.[19]

As periodontal infections are one of the reasons for the loss of teeth, the number of remaining teeth may indicate the risk for CHD. A study suggests that there was a 7-fold increased risk of mortality from CHD in subjects with <10 teeth compared with those with >25 teeth.[20]

A statistically significant association has been reported between periodontal disease and fatal CHD with risk ratios of 2.15 (95% CI 1.25–3.72) and 1.90 (95% CI 1.17–3.10) for severe gingivitis and edentulous status, respectively.[21] The Consensus Report of the Sixth European Workshop on Periodontology 2008[22] suggested that periodontitis contributes to the total infectious and inflammatory burden which, in turn, may contribute to cardiovascular events and stroke in susceptible subjects.

The association of periodontal disease with atherosclerosis, myocardial infarction and CVD is of public health importance due to the high prevalence of periodontal diseases in the community. Gingival bleeding is highly prevalent among adult populations in all regions of the world; advanced disease with deep periodontal pockets (≥6 mm) affects 10%–15% of adults worldwide.[23]

The 'National Oral Health Survey and Fluoride Mapping 2002–2003' found that the prevalence of periodontal disease in India increased in those above the age of 12 years. In children aged 12 years, the prevalence was 57%, and peaked at 89.6% in the age group of 35–44 years. The prevalence was lower in the age group of 65–74 years (79.9%). Calculus was more prevalent than bleeding across age groups. Periodontal pockets, both shallow (4–5 mm) and deep (≥6 mm), were markedly more common in older adults (65–74 years).[24]

Biological plausibility

Atherosclerosis is considered to be an inflammatory disease and infections are an important cause of systemic inflammation.[25] Exposure to periodontal pathogens, particularly *P. gingivalis,* causes systemic inflammation and an increased risk for CVD.[26] Periodontal infection predisposes individuals to an increased incidence of bacteraemia resulting in a persistent bacterial challenge to the arterial endothelium. *P. gingivalis* has been found to invade and proliferate in human coronary artery endothelial cells and coronary artery smooth muscle cells.[27]

The microbial challenge contributes to a macrophage/monocyte-derived inflammation, resulting in increased levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α.[28] It also results in increased levels of CRP which is a risk factor for CVD.[29] Findings in animal models have shown that macrophages/monocytes proliferate in the smooth muscles of the heart, and the arterial intima, ingest LDL and become engorged 'foam cells'. These lead to an autoimmune phenomenon resulting in atheroma or arterial plaque formation. *P. gingivalis* is predominantly involved in this process.[30] Various studies have reported the presence of bacterial DNA of oral pathogenic microorganisms in coronary atherosclerotic plaques. The presence of bacterial DNA in coronary atherosclerotic plaques in considerable proportions may suggest a possible relationship between periodontal bacterial infection and genesis of coronary atherosclerosis.[31,32] A few studies have negated these findings.[33,34] Even though many clinical, laboratory and animal-based models have been used to ascertain the biological plausibility, the exact mechanism is still unclear and more studies are necessary.

PERIODONTAL INFECTIONS AND STROKE

Various studies have correlated periodontal disease with stroke.[35–38]

Strength of association

In a case–control study, periodontitis (clinical attachment loss [CAL] ≥6 mm) was found to be significantly associated with haemorrhagic stroke (odds ratio [OR] 2.5, 95% CI 1.1–5.6), but this association did not exhibit a dose-dependent response for periodontitis.[39] Findings from an Indian study showed that a probing pocket depth (PPD) of >4.5 mm was the most significant risk factor for stroke (OR 8.5, 95% CI 1.1–68.2) followed by hypertension (OR 7.6, 95% CI 3.3–17.1) and smoking (OR 3.1, 95% CI 1.3–7.4).[35]

Biological plausibility

Periodontal infections are associated with systemic inflammation characterized by an increased burden of periodontal pathogens, antigens, endotoxins and liberation of pro-inflammatory cytokines, which may contribute to atherogenesis and thrombo-embolic events culminating in ischaemic stroke.[36,38]

PERIODONTAL INFECTIONS AND LOW BIRTH-WEIGHT AND PRETERM BABIES

Many prospective cohort studies, case–control studies and cross-sectional observational studies have correlated poor maternal periodontal health with low birth-weight (LBW) and preterm babies.[40,41]

Strength of association

A case–control study by Pitiphat *et al*.[42] found that the OR associated with periodontitis was 1.74 (95% CI 0.65–4.66) for preterm delivery and 2.11 (95% CI 0.76–5.86) for small-for-gestational age (SGA) babies. When preterm delivery and/or SGA were combined, the OR was 2.26 (95% CI 1.05–4.85). Another case–control study found that maternal periodontitis was associated with preterm birth (OR 1.77, 95% CI 1.12–2.59), LBW (OR 1.67, 95% CI 1.11–2.51) and intrauterine growth restriction (OR 2.06, 95% CI 1.07–4.19).[43]

A meta-analysis by Khader and Ta'ani[44] showed that pregnant women with periodontal disease had an overall adjusted risk of preterm birth that was 4.28 (95% CI 2.62–6.99) times more than that of healthy subjects. The overall adjusted OR of preterm LBW was 5.28 (95% CI 2.21–12.62), while the overall adjusted OR of a preterm delivery or LBW was 2.3 (95% CI 1.21–4.38).

Dose–response relationship

The severity of periodontitis may adversely affect pregnancy outcomes in a dose-dependent manner. One report suggested that the average PPD and average CAL were significantly higher among women who gave birth to preterm LBW babies.[45] The extent and severity of periodontal diseases appeared to be associated with increased odds of preterm LBW delivery. Larger studies are needed before one can be sure that periodontal infection is a true risk factor for preterm LBW.

Biological plausibility

Chronic infections during pregnancy are associated with premature labour.[46] Periodontal infection may lead to systemic inflammation, which is associated with an increase in CRP levels. Very high CRP levels in early pregnancy have been found to be associated with preterm delivery.[47]

The response of the mother's immune system to infection by these periodontal pathogens brings about the release of inflammatory mediators which may trigger preterm labour or result in LBW infants.[48] *P. gingivalis* and *Fusobacterium nucleatum* may colonize placental tissue and contribute to preterm delivery. Studies in animals have shown that these microorganisms can invade maternal and foetal tissues resulting in chorioamnionitis and placentitis.[49,50]

In view of the possible adverse effects of periodontal infections on pregnancy outcomes, it is important to promote good oral hygiene during routine pre- and antenatal visits.

PERIODONTAL INFECTIONS AND RESPIRATORY DISEASES

Dental plaque may promote oral and oropharyngeal colonization by respiratory pathogens.[51] Bacteria from oral biofilms may be aspirated into the respiratory tract to initiate and cause progression of conditions such as aspiration pneumonia, chronic obstructive pulmonary disease (COPD) and lower respiratory tract infections.[52–54] Reports suggest that patients on ventilators are at higher risk for acquiring fatal pneumonia due to periodontal infections,[55] and poor periodontal health in the elderly may be associated with increased mortality from pneumonia.[56] The results of a systematic review suggest that oral colonization by respiratory pathogens, due to poor oral hygiene and periodontal diseases, appears to be associated with nosocomial pneumonia.[57]

Strength of association

In a systematic review, Azarpazhooh and Leake[58] showed evidence of association of pneumonia with oral health (OR 1.2–9.6) but a weak association (OR<2.0) between COPD and oral health. The review showed good evidence that improved oral hygiene and frequent professional oral healthcare reduces the progression or occurrence of respiratory diseases among high-risk elderly adults living in nursing homes, especially those in intensive care units (relative risk reduction 34%–83%).

Biological plausibility

It has been reported that dental plaque may act as a reservoir for respiratory pathogens such as *Staphylococcus aureus, Pseudomonas aeruginosa, P. gingivalis, A. actinomycete-mcomitans* and enteric species, and thus be an important risk factor for various respiratory infections.[59] Enzymes released from oral bacteria may act on the respiratory mucosal surface promoting adhesion and colonization of respiratory pathogens.[60]

In addition, oral bacterial products in oropharyngeal aspirates may stimulate cytokine production from the respiratory epithelial cells, resulting in recruitment of inflammatory cells. The resulting inflamed epithelium may be more susceptible to respiratory infection.[61] The findings of many studies underline the necessity of improving oral hygiene among patients who are at risk for life-threatening respiratory infections, such as those living in long term care institutions.

PERIODONTAL INFECTIONS AND DIABETES MELLITUS

The association of periodontal infections and diabetes mellitus is bidirectional.[62] Various oral conditions are associated with diabetes such as dry mouth, candidal infections, delayed wound healing and periodontal disease. Periodontitis has been described as the sixth complication of diabetes, together with retinopathy, nephropathy, neuropathy, macrovascular disease and altered wound healing.[63,64]

Poorly controlled diabetes is also associated with periodontal diseases.[64,65] Severe periodontitis in people with diabetes increases the risk of poor glycaemic control due to release of pro-inflammatory cytokines such as TNF-α, which are known to play a role in inducing insulin resistance in a manner similar to that of obesity.[66,67]

Based on their systematic review, Taylor and Borgnakke[68] concluded that periodontitis poses an increased risk for worsening glycaemic control. The risk of developing ketoacidosis, retinopathy and neuropathy is also higher among people who have diabetes and periodontitis.[69]

Dose–response relationship

Chronic periodontitis may have an effect on insulin resistance, since increased levels of TNF-α are seen in patients with severe periodontitis. In chronic periodontitis, there is persistent release of lipopolysachharides (LPS) from *P. gingivalis* and prolonged upregulation of TNF-α, which may increase the severity of diabetes.[70] A chronic increase in serum TNF-α due to periodontal infection may actually cause type 2 diabetes as insulin resistance increases, and the patient can no longer metabolize glucose appropriately.[71]

Taylor *et al*.[72] found that patients with severe periodontitis had an increased risk of developing poor glycaemic control over time.

Biological plausibility

There is no clear evidence of a causal association between periodontitis and diabetes, but severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. Microorganisms that cause periodontitis and the host inflammatory response to these may increase insulin resistance in people with diabetes. This process may be reversed following treatment for periodontitis.[72,73]

Studies have reported that periodontal diseases lead to a significant increase in glycated haemoglobin (HbA1c) and high-sensitivity CRP, which may be associated with poor glycaemic control.[74] The virulence of *P. gingivalis* is also one of the factors associated with poor glycaemic control.[75]

PERIODONTAL INFECTIONS AND RHEUMATOID ARTHRITIS

There is evidence to suggest a relationship between the extent and severity of periodontal disease and RA.[76–78]

Biological plausibility

Many studies suggest that periodontitis could indeed be a causal factor in the initiation and maintenance of the autoimmune inflammatory response that occurs in RA.[79,80] Studies also support the fact that both conditions manifest as a result of an imbalance between pro- and anti-inflammatory cytokines. As a result, new treatment strategies are expected to emerge for both diseases that may target the inhibition of pro-inflammatory cytokines and destructive proteases.[78–80] Findings that support the hypothesis that oral infections play a role in the pathogenesis of RA are the impact of periodontal pathogens such as *P. gingivalis* on citrullination, and the association of periodontitis in RA patients with seropositivity for rheumatoid factor and the anti-cyclic citrullinated peptide antibody.[81] The findings of a case–control study suggest that antibodies to *P. gingivalis* are more common in patients with RA than in healthy controls. An association of *P. gingivalis* titres with RA-related autoantibody and CRP levels suggests that infection with this organism may play a role in the risk for and progression of RA.[82]

Patients with RA should be carefully screened and their periodontal condition treated appropriately.

EFFECT OF PERIODONTAL TREATMENT

Periodontal treatment, a relatively simple and cost-effective intervention, has many benefits. Many studies report a decrease in plasma levels of pro-inflammatory cytokines, CRP and other markers of systemic inflammation.[83–86] Periodontal management markedly reduces systemic inflammatory markers after 1 year but not in the short term, and also improves endothelial function.[87,88] It decreases insulin resistance in patients with diabetes, improves periodontal health[89] and reduces the severity of RA if anti-TNF-α therapy is used along with standard periodontal therapy.[90] Use of chlorhexidine (0.12%) mouth rinse also decreases the risk of ventilator-associated pneumonia (VAP).[91] Timely dental treatment can not only halt progression of the disease but possibly also reduce the risk of developing various systemic conditions.

CURRENT GAPS IN RESEARCH

Even though initial descriptive studies and recent cohort, case–control and experimental studies have sought to find links between periodontitis and various systemic diseases, a causal relationship needs to be shown through prospective cohort studies and randomized controlled trials. A temporal relationship has been shown for CVD, stroke and adverse pregnancy outcomes but not for diabetes and RA.

CONCLUSION

Periodontal disease is possibly an important risk factor for various systemic diseases. Maintenance of good oral health should be given priority. People should be educated on the importance of good oral health and the risks associated with poor oral health. Dentists and medical practitioners should work together to provide comprehensive healthcare, thereby reducing the morbidity and mortality associated with periodontal infections.

Conflict of interest: None declared

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