Review Article

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Periodontal Disease Contribution to Systemic Disease: An overview of Potential Mechanism

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Abstract

Throughout the history of mankind there has been the belief that diseases which affect the oral cavity, such as periodontal disease can have an effect on the course and pathogenesis of a number of systemic diseases, such as cardiovascular disease, bacterial pneumonia, diabetes mellitus and low birth weight. The purpose of this review is to evaluate the current status of oral infections, especially periodontitis as a casual factor systemic disease.

Keywords: Periodontal infection; Respiratory disease; Diabetes mellitus; Preterm low birth weight.

Introduction

The theory of focal infection which was promulgated during the 19th and early 20th centuries. The foci of sepsis were responsible for the initiation and progression of various inflammatory diseases, such as peptic ulcers, arthritis and appendicitis. It has been increasingly clear the oral cavity can act as the site of origin for dissemination of the pathogenic organisms to distant bodies. Especially in immunocompromised host human endodontal and periodontal infections are associated with complex microfloras approximating 200 species in apical periodontitis and more than 500 species in marginal periodontitis has been encountered.

The anatomic closeness of these microfloras to the bloodstream can facilitate bacteremia and systemic spread of bacterial products, components, and immunocomplexes.

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Proposed mechanism of linking oral infections to systemic disease

Three mechanisms of linking oral infection to secondary systemic effect have been proposed. These are metastatic spread of infection from the oral cavity as a result to transient bacteremia, metastatic injury from the effect of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral microorganisms.[1]

Metastatic infection

Oral infections and dental procedures can cause transient bacteria. The micro-organism that gain entrance to blood and circulate throughout the body are usually eliminated by the reticuloendothelial system within a minute possible clinical symptom is slight increase in body temperature. If the disseminated micro-organism find favourable condition to settle and multiply.[1,2] This diseases caused by this mechanism are subacute infective endocarditis, acute bacterial myocarditis, brain abscess, cavernous sinus thrombosis, skin ulcer, Ludwig angina.[3]

Metastatic injury

Gram positive and negative bacteria have ability to produce diffusible proteins or exotoxins. The exotoxins have specific

pharmacological action and are considered the most powerful and lethal poisons. Endotoxins are part of the outer cell membrane released after cell death. Endotoxin is compositionally a lipopolysaccharide that when introduced into the host give rise to large number of pathological manifestation. The possible disease caused by this mechanism are acute myocardial infarction, abnormal pregnancy outcome, trigeminal neuralgia, toxic shock, chronic meningitis.[3,4]

Metastatic inflammation

Soluble antigen may enter the blood stream react with specific antibody and form macro-molecular complex. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the site of deposition. The diseases caused by this mechanism are chronic urticaria, Crohn's disease, Behcet's syndrome.[1]

Page proposed periodontitis may affect host's susceptibility to systemic disease in three ways.

1. *Shared risk factors:* Factors that is individual at high risk for periodontitis may also be at high risk for systemic diseases. Among the environmental risk factors and indicators shared by periodontitis and systemic diseases, such as cardiovascular diseases are tobacco smoking, stress , race, aging and gender.[5]
2. *Subgingival bio-film:* Subgingival bio-film constitute of bacteria. They are reservoirs of LPS and gram negative bacteria. It induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, smooth muscles proliferation, vascular fatty degeneration and intra vascular co-agulation.[5]
3. *Periodontium as cytokine reservior:* The pro inflammatory cytokine TNF-alpha interluekin-1â and gamma interferon and prostaglandin E2 reach high concentration in periodontium. The periodontium can serve as reservoir for spill over of these chemical mediators which, can enter the circulation and induce and perpetuate system effect.[5]

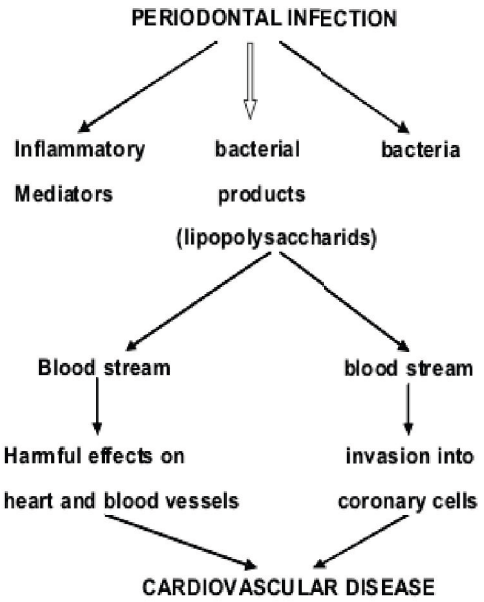
Heart disease

Cardiovascular disease which includes coronary heart disease, atherosclerosis, coronary thrombosis, ischemic heart disease and peripheral vascular disease.

Three biological mechanisms have been proposed to explain the association between periodontal disease and cardiovascular disease (CVD).

a. Bacteria from the periodontal infection enter the blood and invade heart and blood vessel causing harmful effects.
b. The body responds to periodontal infection with production of inflammatory mediators that travel through the blood and cause harmful effect on heart and blood vessels.
c. Bacterial products like lipopolysaccharides enter the blood and cause harmful effects on the heart and blood vessels.[6]

The most recent evidence of these biological mechanisms comes from a 2005 study showing that people with higher levels of bacteria in their mouth also tend to have thicker carotid



arteries, an indicator of cardiovascular disease.[7]

In a study it is reported that, antibody response to periodontal bacteria was associated with coronary heart disease. In this study the clinical signs of periodontal disease were not associated with CHD but it was suggested that the quantity and quality of the immune response against oral bacteria provides a better measure of the association between periodontal disease and CHD.[8] A recent finding shows that the inflammatory mediators such as lipoprotein and triglycerides are significantly higher in subjects with periodontitis than in control. In addition to this they also mentioned C – reactive protein were associated with periodontitis.[9] C – reactive protein is considered a biomarker for inflammation and in association with elevated risk of heart disease.

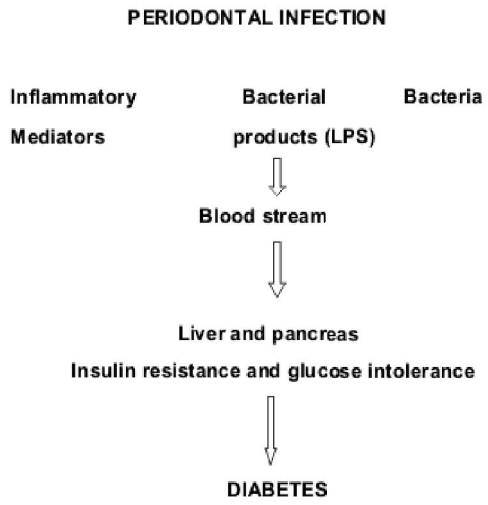
Proposed biological mechanism

Researchers are suggesting there may also be a need for randomized controlled trials to explore the association between biological markers of periodontal disease and specific periodontal pathogens, instead of only clinical signs.

Diabetes mellitus

There is growing research indicating a bidirectional relationship between periodontal disease and diabetes. Periodontal disease may deteriorate the periodontal condition. A double blind study confirms that periodontal therapy (scaling, root planning and metronidazole) leads to improvement in glucose control.[9] Other research shows that improved glucose control can result from mechanical periodontal therapy combined with antimicrobial treatment.[10]

AAP also recommended that the oral health professionals contact physicians to inform them of any periodontal infections may increase insulin resistance lead to a worsening of the diabetic state and increase the risk for diabetic complication.[11,12] Although the exact biological mechanism of action has not been clearly understood, there are several possible explanations.

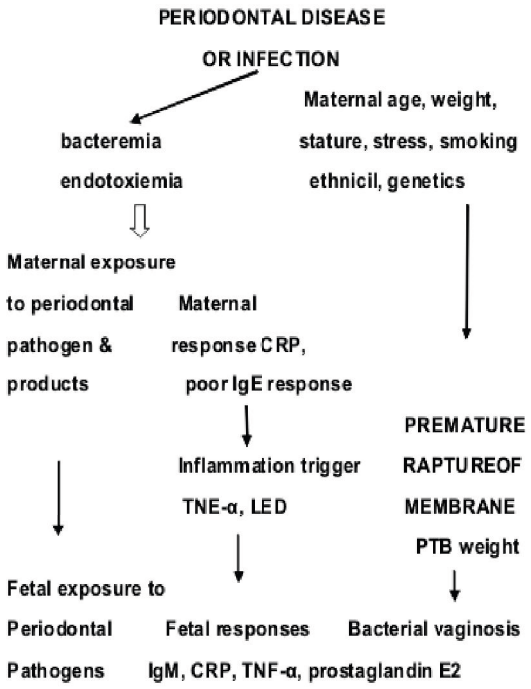


One of the proposed mechanism to explain the bi-directional relationship between periodontal disease and diabetes is that they both stimulate the chronic release of pro-inflammatory cytokines that have deleterious effects on periodontal tissue and interfere with insulin action. Bacteria and bacterial by-products also may produce insulin resistance and glucose intolerance. Periodontal pathogen products such as lipopolysaccharide, which may amplify the magnitude of the advanced glycation end products - mediated cytokine upregulation.[6] Some study also reported that periodontitis may even predispose individuals to the development of type 2 diabetes.[13]

Preterm low birth weight (PTLB)

In 1996 following a landmark reported by Offenbacher and colleagues periodontitis may be a possible risk factor for adverse pregnancy outcomes. Adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth, low birth weight, miscarriage or pre eclampsia. Pre eclampsia and pre term birth are major causes of maternal and prenatal morbidity and mortility.[14]

In 1990's it was hypothesized that oral infections, such as periodontitis could represent a significant source of infections



during pregnancy. It was noted that periodontal disease is a gram negative anaerobic infection with the potential to cause a gram negative bacteremia in persons with periodontal disease. It was hypothesized that periodontal infections which serve as reservoir for gram negative anaerobic organisms. Lipopolysaccharids and inflammatory mediators including prostaglandin E2 and tumor necrosis factor á may be potential threats to the fetal placental unit.[15]

Offenbacher and colleagues (1996) conducted a case-control study on 124 pregnant or postpartum women. Preterm low birth weight causes were defined as a mother whose infant had birth weight of less than 2500 gram. They reported from their study, that mothers of preterm low birth weight cases had significantly more advanced periodontal disease than the respective mothers with normal birth weight controls. Multivariate logistic regression models demonstrated that periodontitis was a statistically significant risk factor for preterm low birth weight. This was the first research that demonstrated the association between periodontal infections and adverse pregnancy outcomes in humans.[16]

The second study of Offenbacher group implicated maternal periodontal disease exposure and progression as independent risk factors for PTLB outcome.[17]

Moliterno and co-workers (2005) measured periodontal disease and birth outcomes for 150 Brazilian mothers and reported as a significant association between periodontitis and low birth weight.[18]

Periodontitis as a risk for respiratory Infections

There is emerging evidence that in certain at risk population periodontitis and poor oral-health may associated with several respiratory conditions.

Bacterial pneumonia is either a community acquired or hospital acquired pneumonia is usually caused by bacteria that reside on the oropharyngeal mucosa such as streptococcus pneumonia and haemophilus influenza. Scannapieco's group reported that oral and periodontal infections may increase the risk for bacterial pneumonia or chronic obstructive pulmonary disease.[19]

Oral bacteria from periodontal pocket can be aspirated into lung to cause aspiration pneumonia. Typical respiratory pathogens have been shown to colonize the dental plaque. Once established in the mouth, these pathogens may be aspirated into lungs to cause infections. Periodontal disease associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens. These enzymes may also destroy salivary pellicle from mucosal surface. Cytokines originating from periodontal tissue may alter respiratory epithelium to promote infection by respiratory pathogens.[20]

In a survey by Scannapieco showed that subject with a mean periodontal attachment loss 2 mm have higher risk of chronic lung disease than those who have a mean attachment loss is less 2 mm adjusting for age race, gender, ethenicity, education, income,

frequency of dental visit, smoking and alcohol consumption. There is emerging evidence for an association between hospital acquired bacterial pneumonia and periodontal disease. It is thought that potential respiratory pathogen from gastrointestinal tract, can colonize oral cavity where they are subsequently aspirated leading to pneumonia.[20]

Conclusion

The current theories that oral conditions may affect systemic health are largely unproven and remain speculative. Nevertheless they represent a new and exciting area of research that has far reaching clinical and a public health implication. The strongest evidence for the role of periodontal disease as a risk factor for systemic health, for example, if resolution of periodontal infection can be shown to lead to better glycemic control in diabetes, this would lend credence to the hypothesis that periodontitis is true risk causally linked to important systemic health outcome. The mouth is truly connected to rest of the body. Much recent work has been devoted to clarifying the directionality of specific relationship. Often the associations are bi-directional. The success of periodontal treatment shift from preventing attachment loss to more on measurable reduction in bacteremia infection, inflammatory mediators. New recall regimens may be developed that focus on the reducing risk of systemic bacteremia or reducing levels of endotoxin or host cytokines.

As the multiple risk factors for periodontal diseases become more clearly elucidated the practitioner will be able to more accurately determine an individual risks for periodontal disease, based on a systemic assessment of then individual risk characteristics. Risk factors include age smoking status, level of oral hygiene and systemic health level. For identification of high risk individuals, microbial sampling and genetic testing may become standard practice.

The future dental practitioner will be dramatically, altered if subsequent research confirms that periodontal disease is true risk factor for systemic disease and that the intubation or progression of these medical conditions can be reduced by periodontal treatment.

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