Oral health and systemic diseases relationship

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Abstract

Research has demonstrated that the association between oral inflammation and systemic inflammation may be the key to understanding the deleterious effects on multiple organ systems. However, is the relationship so complex that it is like trying to crack the DaVinci Code, or can health care professionals and the public understand the role of inflammation in oral and systemic health? The purpose of this article is to review how the inflammatory process functions in the human body. This review considers the systemic consequences of odontogenic infections and the possible mechanisms by which oral infection and inflammation can contribute to cardiovascular disease, as well as the oral conditions associated with medically compromised patients. Clinicians should increase their knowledge of oral diseases, and dentists must strengthen their understanding of general medicine, in order to avoid unnecessary risks for infection that originate in the mouth.

Keywords: Inflammation, Periodontal diseases, Periodontitis, Infection

Introduction

Studies of the relationship between periodontal disease and certain systemic disorders have shown that a positive association may exist. Dr. Willoughby Miller, in 1891, recognized and outlined the concept in a book called *The Dental Cosmos*, describing the mouth as a "focus of infection where microorganisms or their waste products obtain entrance to parts of the body adjacent to or remote from the mouth". As oral systemic science continues to develop, it will have a dramatic impact on the practice of dentistry. There has been a resurgence of interest in recent years in the systemic effects of oral infections such as periodontal diseases. The study of the various means by which periodontal infections and inflammation may influence a variety of systemic conditions is collectively referred to as periodontal medicine. The periodontium responds to tooth-borne biofilm (dental plaque) by the process of inflammation. Dental biofilms release a variety of biologically active products, such as bacterial lipopolysaccharides (endotoxins), chemotactic peptides, protein toxins, and organic acids. These molecules stimulate the host to produce a variety of responses, among them the production and release of potent agents known as cytokines. These include interleukin-1 beta, interleukin-8, prostaglandins, and tumor necrosis factor-alpha.(Fig. 1) There is a spectrum of periodontal response to these molecules, from mild gingivitis to severe destructive periodontitis. These and other host products and responses may influence a variety of important disease pathways, including atherosclerosis, mucosal inflammation, and premature parturition.[1] (Fig. 2)

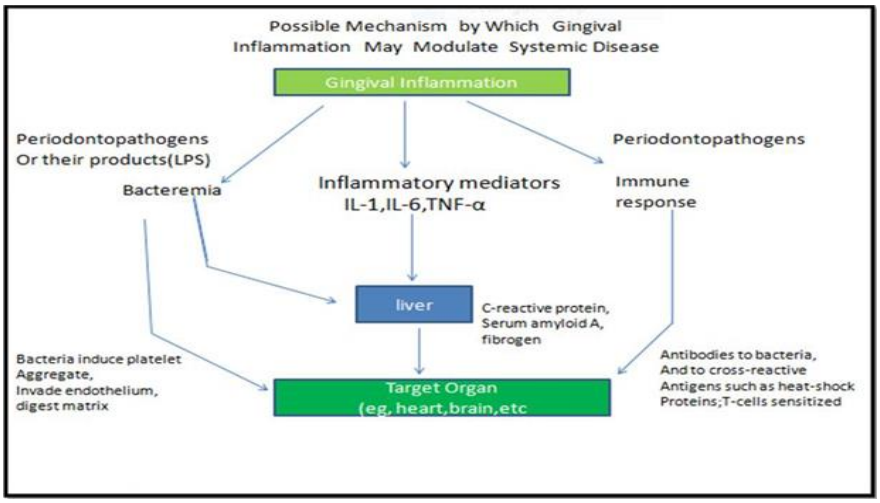

Fig. 1: Model to explain oral inflammation-systemic disease association

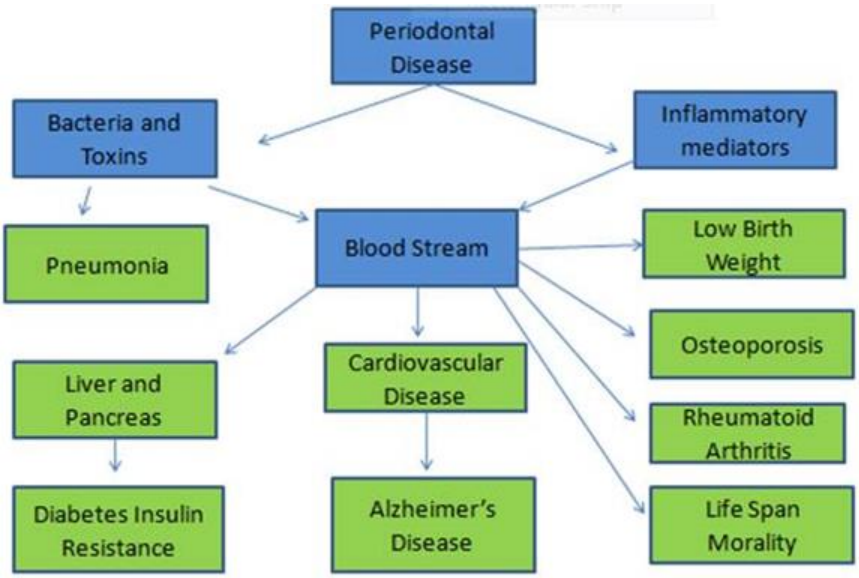

Fig. 2: The Oral-Systemic Link

The Cardiovascular Impact of Periodontal Disease

Human periodontal disease and atherosclerosis both have complex causes and genetic and sex-related predispo-sitions. In addition, they may share some risk factors, such as the smoking status. It is now becoming clear that chronic inflammation and infection such as periodontitis may influence the atherosclerotic process.[2] Severe, chronic periodontal disease provides a rich source of subgingival micro-bial and host–response products and may exert its effect over a long period. Three pathways linking oral infections to systemic effects have been proposed: metastatic spread of infection as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins and metastatic inflammation caused by an injury induced by oral microorganisms.[3] (see Fig. 3).

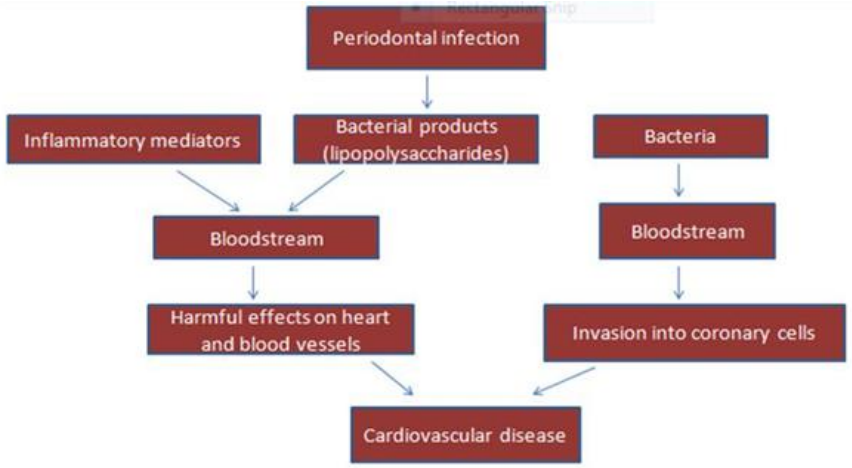

Fig. 3: Proposed biological mechanism (association between periodontal disease and CVD)

Infection theories: Chronic bacterial infections such as those caused by *Chlamydia pneumoniae* and dental infections have been suggested as risk factors for various atherosclerotic diseases. It has been reported that in patients with periodontal inflammation, a *Streptococcus sanguis* protein associated with platelet aggregation and bacteremia associated with *Porphyromonas gingivalis* may contribute to some acute thromboembolic events.[4] Furthermore, *P. gingivalis* can multiply within and activate endothelial cells, thus providing mechanistic support to the above-described association between periodontitis and cardiovascular pathology such as atherosclerosis.

Distant injury: Distant injury may derive from the effects of circulating oral microbial toxins or products associated with bacteremia. Although the molecular mechanisms are still unclear, one possibility is that bacteria derived lipopolysaccharides trigger hyperreactive leukocyte responses to initiate the association, whereby both processes collaborate to promote cardiovascular pathology.

Distant inflammation: It has been suggested that 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 (for example, interleukin 1ß [IL-1ß] and tumour necrosis factor alpha) may exert systemic effects by predisposing the patient to a systemic disorder such as atherosclerosis.(Fig. 4)

Whatever mechanisms are involved, it is evident that periodontitis may affect the host's susceptibility to systemic disease through subgingival biofilms acting as reservoirs of gram-negative bacteria and creating transient bacteremia, through release of microbial toxins and through a reservoir of inflammatory mediators. In parallel, all these factors are capable of predisposing the host to vascular changes or disorders. Further studies are required to find ways of intercepting these pathological changes, which may involve developing new generations of antimicrobial, anti-inflammatory, anti-infective or antithrombotic therapeutic agents.

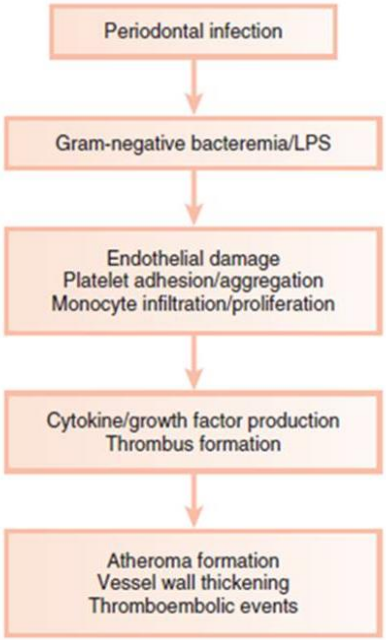

Fig. 4: Influence of periodontal infection on atherosclerosis. Periodontal pathogens and their products result in damage to vascular endothelium

Periodontal Disease and Low Birth Weight or Early Delivery Births

In February, 2010, the National Institute of Health published an announcement saying that premature birth affects 13 million infants worldwide each year and that 1 out of 3 preterm infants is born to a mother who has a silent infection of the amniotic fluid. The findings support preterm labor as an immune response to infection or injury and substantial evidence indicates that inflammatory hormones, specifically Interleuken 1 and 6 may play a significant role in the labor process.[5] The Lopez[6] and Jeffcoat[7] studies demonstrated that for the group of women who had scaling before delivery there was a substantial reduction in the rate of early delivery as compared to those women who had their teeth scaled after delivery. Other studies have also linked low birth weight babies and early delivery to levels of prostaglandin, an inflammatory response chemical.

Periodontal Disease and Diabetes Mellitus

Although the relationship between periodontal disease, inflammation and overall health has been suspected, new studies are providing more comprehensive evidence for this link. We recognize that diabetes predisposes oral tissues to greater periodontal destruction but several studies have now identified that periodontal disease leads to poor glycemic control. Recent studies have presented evidence of a bidirectional adverse relationship between periodontal disease and diabetes mellitus, both type I and type II. Although diabetes is a metabolic disorder and periodontitis is an infectious disease, the relationship occurs through the ability of both conditions to induce an inflammatory response leading to the production of inflammatory mediators. These proinflammatory cytokines such as Interleukin-6 impair the glucose- stimulated release of insulin from the pancreas. Periodontal therapy, on the other hand, can stabilize glycemic control and reduce complications from unstable blood sugar levels.(Fig. 5)

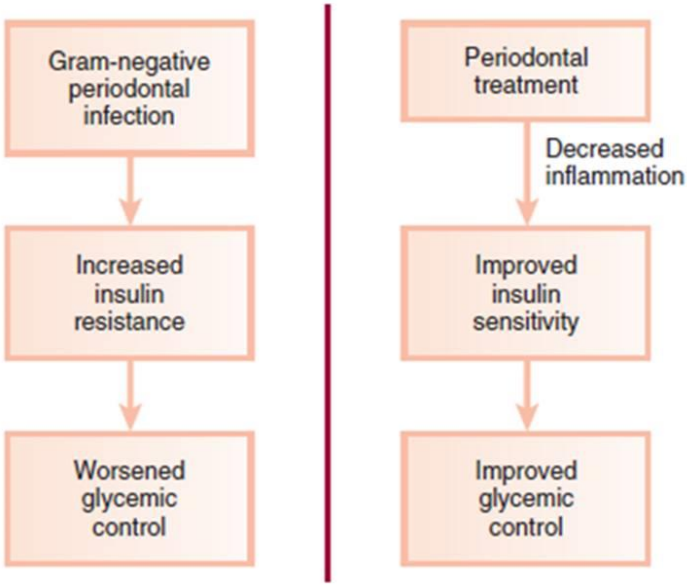

Fig. 5: Potential effects of periodontal infection and periodontal therapy on glycemia in patients with diabetes

In a U.S. population-based study of 12,367 non-diabetic individuals, it was found that there was an association of periodontal disease with body mass index (BMI). Approximately a 40% to 50% increase in the risk for periodontal disease was found in those with obesity. Studies show that fatty tissue produces pro-inflammatory mediators which lead to systemic inflammation. The result is a hyper-inflammatory state that can exaggerate the response to periodontal infection.[8,9]

Respiratory Disorders and Periodontal Disease

Recent studies suggest that the mouth may play an important role in infections acquired in hospitals and nursing homes, especially infections of the respiratory tract. Dental plaque, a complex biofilm, can serve as a reservoir of infection in hospital in patients.[3] Several studies have demonstrated that the teeth of patients in the intensive care unit (ICU) become 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. One ICU study demonstrated that only patients with oral colonization by a respiratory pathogen went on to experience pneumonia. In some hospitals, a large proportion of the cultivable oral microflora from ICU patients consists of pathogenic species such as *S. aureus, P. aeruginosa* and *Klebsiella pneumoniae*. Superinfection by these bacteria is probably due to exposure of the patients to antibiotics, which suppress the normal flora and allow pathogenic bacteria from the environment (e.g., the hospital) to flourish in the mouth. Several studies have demonstrated that daily mechanical oral hygiene with or without use of an oral antiseptic such as 0.12% chlorhexidine gluconate or 1% povidone–iodine not only reduces the prevalence of colonization by oral pathogens but also reduces the rate of pneumonia by about 50%.[10]

Other studies have suggested an association between poor oral health (e.g., periodontal disease) and chronic obstructive pulmonary disease (COPD). In particular, this association was observed on analysis of existing large databases such as the Veterans Administration Normative Aging Study and the National Health and Nutrition Examination Survey III (NHANES III), after controlling for confounding variables such as smoking, sex, age and socioeconomic status.4 It is well known that some patients with COPD suffer from periodic acute exacerbations or worsening of lung function. These exacerbations are due in part to infection, typically by bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Branhamella catarrhalis*, or rhinovirus. It is presumed that frequent exacerbations accelerate the decline in lung function and lead to disease progression. Perhaps aspiration of saliva into which oral bacterial antigens, lipopolysaccharide and enzymes have been released promotes inflammation and infection of the lower airway. It is also possible that host-derived mediators such as cytokines and prostaglandins, which are elevated in the saliva of subjects with periodontal disease, promote lung inflammation and infection if aspirated into the lower airway. 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. Further studies are required to verify the importance of

oral conditions in the pathogenesis of lung diseases such as COPD.[11]

Periodontal Disease and Rheumatoid Arthritis

Periodontal disease has also been associated with rheumatoid arthritis (RA), an autoimmune disease that inflames joints and causes destruction of cartilage, bone and ligaments. The two diseases share some basic characteristics: both diseased gingival tissues and joints affected by RA produce similar cytokines and growth factors. These chemicals promote the dissolution of bone, a problem shared by both diseases.

This suggests the presence of a common underlying inflammatory mechanism. Levels of anti-CCP antibodies (anti-cyclic citrullinated peptide antibody) are considerably higher in RA patients with periodontal disease, suggesting that periodontitis may be a contributing factor in the pathogenesis of RA. Coincidently, P.gingivalis produces an enzyme that induces citrullination of various autoantigens. Patients with RA are likely to benefit from increased periodontal care.[12,13,14]

Periodontal Disease and Osteoporosis

Bone loss is a condition shared between periodontal disease and osteoporosis. In the early stage, called osteopenia, there is a reduction in bone mass due to an imbalance between bone formation and bone resorption. Osteoporosis occurs as bone resorption becomes more prevalent and there is considerable demineralization. The common factor between osteoporosis and periodontal disease is the excessive osteoclastic activity and bone loss initiated through chronic inflammatory conditions. This shared chronic inflammatory response may predispose individuals with periodontitis to osteoporosis. Further, risk factors such as age, smoking and estrogen deficiency are the same for both, periodontal disease and osteoporosis. Estrogen modulates cytokines that regulate bone metabolism and the host inflammatory response. Lack of estrogen increases the number of osteoclasts causing an imbalance in bone metabolism and a reduction in bone density. Periodontitis also activates the inflammatory response and the osteoclasts. Many investigations have found significant correlation between periodontal disease and estrogen deficiency. These two risk factors, working together, can induce osteoporosis.[8]

Periodontal Disease and Alzheimer's Disease

There is evidence that periodontal disease may be a risk factor for dementia through the bacterial and viral infections commonly found in periodontal disease. Oral infection can either directly or through systemic signals to the brain contribute to the development of Alzheimer's disease. Periodontal infections may result in elevating the systemic inflammatory response which in turn may contribute to existing brain and vascular pathologies that would impact brain function. Timely treatment of periodontal infections that reduces oral pathogens would also reduce the risk of systemic infection and inflammation and would be most important to those individuals susceptible to infection and hyperinflammation.[12]

Periodontal Disease and Systemic Health

Proper use of the knowledge of potential relationships between periodontal disease and systemic health requires the dental professional to recognize the oral cavity as one of many interrelated organ systems. An infection the size of one's palm on the leg of a pregnant woman would be a major concern to the patient and her health care provider, given the potential negative consequences of this localized infection on fetal and maternal health. A similar suppurating infection on the foot of a person with diabetes would be cause for immediate evaluation and aggressive treatment, knowing the effects of such infections on metabolic control of diabetes.

Periodontal infection must be viewed in a similar manner. Periodontitis is a gram-negative infection often resulting in severe inflammation, with potential intravascular dissemination of microorganisms and their products throughout the body. However, periodontitis tends to be a "silent" disease until destruction results in acute oral symptoms. Most patients, as well as many medical professionals, do not recognize the potential infection that may exist within the oral cavity.

Patient Education

Patient education is a priority. Only 30 years ago, the factors involved in Coronary Heart disease (CHD) were unclear. At present, however, it would be difficult to find an individual who was unfamiliar with the link between cholesterol and heart disease. This change was precipitated by research clearly demonstrating the increased risk for heart disease in individuals with high cholesterol levels, followed by intensive education efforts to spread the message from the scientific community to the public at large. It is important to recognize that high cholesterol levels have not been shown to *cause* heart disease in all individuals, but rather significantly increase the *risk* of disease.

Cholesterol has also been demonstrated to have a biologically plausible role in the pathogenesis of CHD. Similarly, patient education efforts in the realm of periodontal medicine must emphasize the inflammatory nature of periodontal infections, the increased risk for systemic disease associated with the infection, and the biologically plausible role periodontal infection may play in systemic disease. Few individuals had their cholesterol levels evaluated until the knowledge of the link between cholesterol and heart disease became widespread. Likewise, increased appreciation of the potential effects of periodontal infection on systemic

health may result in increased patient demand for periodontal evaluation.

Enhanced community awareness may be derived from newspapers, magazines, and other lay sources. However, the most reliable origin of information should be the dental and medical professions through daily contact with patients. The pregnant woman usually knows that infections may adversely affect her pregnancy. Individuals with diabetes generally know that infections impair glycemic control. However, many of these patients do not know that occult periodontal infections can have the same effect as more clinically evident infections. The dentist is responsible for diagnosing periodontal infections, providing appropriate treatment, and preventing disease recurrence or progression. Because many medical professionals are unfamiliar with the oral cavity and oral health research, dentists must reach out to the medical community to improve patient care through education and communication. Likewise, patients must be educated in disease prevention. Just as patients know that lowering cholesterol levels may decrease their risk for heart disease, prevention of periodontal infection should be emphasized. Likewise, controlling the risk factor of periodontal infection requires the dentist to emphasize personal and professional preventive measures focused on thorough oral hygiene and regular recall.

Conclusion

The mouth is a significant potential source of infection and inflammation that contributes to the total burden of disease, and to overall health, which should be systematically taken into account by all clinicians. Research suggests that there is an interrelationship between oral infection, inflammation and systemic health. Patients, dental hygienists, dentists, dental specialists and other health care providers should be aware of the consistent relationships between oral inflammation and systemic diseases. They should value the need to modify assessment, prevention, and treatment protocols to improve the oral health as well as total health of the patients they treat in the office each day.

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