

The Relationship of Periodontal Disease to Cardiovascular diseases - Review of Literature

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Abstract

Association of Oral and Systemic diseases has gained importance because the high occurrence of oral diseases is an extremely common source of infection. Epidemiological Studies have presented periodontal diseases as a risk factor for development of cardiovascular diseases. A chronic oral infection such as periodontitis is a constant potential source of infection and has now been considered as a separate risk factor for cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease and respiratory diseases as well as delivery of low-birth-weight infants.

The possible pathways linking oral infections to systemic diseases are metastatic infections, bacterial endotoxins, and systemic vascular injury. People with a history of periodontal disease and/or tooth loss were found at higher risk for Peripheral arterial disease (PAD) as compared to those without periodontal disease and/or tooth loss.

All studies on the relationship of periodontal diseases to cardiovascular diseases are inconclusive and most of the data is based on epidemiological studies.

Introduction

Epidemiological Studies have presented periodontal diseases as a risk factor for development of cardiovascular diseases. The association between oral infection and systemic diseases is not a new one. Chronic oral infections such as periodontal diseases are a constant potential source of infection. The oral cavity and oropharynx have been described as an "open mouth system" for bacteria and other organisms to adhere to both shedding (soft tissues) and non-shedding (teeth, restorations, dentures) surfaces.¹ The mouth serves as a mirror of health or disease, as an essential or early warning system, as an accessible model for the study of other tissues and organs and as a potential source of pathology affecting other system and organs.² The most common diseases of oral cavity are dental caries and periodontal diseases and are taken as measures of oral health status. Periodontitis, periapical lesions, pericoronitis, and abscesses are the possible sources of infection in the oral cavity. Many systemic diseases, such as diabetes mellitus, cardiovascular diseases,

respiratory diseases and low-birth-weight infants are related to oral infections. More recently epidemiological studies have presented periodontal diseases as a risk factor for the development of Cardiovascular (CHD), cerebrovascular diseases (Stroke), and Peripheral arterial disease (PAD) and this relationship has been reviewed here.

Association of Oral Infection to Systemic diseases

Herzberg quoted the Assyrians who proposed the effect of oral health on the rest of the body as early as the seventh century B.C.³ "Focal infection theory" was published in 1891 suggesting that microorganisms or their waste products gain entrance to parts of the body adjacent to or remote from the point of entry.⁴ Other proponents of this theory blamed oral foci of infection for a number of regional and systemic diseases, ranging from tonsillitis and middle ear infections to pneumonia, tuberculosis, syphilis, osteomyelitis, endocarditis, meningitis, and septicemia.⁴ The "Focal infection theory" was not given any attention until recent progress in identification and characterization of periodontal pathogens, as well as elucidation of potential systemic mechanisms of action of bacterial products and inflammatory cytokines. This has opened the way for a more realistic assessment of the systemic importance of periodontal disease. Studies have lent credence to the concept that periodontal disease may be a separate risk factor for cardiovascular disease, cerebrovascular disease and respiratory disease, as well as delivery of low-birth-weight infants.⁵⁻⁸ However the important issue is that oral infections often are only one of the many confounding factors that can influence systemic diseases.⁴

Periodontal diseases

Periodontal diseases have been prevalent throughout human history, although without the obvious secular variations.⁹ Research and clinical evidence indicated that the damage caused to the supporting structures of the teeth by periodontal disease in early adult life is irreparable, whilst in the middle adult life it destroys a large part of the natural dentition and deprives many people of all their teeth long before old age. The effects of periodontal disease on the

general health of the population are un-assessable.¹⁰ Inflammatory periodontal diseases constitute probably the most common infections in the world. Gingivitis is present in the great majority of adults throughout the world but is most pronounced in developing countries. Moderate periodontitis affects approximately 30% and advanced periodontitis approximately 10% of the adult populations of USA. Deep pockets are present in 2-18% of adults in western countries and at higher prevalence in developing countries.¹¹

Periodontal diseases are currently thought to progress in periodic, relatively short episodes of rapid tissue destruction. Some people have frequent episodes of active disease at many sites in their mouth, while others experience far less active disease with signs of gingivitis and may be some pockets but no loss of attachment over long periods. Its initiation and progression is influenced by a wide variety of determinants and factors, including subject characteristics, social and behavioral factors, systemic factors, genetic factors, tooth -level factors, microbial composition of dental plaque and other emerging factors.¹² Because periodontal disease is common in the populations, it may account for a significant portion of the proposed infection-associated risk of CVD. Interestingly periodontal diseases share a number of characteristics; old age, smoking, low education status, diabetes and stress, all common with cardiovascular diseases.¹³

Cardiovascular Diseases (CVD)

Cardiovascular Diseases (CVD) make up the most prevalent category of systemic diseases in developed as well developing countries and are increasing with age.¹⁴

World Health Organization statistics in 1995 indicated that CVD were responsible for 20% of deaths worldwide and in some developing countries accounted for 50% of deaths.¹⁵ CVD has contributed to a third of global deaths. The low and middle-income countries were responsible for 78% of CVD deaths in 1999. By 2010 CVD is estimated to be the leading cause of death in developing countries.

1. Periodontal disease and Cerebrovascular Disease-Stroke

The relationship of periodontal disease to ischemic stroke has been evaluated in a number of studies. The outcome is different across the reported studies, ranging from total stroke to fatal stroke, nonfatal stroke and ischemic stroke.^{5,6,16} The study of Beck and colleagues compared men who had any type of stroke with men who did not develop CVD during the follow up. They found a significant association between periodontal disease and total stroke: relative risk (RR) of 2.80.⁵ Wu and colleagues found a possible association between periodontal disease and

ischemic stroke (RR=2.11); the risk was even higher when limited to fatal stroke.¹⁶ Although studies have shown an association between tooth loss or periodontal disease and stroke, no two studies are consistent in defining the outcome and exposure. Hence, no association has been truly replicated. It is difficult to rule out residual confounding variables, as there are several common risk factors.¹⁷

2. Periodontal disease and Coronary Heart Disease (CHD)

Periodontal disease is a chronic infection and may be associated with inflammatory systemic conditions. A number of studies provided a significant data and statistics to suggest and support the relationship of periodontal disease to cardiovascular diseases. Most of the risk factors for cardiovascular disease are also regarded as risk factors for periodontal disease.¹⁸

Mattila et al suggested a statistical association between severity of coronary stenosis and dental infections. Data are compatible with hypothesis that oral infections might play a role in the development of adverse cardiovascular outcomes. Studies conducted by Beck et al and Arbes et al also provided some support to the hypothesis that periodontal disease and tooth loss might play a role in the development of CHD.^{18,19} However likelihood of considerable residual confounding remains there in all these studies.

Hujoel et al presented a negative association between periodontal disease and subsequent CHD in first National Health And Nutrition Examination Surveys (NHANES-I) longitudinal study with a 21 years follow-up.²⁰

Periodontal disease and Peripheral Arterial Disease (PAD)

PAD shares a common underlying pathological change, atherosclerosis, with coronary heart diseases and stroke. Very few studies have been reported on the relationship of periodontal disease to PAD.

In a cohort study of 51529 health professionals aged 40-75 including 29683 dentists conducted between 1986-1998, tooth loss and periodontal disease experience was recorded through self reported biennial questionnaires.²¹ A total of 342 cases of PAD (255 definite and 87 probable) were recorded. In this multivariate model age, smoking, alcohol, family history of myocardial infarction, multivitamin supplement use, vitamin E intake, history of hypertension, diabetes, hypercholesterolemia and the profession (dentist/nondentist) were adjusted and updated on the basis of biennial questionnaires. Periodontal disease was also taken as a causative factor for tooth loss. From the study it was concluded that men with a history of

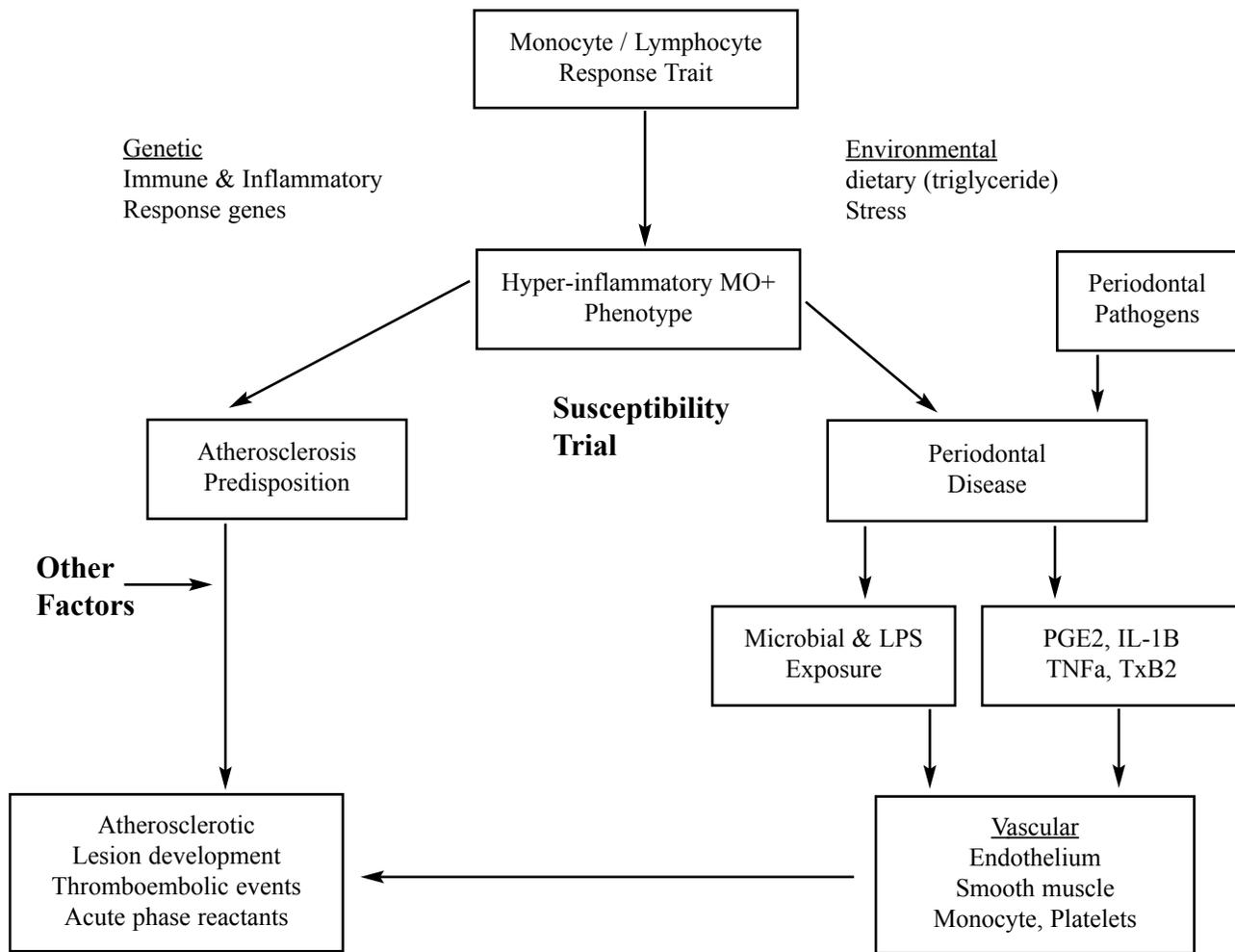


Figure. Proposed model. Source: Beck et al.⁵
 LPS: Lipopolysacchride; PGE2: Prostaglandin E2; IL-1B: inter-leukin 1B; TNFa: Tumor Necrosis factor a; TxB2 : thromboxane B2

periodontal diseases or any tooth loss during follow-up had a significantly higher risk of PAD than men without any periodontitis or without any tooth loss. Incident tooth loss was significantly associated with PAD, especially among men with periodontal diseases. In a follow up study on 1030 subjects of 25-30 years, Mendez et al reported that subjects with clinically significant periodontal disease at baseline had a relative risk of 2.27 of having PAD.²²

Mechanism for the proposed Periodontal infection and CHD / Stroke association

Infection has been recognized as a risk factor for atherogenesis and thromboembolic events.²² Gram-negative bacteria or the associated lipopolysacchride (endotoxin), when presented as a systemic challenge in animal models, can induce inflammatory cell infiltration into major blood vessels, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular coagulation. The remarkable similar-

ities of bacterially induced vascular pathology, natural history of atherogenesis has led certain investigators to suggest that, in addition to genetic, lifestyle and dietary influences, infections of unknown origin may contribute to the observed cardiovascular pathology. The chronic inflammatory burden of periodontal infection and the host response provide the bases for our hypothetical model of the observed associations between periodontal disease and atherosclerosis, coronary heart disease and stroke. The conceptual model is explained through Figure1.⁵ This model emphasizes that among certain individuals there may be an underlying hyperinflammatory trait in response to stimuli that is manifest by an excessive production of pro-inflammatory cytokine and lipid mediators by monocytes and other cell types.²³

Four potential mechanisms by which periodontal infections might contribute to the pathogenesis of CHD and

stroke have gained importance. 1) Effects of Endotoxins in the circulation, 2) Role of heat shock proteins, 3) Infection-induced perturbations in lipid profiles, and 4) Formation of acute-phase reactants.

1. Effects of endotoxins in the circulation

The microflora associated with periodontal infections is a rich source of endotoxins, which are lipopolysaccharide (LPS) components of the cell walls of all gram-negative bacteria. Entry of endotoxins into the circulation can occur from many sources including respiratory infections (*C. Pneumoniae*), gastric ulcers (*H. Pylori*), and periodontitis (*P. gingivalis*, *A. actinomycetemcomitans*, *B. forsythus*, etc). Once endotoxins enter the circulation they present a considerable threat to the well-being of the host. They can directly injure endothelial cells²⁴, promote adhesion of monocytes to endothelium²¹, induce macrophage foam cell formation²⁵, and cause general endothelial dysfunction.²⁶ All of these effects play a significant role in the initiation and development of atherosclerosis.²⁷ One of the primary features of acute occlusion of vessels in CHD and Stroke is the disruption of existing atherosclerotic plaques by macrophage-mediated inflammation.²⁸

2. Role of heat shock proteins

Heat shock proteins (Hsp) are produced by a wide variety of bacteria and human cells under a variety of stressful or harsh conditions such as high temperature, infection, inflammation, and mechanical stress.²⁹ It is well established that endothelial cells produce Hsp under stressful conditions such as exposure to endotoxins.³⁰

3. Infection-induced perturbations in lipid profiles

It is known from some studies that hyperlipidemia frequently accompanies many bacterial infections.²⁷ Low doses of endotoxins cause a rapid rise in serum triglycerides due to an increase in triglyceride-rich very-low-density lipoprotein (VLDL).³¹ Hyperlipidemia may have negative effects such as promoting the release of proinflammatory cytokines from neutrophils. It is interesting to note that hyperlipidemia occurs during periodontal infections.³² Cytokines like IL-1, IL-6, and TNF- α have been implicated as risk factors for CHD and prolonged hyperlipidemia is likely to have deleterious clinical effects.³³

4. Formation of acute-phase reactants

Acute phase reactants appear in the circulation in response to infections and tissue injury. C-reactive protein (CRP) is of particular interest since at "high-normal" levels it has been shown to be an important risk factor for CHD and is also elevated in patients with extensive periodontal disease.³⁴ It remains to be determined if CRP elevations occurring during periodontal infections play a role in atherosclerosis.

Conclusion and Recommendations

The findings of epidemiologic studies conducted on the relationship of periodontal disease to cardiovascular disease are inconsistent and lead to conservative conclusion. Studies do not prove a causal relationship rather present periodontal disease in weak association as one of the confounding factors. The studies show a lack of control of confounding factors, residual confounders, and over-control of cofounders. Although both periodontal and cardiovascular diseases share common potential biological risk factors (Diabetes) and behavioural risk factors (diet, smoking etc.), the link between periodontal and cardiovascular diseases is weak and it is a challenging task to prove the role of periodontal disease in the etiology of cardiovascular diseases. Intervention studies are needed to understand the role of periodontal disease in the initiation and progression of cardiovascular diseases. Longitudinal and Case-control studies are also required to track down the association of both diseases with well controlled confounding factors and outcome measures for periodontal diseases.

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