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Periodontal Disease & Cardiovascular Disease- The Mouth to Heart Connection: An Overview

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Review Article

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ABSTRACT

The concept of periodontal medicine has been debated for years since its introduction. Research in the past has made it clear that there exists a strong positive correlation between periodontal disease and cardiovascular disease. The microbes of periodontal disease have been seen to colonize the cardiac tissues and create inflammation. The host's inflammatory response to the bacteria insult also causes damage to the cardiovascular system especially the chemical mediators such as cytokines, prostaglandins, and matrix metalloproteinases. Thus, this literature review aims at highlighting the pathophysiology of cardiac disease and the role of periodontitis in the etiology. It also aims at highlighting the various novel biomarkers that can be used for the early detection and diagnosis of both inflammatory conditions.

Keywords: Periodontitis, Cardiovascular Disease, Inflammation, Pathophysiology, Biomarkers, Periodontal Microbes, Endothelial Injury.

Introduction

Cardiovascular diseases (CVD), such as acute myocardial infarction and angina pectoris, are major public health concerns in developing countries and are among the most common medical conditions in the general population.[1,2] According to the Framingham Heart Study, by the time an individual turns 40years, 49% of men and 32% of women may have clinical symptoms of ischemic heart disease. In developing countries and populations with limited access to health education and dental care, gingivitis with substantial plaque and calculus deposits is the most common, extreme, and widespread etiology for cardiovascular disease.[3,4]

Periodontal disease (PD) affects 75% of adults, with 20 to 30% of adults suffering from more serious forms. Since PD is so prevalent in the population, it could account for a significant portion of the infection-related CVD risk.[5] This can be clarified adequately by current research, which claims that atherosclerosis is the primary underlying vascular disorder that causes cardiovascular and cerebrovascular morbidity and mortality.[6] Many millions of people are affected by cardiovascular disease, and the number of cases affecting the geriatric population is on the rise. Since this population group is more in size and because more elderly people are dentate than in the past, PD is becoming more common in this patient community.[5] This perplexing finding applies to the entire world's population, resulting in the proportionate risk of CVD. This evidence, together with recent evidence linking periodontal disease to coronary heart disease, suggests that it is time to assess the strength of this correlation, which has been identified in many scientific studies over the last two decades. It has been shown after two decades of study that there is a connection between periodontal disease and cardiovascular disease (CVD).

The pertinent question, on the other hand, is the existence and significance of this connection. Is the infectious and inflammatory periodontal disease mechanism causal in the development of heart attacks and strokes, or are these two conditions linked by chance? Despite mounting evidence of a possible contributory effect of periodontal infections in the natural history of CVD, there are good reasons to be skeptical. This review of literature focuses on the various studies done so far and the role of biomarkers in the early identification of the two inflammatory diseases in question.

Pathophysiology of atherosclerosis

Atherosclerosis (ATH) is a slow-moving disease that usually takes decades to manifest into signs and symptoms. The term is derived from the Greek terms sclerosis (hardening) and at here (lipid accumulation). The mechanism of lipid accumulation is restricted to the inner walls of arteries, with a proclivity for forming at points where blood flow is "disturbed," such as where arteries branch. The deposition of lipoproteins in the intimal layer of the affected artery is the first sign of atherosclerosis. Lipoprotein particles, such as low-density lipoproteins (LDLs), appear to enable monocytes and lymphocytes to accumulate in the intimal layer.[7]

Circulating monocytes bind to vascular endothelium early in the development of atherosclerotic plaques. Intercellular adhesion molecule 1 (ICAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), and vascular cell adhesion molecule 1 (VCAM-1) are among the adhesion molecules on the endothelial cell surface that mediate this adherence.[8,9] The release of hydrolytic enzymes, cytokines, chemokines, and growth factors by activated monocytes (macrophages) in blood vessels causes further damage, leading to focal necrosis.

Monocytes are recruited from the bloodstream and move through the endothelium into the blood vessels, where they differentiate into macrophages, which then become the lipid-laden "foam cells" that characterise atheromatous plaques.[7,10] Macrophages store lipids in both oxidised and modified forms, especially LDLs. Modified LDL can cause damage to the endothelium as well as the underlying smooth muscles.[5] As these lipid-rich cells die, they leave a necrotic lipid-rich element in the arterial wall. To different degrees, these lipid-rich areas calcify. Smooth muscle cells in the arterial wall are also activated to move through the intimal layer at the same time where they can proliferate.[7]

In the meantime, microvessels infiltrate the affected region, causing intraplaque haemorrhages. The atherosclerotic lesion is gradually covered by a fibrous cap that faces the interior of the artery.[7] A fatty streak may develop into a fibrous plaque with a lipid centre, calcification, and extracellular matrix protein deposition. Activated T-cells can stimulate macrophages to produce metalloproteinases, which help to remodel the fibrotic plaque. The fibrous cap may thin and rupture as a result of extracellular matrix remodelling, triggering the clotting mechanism with thrombosis and subsequent artery occlusion, which may account for up to half of all cases of myocardial infarction.[11]

For many years, the position of infections has been debated. Evidence has recently emerged that some common oral infections play a key role in ATH.[5] Large and medium-sized elastic and muscular arteries may develop atherosclerosis. They can cause ischemic lesions in the brain, heart, or extremities, as well as thrombosis and infarction in the infected arteries, which can result in death.[12]

Atherosclerosis is a silent disorder that is accompanied by a large body of evidence that it is an inflammatory condition.[6] The Ross', "Response to Injury Theory" of ATH was popularised by pathologist Dr. Ross, who suggested that the initial lesions are caused by endothelial injury and contribute to a persistent inflammatory phase in the artery.[13] However, European pathologists proposed this theory in the mid-1800s.

Role of infections in endothelial injury

There is mounting evidence of a connection between ATH and a number of common human infections. One potential mechanism is endothelial damage caused by infectious agents, which causes an inflammatory response similar to that seen in ATH. Danesh and colleagues recently examined the function of infections in heart disease; there is growing evidence that infection with *Chlamydia pneumoniae, Helicobacter pylori,* Periodontal bacteria, and *Cytomegalovirus* is linked to heart disease.[10,14] Periodontal infections can directly contribute to the pathogenesis of ATH and thromboembolic events by providing repeated systemic challenges with liposaccharides and inflammatory cytokines, according to growing evidence.[3]

S. sanguis and *P. gingivalis* have been shown to induce platelet aggregation and activation through the expression of collagen-like platelet aggregation-associated proteins, according to Herzberg and colleagues. Atheroma development and thromboembolic events may be influenced by aggregated proteins.[15] Haraszthy et al. found periodontal pathogens in human carotid atheromas in recent research where PCR (polymerase chain reaction) was used to test 50 carotid atheromas acquired during endarterectomy for the existence of bacterial 16S rDNA using synthetic oligonucleotide probes specific for periodontal pathogens such as *A.a, T.f, P.g, and P.i.* His results demonstrated that *T. forsythus* was found in 30% of the samples, while *P. gingivalis* was found in 26%, *Aggregatibacter actinomyecetemcomitans* was found in 18%, and *P. intermedia* was found in 14%.[16]

Animal studies (mice) demonstrate calcification of aortic atherosclerotic plaque with exposure to P. gingivalis infection, providing more clear evidence that infections with P. gingivalis lead to systemic inflammation.[17] The number of calcification increases as the duration of exposure to the pathogens increases. Furthermore, one or more periopathogens are found in 44% of atheromas.[16]

These and other studies indicate that periodontal pathogens may be present in atherosclerotic plaques and that periodontal pathogens, like other infectious species, play a role in atherogenesis.

Pathways of Action

- **Direct pathways**

Oral microbes and their by-products may enter the circulatory system and gain systemic access. Gentle mastication can cause endotoxemia, according to Geerts and colleagues[18], and this risk is increased with the severity of the periodontal disease. Dental procedures and toothbrushing have been shown to cause

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bacteremias by Kinane and colleagues[19], Rajasuo and colleagues[20], Roberts[21], and Forner and colleagues.[22] According to new studies, the severity of bacteremia after scaling was increased in periodontitis patients compared to gingivitis patients or stable control patients.[23] Oral microbes have the capacity to directly influence subclinical mediators of cardiovascular events such as hypercoagulability, atherosclerosis growth, or both, through acquiring systemic entry.

In a mouse trial, intravenous inoculation with *P. gingivalis* accelerated the progression of atherosclerosis.[23] Lalla and colleagues[24] used oral inoculation with *P. gingivalis* to cause periodontal infection, and they were able to recover *P. gingivalis* DNA from the aortic tissue of infected mice only, as well as see signs of accelerated early atherosclerosis in infected mice. Certain strains of *P. gingivalis* can infect macrophages and enhance foam cell formation in the vascular wall, according to Giacona and colleagues[25], contributing to *P. gingivalis'* potential to trigger or intensify the atherosclerotic phase.

- **Indirect pathways**

Increased levels of systemic inflammation are predictive of cardiovascular events, according to epidemiologic data.[26,27] Systemic inflammatory markers, such as C-reactive protein, are elevated in people with periodontal disease, and periodontal disease treatment has been shown to reduce systemic inflammation levels.[28] Transient bacteremias and the local release of bacterial by-products such as lipopolysaccharide are two possible causes for this increased systemic inflammatory response.[29,30]

Another possible connection between oral infection and CVD is molecular mimicry, which occurs when antibodies aimed at bacterial species cross-react with host cells inadvertently. Since human and bacterial heat shock proteins[30] are highly conserved, researchers have looked into their potential function in mediating infection-induced atherosclerosis. These misidentifications have the potential to trigger artery inflammation and atherosclerosis.

Common Risk Factors for PD and CVD

Local, structural, and genetic factors are all linked to the development of cardiovascular disease. While several bacterial species have been casually linked to CVD, simply colonising the gingival niche by these species is not enough for disease to develop. Instead, gingivitis, a local inflammatory process without loss of periodontal tissue support, is thought to have developed in the periodontium against bacterial insult and acts as a largely protective host reaction to periodontitis which is a disease characterised by the loss of connective tissue attachment and alveolar bone, affected by environmental exposures and unique genetic predisposition.

Viruses are considered to be a newer family associated with inflammatory diseases. Yet the role of periodontal viruses in coronary artery diseases remains unclear. **Ilango P and Mahendra J** et al[31] in their study aimed to evaluate the prevalence of periodontal viruses and compare it in cardiac samples of coronary artery disease patients with and without periodontitis. The results revealed a higher prevalence of periodontal viruses such as EBV and CMV in CHD patients with periodontitis suggesting it is one of the risk factors for CHD. This is supported by the fact that the severity of the periodontal disease is associated with the presence of EBV in coronary artery plaque samples. Thus, this indicates that apart from the common periodontal bacteria that have been linked with CVD, viruses do play a pivotal role.

The causes for CVD and PD are multifactorial as well as involving a dynamic interplay of genetic, environmental, and lifestyle influences. Smoking, alcohol misuse, race/ethnicity, education, and socioeconomic status, male sex, diabetes mellitus, and overweight are all factors associated with both CVD and PD and could confound a relationship between the two.

Diagnostic Biomarkers for PD and CVD

The discovery of new diagnostic tests that can diagnose the existence of the active disease, predict possible disease progression, and assess the response to therapy is needed to improve the clinical management of the affected individual. Clinicians often face difficulties in diagnosing active phases of disease and identifying patients at risk for active disease. To overcome these situations, the discovery of biomarkers in the human body has paved way for more research and diagnosis of a disease.

In a study, **Mahendra J et al** (2015)[32] sought to identify predictable biomarkers that could be used in combination with the Framingham risk score to predict the risk of CVD in non-cardiac patients. When compared to the control group, atherosclerotic biomarkers such as E-selectin, Leptin, osteoprotegerin (OPG), and Ox-LDL were found to be elevated in the study groups. Individual risk scores (30 year Framingham risk for CVD) and the above biomarkers had a strong correlation, according to Pearson correlation. The Receiver operating curve (ROC) revealed a larger region under the curve, as well as increased sensitivity and specificity.

The function of Lipoprotein Associated Phospholipase A2 (Lp-PLA2) as a biomarker to predict CVD in patients with metabolic syndrome (MS) in the South Indian population was investigated by **Mirshad P, Mahendra J**, and colleagues (2017).[33] The study's findings showed that Lp-PLA2 is a good marker for predicting CVD. When compared to traditional markers, Lp-PLA2 was a more specific cardiac marker for predicting CVD.

Recent research has been focused on the role of miRNA's in the pathogenesis of CVD and PD. In chronic periodontitis patients with and without coronary heart disease, **Yagnik K, Mahendra J**, et al (2019)[34] sought to quantify the levels of miRNA-146a in subgingival plaque samples and compare them with periodontal and cardiac parameters. The CP+CHD community had the highest levels of miRNA-146a, which also had a positive association with BMI, periodontal, and cardiac parameters, implying that miRNA-146a is involved in the pathogenesis of both periodontitis and coronary heart disease.[35] As a result, the authors concluded that detecting miRNA 146a could aid in the diagnosis of both periodontal disease and cardiovascular disease.

Future Perspectives

Recent research has thrown light on the pathogenesis and also the various etiological agents that link PD and CVD. Studies have shown that not only periodontal bacteria play a role in the causation of CVD but other microbes such as viruses in the periodontium can also initiate the disease. Thus, future research should be aimed at employing and designing methods to detect the presence of these organisms at an earlier stage so as to prevent the mortality associated with untreated CVD. Research should also be aimed at discovering new non-invasive biomarkers which can help the clinician to detect the disease and also to check the response of the host to the treatment given. Finally, all research should culminate in creating awareness amongst the society regarding the link between PD and CVD and the hazards that accompany the diseases, and the importance of maintaining good oral hygiene so that they seek medical and dental care at the earliest.

Conclusion: Epidemiologic studies have shown a possible correlation between PD and oral health care for CVD patients. Professionals may recognise patients who are unaware of their risk of severe CVD complications and who need CVD treatment as well as those who need medical attention. In the coming decades, as ongoing studies report and validate the strength of the connection between PD and CVD, oral healthcare practitioners and medical professionals must prepare for better preventive programme planning. According to the scientific evidence gathered so far, interventional treatment is still beneficial not only to oral health but also to overall health. A holistic approach to treatment can only benefit patients and public health as a whole, like dental, public health, and medical researchers and practitioners reach across disciplines.

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