

ASSOCIATION OF CHRONIC PERIODONTITIS WITH CARDIOVASCULAR DISEASES

Ayesha Sadiqa, Abdul Majeed Cheema

1 Shalamar Medical and Dental
College, Lahore, Pakistan
2 The University of Lahore,
Pakistan

Address for Correspondence:

Dr. Ayesha Sadiqa
Shalamar Medical and Dental
College, Lahore, Pakistan
Emails: ayeshaias@yahoo.com

Contribution

AS conceived the idea and designed the review. Data collection and manuscript writing was done by AS and AMC. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Aim of this review was to publish a brief literature review based on recent studies, highlighting the association of chronic periodontitis with cardiovascular ailments. A comprehensive literature study was completed by using two databases and one search engine namely: 'MEDLINE', 'PUBMED' and 'GOOGLE SCHOLAR' respectively. The referenced literature comprised of observational and case studies, systematic reviews, randomized control trials and short communications. Etiological pathophysiology, significance of the association and common mediators of periodontitis as well as cardiovascular diseases were briefly described. Epidemiological studies declared the causative role of chronic periodontitis in cardiovascular pathologies. Periodontal flora and its toxins have been linked to atherosclerosis. Common immune-inflammatory mediators possessed a significant role in the pathogenesis of heart-vascular pathologies. Periodontitis has been considered as an independent risk factor for the initiation and aggravation of cardiovascular ailments. However, by using primary periodontal measures, the chances of periodontitis can be minimized and the risk for cardiovascular diseases can be controlled.

Keywords: AChronic Periodontitis, Cardiovascular Diseases, Association.

INTRODUCTION

Dental pathology is very common all over the world, similarly a particular disease namely 'chronic periodontitis' is also termed as a community oral periodontal problem. It is referred to a chronic state of inflammation of tooth supportive structures that consist upon: gums, bony socket, periodontal ligaments and tooth cementum. Chronic periodontitis is a common disease of oral cavity consisting of chronic inflammation of periodontal tissues that is caused by accumulation of profuse amounts of dental plaques. Tooth plaque is indeed a biofilm, of light yellow colour that itself grows over the surface of tooth and the colonies of bacteria under this biofilm, establish themselves.¹

Bleeding gums, bad breath, gum recession and pathological periodontal pocketing are the sign and symptoms of chronic periodontitis. Socket osseous decay along with inflamed gums is most of the time pain-free, though sub-gingival calculus is a frequent finding. Highest rate occurs between 50 - 60 years of age. Anaerobic variety of bacteria such as *Fusobacterium Nucleatum*, *Porphyromonas Gingivalis*, *Fusobacterium Nucleatum*, *Eubacterium Species*, *Bacteroides Forsythus*, *Prevotella Intermedia*, and *Treponema Denticola*, all have been profoundly present in chronic periodontitis.²

The very first investigators in year 1989 by Mattila et al. indicated an association of oro-periodontal infective diseases with atherosclerosis, they announced periodontal pathology as an independent risk predictor of cardiovascular disease including Myocardial Infarction.³

World-wide the pertinent link between periodontitis and heart vascular ailments has been in prime consideration of the researchers since last two decades. It became a global trend in bioscience researches to explore the prevailed linkage in-between cardiac pathologies and periodontitis, more specifically when cardiac diseases would become a life threatening disease all over the world. Moreover, by improving the public oro-periodontal care, the risk for heart diseases can be minimized and even avoided at primary health care level.^{4,5}

The research on the relationship with respect to periodontitis and CHD (coronary heart diseases) also showed the same consistent association in scanty study on Pakistani population. In 2012 Bokhari et al. explained that in patients with cardiac ailments along with chronic (adult) periodontitis, the least-invasive periodontal measures considerably decline the concentrations of C-Reactive Protein (a common mediator of both pathologies i.e. cardiac diseases and chronic periodontitis).⁶

SIGNIFICANCE OF THIS ASSOCIATION

Periodontitis and heart related pathologies are the mutual chronic disorders, where the later one is considered a significant contributor to high mortality rate in mankind. Recently the prime attention has been shifted to a possible association between periodontal pathologies and heart disorders. On the crucial health related relationship between these two disorders several studies have been appearing on the issue from the different regions of the world. Many observational studies have documented that affected individuals with progressive periodontitis are 1.3-2 times more prone towards heart related diseases.⁷ In Australia, another related observational study aimed to know whether the early periodontal management had an advantageous effect on associated serum inflammatory mediators or not. The risk of heart vascular ailments, came up with the positive outcomes confirming that the periodontal treatment leads to improve the status of some inflammatory markers in relation to coronary heart disease.⁸

The prevalence of these two disorders and their relationship with greater health risk has also received attention. It has been reported that 30 to 64 years of age is the most prevalent age in men, in which periodontal disease leads to cardiovascular disease along with high rate of mortality. However, in women more than 65 years of age, shows no significant association.⁹ This study demonstrates that there is distinct gender variation of posing far greater risk in males than the females when both periodontitis and coronary heart disease is in existence. More specifically between 30 to 64 year of age, middle aged men are more prone to fetal coronary heart diseases influenced by periodontitis. A similar research conducted in Japan about the age group of patients who are at higher risk in relation to periodontal disease causing coronary artery disease reported that the population between 54 to 60 years, is at high risk in comparison to population above 60 years with no significant relation.¹⁰

CAUSAL PATHOGENESIS

Now, a pertinent question arises that how does this link develop? This question leads to suggest us certain pathological processes which counter-play a significant part in the genesis of coronary heart disease in the affected individuals of chronic periodontitis. Many types of pathogenesis and pathological mechanisms have been elaborated in different studies. One view point has explained that proinflammatory mediators like TNF-alpha and C-RP in periodontitis, initiate cytokine pathway of immune mediated reactions and cause damage to endothelium that facilitate cholesterol build-up that ultimately lead to narrowing of the related vessel and hence enhances the chances for coronary heart diseases.¹¹

The other perspective suggests that number of erythrocytes and level of Haemoglobin are reduced in periodontitis, giving rise to anemic condition. Common systemic inflammatory mediators like C-reactive protein, total leukocyte count, RBC and thrombocytes are also considered as predicted mediators for heart vascular disease. Thus variation in these above mentioned mediators in chronic periodontitis can explain its etiological association with coronary heart disease.¹²

Another group of scientists proposes that immunity and inflammation both are the critical players in each stage of atherosclerotic growth. That's why, this "inflammation hypothesis" increases the chances to elevate pro-inflammatory mediators and aggravate the periodontal disease that may also a major contributor to distant systemic inflammation. Indeed, it is also evident that periodontal diseases have an association with raised systemic C-RP concentrations along with gradual subsequent systemic inflammation.¹³

Another mechanism explains that as in periodontitis, gradual systemic inflammation and bacteremia occur constantly, this may trigger thrombocytes to activate and thus create a pro-coagulant condition. Patients with severe staged periodontitis were more prone to pro-coagulant state; this also justified the epidemiological link in-between periodontitis and heart vascular illnesses.^{14,15} A study on Japanese population supported the perception that periodontal pathology has been linked with greater chances of atherosclerotic cholesterol plaque attachment via endothelial cellular dysfunction triggered by periodontal pathogenic microflora, along with their end-products and immune-inflammatory markers.¹⁶ Furthermore, it has also been explained what literature says about the significant bio-inflammatory markers of chronic periodontitis alone and systemic markers in patients with only heart vascular pathologies. The research data explained the positive correlation of heart vascular disorder and periodontitis in terms of their common markers. It also clarified the association between the two diseases and causative role of periodontal disease by elaborating the pathophysiological processes that were involved in the genesis of atherosclerotic plaques in a patient of periodontitis.⁶

Thus, based on literature review, it can be concluded that all these proinflammatory biochemical serum mediators included C-RP, TNF- α , Fibrinogen, IL-6 and WBC Count, are found in an increased concentration in the following disorderly states:

- patients affected with periodontitis alone
- patients with cardio vascular disorder
- patients with both pathologies i.e. periodontitis and cardiovascular disease

Work done in Pakistan on these markers with respect to periodontitis and CHD (coronary heart diseases) also shows the same consistent relationship that in heart patients affected with chronic periodontitis, the non-surgical periodontal intervention can reduce serum C-RP concentrations. A study of Faisalabad, Punjab has suggested that "In CHD patients with periodontitis, non-surgical mechanical periodontal therapy significantly reduced systemic levels of C-reactive protein, fibrinogen and white blood cells."^{6,17}

In Florence, Italy, a cross-sectional study on adults i.e. ≤ 40 years with severe stage of periodontitis in comparison to controls (periodontally healthy) concluded that Full-mouth bleeding score (FMBS) was a good indicator of C-RP concentrations whereas clinical probing depth was an effective predictor of average carotid intimal thickness. It means that severe periodontitis may forecast the undiagnosed atherosclerosis in adult lot.¹⁷

In Helsinki, Finland, the researchers showed the result of their work in a conclusive manner that in adult periodontitis, gram negative anaerobic bacterial overgrowth might produce endotoxemia and slow-grade systemic inflammation that finally depicted in the form of cardio-vascular pathologies. The markers they used were IL-6, C-RP and tumor necrosis factor alpha (TNF- α). As a conclusion, they found that there was a definitive role of periodontal pathogens and endotoxins released by these pathogenic bacteria induced systemic inflammation that resulted into a high risk for cardiovascular disease.¹⁸

In Egypt, research done on the same lines, concluded that increased serum C-RP and IL-6 levels were profoundly high in patients with periodontitis and in that very research article they labeled periodontitis as a powerful modifier of heart related disorders.¹⁹

The study from France was carried out to evaluate the possible association between advancement of periodontitis (inflammatory response) and angiogenic lesions in patients with stable heart vascular pathologies. As a result, the researchers found that severity of Periodontal Disease has a positive correlation with angiographic lesion extent of coronary vessels. Study also suggested that such patients could get benefit from surgical periodontal measures to hinder coronary artery disease advancement.²⁰

In the same context, IL-6 is known as a pro-inflammatory cytokine that also owned a significant role as a myokine. It is released from Macrophages along with T-cells. It plays its role to stimulate immune mediated responses like infections such as Chronic Periodontitis and tissue damage such as Coronary Heart Diseases.²¹ Besides, a substance in human serum called C-reactive protein (C-RP) has also been taken as a vital pro-inflammatory mediator; as its concentration

increases in all such conditions including chronic periodontitis and coronary heart diseases. C-RP first binds on the cellular surface of the necrotic/decayed cellular population and it also binds with few pathogenic bacteria. That binding then cause complement activation along with the process of phagocytosis by monocyte-macrophages system. Which clear all the byproducts of immune mediated inflammatory reactions such as necrotic & apoptotic cells and bacteria.²²

Untreated periodontitis showed a significant association with atherosclerosis that can be evaluated from the thickness of the walls of carotid arteries (Tunica intima and Tunica media) named 'CIMT' (Carotid Intima Media Thickness) and measure of high sensitivity mediators like lipoprotein, fibrinogen, cholesterol, C-RP, ESR (Erythrocyte Sedimentation Rate) and TLC (Total Leukocyte Count) in Spain.²³ From Switzerland various meta-analysis also identified and reported the linkage in-between heart vascular diseases and periodontitis.²⁴ In a study it was strongly assumed that increased level of IL-6 and C-RP in subjects affected with chronic periodontitis acted as a burden for atherosclerosis.²⁵

It was concluded that increased serum level of C-reactive protein and IL-6 were predominantly high in both pathologies (periodontitis and cardiovascular diseases) in Egyptian population.¹⁹ Periodontitis has been declared a possible modifiable threat for Cardio Vascular Disorders in a Chinese study. It was suggested that middle-aged men are more prone to fatal coronary heart diseases influenced by periodontitis.⁹

In Washington DC (US), a study also clarified that periodontal pathology with high bacterial count is linked with coronary vascular disorder and initial atherogenesis. This may suggest that bacterial systemic concentration from focal sites of chronic periodontitis is a natural continuous source of infection with respect to coronary atherosclerotic pathologies.²⁶

COMMON MEDIATORS

Immune mediated cytokines namely IL-8, IL-6 and TNF-alpha are found to promote degeneration of inflamed periodontal tissues. The quantification of the level of these markers in gingival crevicular fluid (GCF) suggest that TNF-alpha, IL-8 and IL-6 have been the concerned mediators in the pathophysiology of periodontitis.²

C-RP is a vital inflammatory mediator of periodontitis. It is concluded in a study where plasma protein C and C-RP were evaluated in controls and in the subjects with periodontitis, resultantly they found a positive correlation of periodontitis with C-RP and negative correlation of periodontitis with protein C.²⁷ Conversely treatment of

chronic periodontitis that includes surgical and nonsurgical interventions like tooth scaling and root planning along with antibiotic medication lead to reduced plasma level of C-reactive protein.²⁸

Various studies clearly verify the common bio-inflammatory markers of inflammation in both chronic diseases i.e. periodontitis and coronary heart diseases. Causative role of IL-6 and C-RP in periodontitis affected patients in relation to heart vascular pathologies was noted as serum inflammatory markers possess a connecting link with periodontitis.^{29,30} In these studies, noteworthy decline of serum C-RP and IL-6 was found out after treating the periodontitis. As a result of that significant serum response, it was concluded that this pilot study indicated a causal relation of periodontal disease with atherogenesis.³¹

Clinical evidences also suggest that periodontitis is linked to the gradual host inflammatory response and it can be evaluated by advanced level of serum C-RP and extended endothelial dysfunction.³² Conclusively, this report claimed the hypothetical link between chronic periodontitis and other systemic inflammatory conditions like coronary heart disease. Research data assessed a strong causal relationship between heart diseases and periodontal inflammation, which have been categorized not only by a high frequency, but also by a steady rise of some common risk factors.³³ Epidemiologic research also noticed that periodontal ailments are independently linked with clinical and subclinical heart related pathologies.³⁴ Such common markers namely LDL-C, factor VII, fibrinogen, tissue plasminogen activator (t-PA) and C-RP were responsible to cause damages towards both diseases and hence their serum level was observed increased in both of these diseases.³⁵ A positive relationship between the periodontal attachment loss and peripheral vascular disease, through systemic markers of inflammation i.e. fibrinogen, C-RP and leukocytes in US based research was analyzed and concluded that inflammation could be a potential connection to peripheral vascular disease with chronic periodontitis.³⁶ The relationship of these both disorder was validated by observing the inflammatory markers response through common risk factors, in a study by raising inflammatory serum mediators like C-RP and fibrinogen through smoking which influence both cardiovascular (Atherosclerotic plaque formation) and periodontal diseases.³⁷

Elevated level of both markers i.e. IL-6 & C-reactive protein in chronic periodontitis and heart vascular pathologies indicates that these are the mutual serum bio-inflammatory markers in of both of these ailments.^{29,30} Numerous studies has shown the contributing relationship of chronic periodontitis with cardiovascular diseases. For instance, in a research study, considerable drop in serum IL-6 & C-RP was noticed after treating periodontitis and because of that significant serum response it was concluded that there was

a causal link of periodontitis in heart vascular pathologies such as atherogenesis.³¹

The inflammatory markers of chronic periodontitis and heart vascular illnesses had reported to be IL-1 β , TNF- α and high sensitive C-RP³⁶ It has been asserted from all those studies that increased level of C-RP and IL-6 in periodontitis affected patients acted as a burden for atherosclerosis.²⁵ Also improvement on cardiovascular surrogate markers i.e. C-reactive protein, fibrinogen, endothelial function; after periodontal therapy³⁹ further confirmed the relationship of periodontitis with heart vascular pathologies.

CRP is considered a screen for inflammation. It is reported that C-reactive protein (CRP) serum level increases in inflammatory diseases and has a role in the process and progression of inflammatory events. Likewise, it is elevated in periodontal and cardiovascular diseases.²² The commonality of bio-inflammatory serum markers (C-RP and IL-6) of inflammation in both diseases i.e. chronic periodontitis and coronary heart diseases have been elucidated with strong evidence.²⁴

These studies of the linkage between chronic periodontitis and coronary heart disease illustrate that in the presence of periodontitis, coronary heart disease would become a life threatening disease across the world. The understanding of the relationship among these two disorders will lead to take more appropriate steps to get rid of risk factors related to both of these diseases and to evaluate more beneficial strategies in terms of primary health care to avoid the occurrence of these diseases.⁴⁰

Literature review strongly revealed the causal connection of chronic periodontitis in aggravation of cardiovascular pathologies, mainly through periodontal pathogens and their toxins which further excite specific immune-inflammatory cytokines that directly involved in the pathogenesis of heart-vascular pathologies. Thus through primary periodontal measures, the risk of cardiovascular diseases can be minimized.

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