Periodontitis & C-reactive Protein as a Cardiovascular Risk Factors : A Causal Relation

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Abstract

Association of Oral and Systemic diseases has gained importance because of the high occurrence of oral diseases in general population. 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. Unrecognized infections such as periodontal disease may induce an acute phase response elevating CRP levels. CRP is also a prognostic marker for cardiovascular disease with reported elevated serum levels during periodontal diseases. However, it is premature to confirm a causal relationship between periodontal disease and cardiovascular disease as measured by C-reactive protein levels. Future longitudinal studies are needed before such an association can be established.

Key Words: C-reactive proteins; Cardiovascular disease; Periodontal disease.

Introduction

Periodontitis is a disease of the tooth-supporting structures that usually has an infective etiology and a subclinical chronic course[1] .Unlike its name, an acute-phase reaction has a chronic component and represents the immuno inflammatory response of the body to different insults including periodontitis[2,3]. C-reactive protein (CRP) has been recognized as one of the markers of acute-phase reactions and inflammation. Detection of this inflammatory marker has been boosted by recent improvements in corresponding assays[4] making it possible to measure very low levels of CRP (referred to as high-sensitivity CRP or hsCRP). Recently, hsCRP has been recognized as an independent predictor of chronic heart disease [5] and increased levels have been noted in acute ischemia and myocardial infarction[6]. The landmark study on the association between oral infections and coronary heart disease was first reported by Mattila[7] and led to a series of case control and cohort studies. Quantification of acute-phase reactions and their association with the extent of periodontitis has been recognized[8,9,10]. An emerging evidence points towards a short term reduction in CRP levels following management of periodontitis. Hujoel[11] et al presented a negative association between periodontal disease and subsequent Coronary heart diseases (CHD) in first National Health and Nutrition Examination Surveys (NHANES-1) longitudinal study with a 21years follow up.

Mechanism for the proposed periodontal infection and CHD / stroke association

Infection has been recognized as a risk factor for atherogenesis and thromboembolic events[12]. 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 similarities 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[13]. Similarly, subgingival dental plaque found in periodontal pocket contain large number of gram negative anaerobic microorganisms, these gram negative anaerobes liberate endotoxins which interact with toll like receptor (TLR) expressed on the surface of neutrophils and monocytes. TLR-ligand complexes activate signal transduction pathways in the both the innate and adaptive immune systems leading to the production of cytokines, which co-ordinate the local and systemic inflammatory response[14].

Proinflammatory cytokines originating at the site of local pathology activate hepatocytes to produce acute phase proteins including CRP[15] and this forms part of the nonspecific response. Experimental studies have shown that CRP binds to ligands exposed in damaged tissues and then activates compliment which may lead to compliment mediated exacerbation of tissues injury [16].

1. Effect of Endotoxins in the Circulation

The microflora associated with periodontal infections is a rich source of endotoxins, which are lipopolysacchride (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. actinomy-cetemcomitans, 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 cells[17], promote adhesion of monocytes to endothelium[18], induce macrophage foam cell formation[19] and cause general endothelial dysfunction[20]. All of these effects play a significant role in the initiation and development of atherosclerosis[21]. 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[22].

2. Role of Heat Shock Proteins

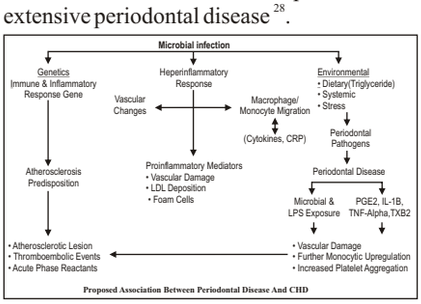
Heat shock proteins (Hsp) are produced by a wide variety of bacteria and human cells under a variety of stressful or harsh conditions such as high temperature, infection, inflammation, and mechanical stress[23]. It is well established that endothelial cells produce Hsp under stressful conditions such as exposure to endotoxins[24].

3. Infection-induced Perturbations in Lipid Profiles

Low doses of endotoxins cause a rapid rise in serum triglycerides due to an increase in triglyceride-rich very-low-density lipoprotein (VLDL)[25]. 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.[26] Cytokines like IL-I, IL-6, and TNF- have been implicated as risk factors for CHD and prolonged hyperlipidemia is likely to have deleterious clinical effects.[27]

4. Formation of Acute-phase Reactants

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 [28].



Proposed Association Between Periodontal Disease And CHD

Acute-phase Reaction & C-reactive Proteins

It has long been speculated that inflammation in different organ systems may have distant effects via proinflammatory mediators. The latter could be produced either at the site of initial inflammation or have a more remote origin, before causing different systemic effects. These systemic effects could be both acute and chronic in nature, but have been classically named as an 'acute-phase response'[2]. C-reactive protein is one of the first acute-phase reactants to be recognized. It was first identified in 1930

among patients suffering from pneumococcal pneumonia. It could produce flocculation by binding with the C polysaccharide from Streptococcus pneumoniae, and was subsequently named CRP. Like most other acute-phase proteins, CRP is synthesized in the liver and its production is induced by interleukin (IL)-6.[29]

The functions of CRP are not clearly defined, but it is reported to have opsonic and proinflammatory activities. Because of its unique pentameric structure, it can bind to negatively charged molecules on cell membranes[30,31]. This mechanism forms the basis of its opsonization function, whereby it binds microbes that are then removed from circulation by phagocytosis. In atherogenesis, the opsonization of low-density lipoproteins appears to mediate uptake by macrophages, which in turn stimulates production of proinflammatory mediators such as IL-1, IL-6, and tumor necrosis factor-α. Moreover, CRP has also been shown to activate the classical pathway of the complement system.[32]

The Centers for Disease Control and Prevention (CDC) and American Heart Association

(AHA) convened a Workshop on Markers of Inflammation and Cardiovascular Disease, march 2002, stating the cut off value for hs CRP - low-risk group (hsCRP, <1mg/L), medium risk group (hsCRP, 1-3mg/L), & high risk group (hsCRP, >3mg/L).

Therefore, CRP & certain other inflammatory mediators have a distinct advantage in that they not only provide predictive information, but because of their role in disease pathogenesis, they may also serve as important therapeutic targets.

C-reactive Protein and Periodontitis

Periodontitis is caused by subgingival microbes, the most important being Porphyromonas gingivalis, Fusobacterium nucleatum, Tannerella forsythia (previously known as Bacteroides forsythus), and Treponema denticola. Most such infections follow a subclinical, chronic course resulting in inflammatory changes and periodontal destruction[13]. Not surprisingly, CRP levels may be elevated in patients suffering from periodontitis [9,10].

Earlier studies utilized the latex agglutination assay available at that time to report the presence or absence of CRP[33, 34]. Recent studies involved more sensitive assays, with detection limits as low as 0.21 mg/L. One such study from Denmark by Loos et al.[35] Investigated systemic levels of inflammatory markers of cardiovascular disease (hsCRP, IL-6, total leukocyte and differential leukocyte count) in an unselected population with and without periodontitis. The patients were divided into three groups based on radiographic evidence of bone loss. While 90% of all the patients had detectable hsCRP, there was a significant difference in median values between the three groups; those with more advanced bone loss exhibited higher hsCRP levels. Similar findings were reported by others [36-38]. Craig et al. [39] estimated an odds ratio of 14.1 for having 'high normal' hsCRP in patients exhibiting disease progression. A trend towards increased hsCRP levels and progression of periodontal disease was evident in this study, leading the authors to suggest that periodontitis may be a modifiable risk marker of increased CRP and subsequent cardiovascular events.

Effects of Periodontal Therapy on C-reactive Protein

Shklair IL et al[40] reported data from 96 patients, of whom 43 had necrotizing ulcerative gingivitis (NUG), 18 had (including 10 with severe) periodontitis, and 21 had gingivitis. A high percentage of individuals with more severe forms of disease were CRP-positive, the highest being in the NUG group (67% positive), followed by the severe periodontitis group (50% positive), and least in the moderate gingivitis group (14% positive). In most instances CRP was not detectable by 3 to 7 days after treatment.

A study carried out by Ebersole et al[41] reported that 40 to 50 % reduction of CRP level was noticed in chronic periodontitis patients, after receiving of 50mg of NSAID (Flubrioprofen) as a part of periodontal therapy. An earlier interventional study carried out by Christgau et al[42] in patients with reasonably well-controlled diabetes noted an improvement in periodontal status of diabetics and healthy controls after periodontal treatment, thus, in well-controlled diabetes, the impact of periodontal therapy on CRP levels and hence cardiovascular risk may be minimal.

Jastrzebski et al[43]. Also did not find a significant impact of dental treatment on CRP or fibrinogen levels in a group of patients with hypertension, and concluded that in the presence of other cardiovascular risk factors, the impact of dental infection on the total inflammatory burden may be masked. Ioannidon et al[44] & Paraskevas S[45] published a systematic reviews, which revealed that there is no consistent agreement regarding the effects of periodontal intervention on CRP levels. Ioannidon concluded that there was inadequate evidence that periodontal treatment reduces CRP levels.

Discussion

The effect of periodontal disease progression on the risk of having higher levels of CRP appears to predict cardiovascular disease and has been well documented in the current literature[35-39]. Setting optimal cut-off levels to predict cardiovascular disease risk remains problematic as does the possible role of CRP in cardiovascular disease. The consensus conference of the AHA 5 advised that in a metabolically healthy individual (i.e. with no active infection), CRP should be measured by a high-sensitivity assay, in a fasting or non-fasting state. Preferably there should be two determinations spaced 15 days apart to ensure a stable estimate. The conference also inferred that hsCRP is an independent predictor of increased cardiovascular risk. The risk prediction based on CRP as proposed by AHA/CDC categorizes patients with 1 to 3 mg/L as being at moderate risk. Ridker et al. recommended a cut-off level of CRP >2 mg/L as a level that predicts cardiovascular risk. In their study, Craig et al.[39] reported this value to be associated with more advanced periodontitis.

Periodontal disorder resulting in increased CRP level elevations could be explained by the inflammatory/infective nature of the disease. The presence of periodontal pathogens could stimulate the inflammatory response sharing a common pathogenic pathway to that in atherosclerosis. This might result in elevated levels of inflammatory markers like tumor necrosis factor-α, IL-6, IL-1, which trigger the inflammatory cascade. These proinflam-

matory effects have been found to have profound effects on endothelial cells, causing upregulation of vascular adhesion molecule 1, intracellular adhesion molecule 2, and E-selectin. All of these modulate monocyte recruitment in the presence of fatty streaks forming foam cells which results in atheroma[46]. In their study, Haraszthy et al[47]. found that periodontal pathogens like P gingivalis have also been isolated in the atheroma of patients with atherosclerosis, which points to a possible infective nature of this disease. Since both periodontitis and cardiovascular events may share a common pathogenic pathway and common risk factors, it is difficult to confirm a cause-and-effect relationship. Interventional studies are therefore needed. The variable results reported could be due to the presence of other confounding factors for CRP levels, namely age, ethnicity, smoking history, systolic blood pressure, BMI, triglyceride and high-density lipoprotein cholesterol levels, IL-6, intake of statins, antibiotics, and medical status[48-50]. In several studies demonstrating a positive outcome in terms of reduction in CRP levels, antimicrobials and NSAIDs have been included in the relevant treatment regimens, which itself would have contributed to a reduction in the inflammatory load[41]. Therefore to understand the possible bi-directional causal relationship between periodontal disease & CRP levels, more randomized clinical trials and the use of other criteria to identify cardiovascular dysfunction are required.

Conclusion

1. Periodontal disease and periodontal therapy may have an impact on cardiovascular risk and have practical implications for the management of patients at risk.
2. Longitudinal & case control studies are required to track down the association of periodontal diseases & CRP.
3. Long-term studies on the effects of CRP antagonists and CRP-lowering strategies on periodontal health and coronary heart disease are needed.

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