A review of C-reactive protein: A diagnostic indicator in periodontal medicine

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Abstract

Periodontitis is a local inflammatory process mediating the destruction of periodontal tissues, triggered by bacterial insult. Recent evidence suggests the presence of chronic inflammatory periodontal disease may significantly affect systemic health conditions such as coronary heart disease, stroke, or adverse pregnancy outcome. C-reactive protein (CRP) is an acute phase protein which reflects a measure of the acute phase response. CRP is used as one of the markers of choice in monitoring the acute phase response because it increases to a relatively high concentration compared to basal concentration. CRP has been shown to predict cardiovascular (CV) mortality in recent studies, and elevated CRP levels have been observed in middle-aged patients with periodontitis. Combination of chronic infections like periodontitis with elevated CRP is associated with higher chronic heart diseases. The recognition of the relationship between periodontal diseases and atherosclerotic events is relatively recent and mostly based on the inflammatory hypothesis of atherosclerosis. Periodontal disease is one of the risk factors for cardiovascular disease and possibly one of its causes. Hence, even associations of modest magnitude have a large impact. The cost to the society directly attributable to atherosclerotic sequelae is very large. Periodontitis is treatable; moreover, it is preventable. Experimental conformation of this shows that another widely prevalent and preventable contributor to the burden of cardiovascular disease would be added to the options available of the clinicians and public health practitioners for the control of the epidemic of cardiovascular disease.

KEY WORDS: Acute phase reactants, C-reactive protein, cardiovascular disease, periodontal disease

C-reactive protein (CRP) is an acute phase protein which reflects a measure of the acute phase response. The term “acute phase” refers to local and systemic events that accompany inflammatory local response which includes vasodilatation, platelet aggregation, neutrophil chemotaxis, and release of lysosomal enzymes. Systemic responses include fever, leukocytosis, and a change in the hepatic synthesis of acute phase proteins.[1] An acute phase protein has been defined as the one whose plasma concentration increases (positive acute phase proteins) or decreases (negative acute phase proteins) by at least 25% during inflammatory disorders. Other acute phase proteins include transport proteins.
(haptoglobin, ceruloplasmin, gamma 1-trypsin inhibitor, etc.), coagulation proteins (fibrinogen, prothrombin, etc.), and complement components (C3, C4, C5, etc.).[1,2]

Periodontal disease is a general term used to describe pathological changes in the periodontium, a functional unit comprising several tissues – the gingiva, the periodontal ligament, the root surface cementum, and the alveolar bone socket.

An inter-relationship between periodontal disease and systemic health has been suspected for centuries, but evidence to explain the connection has only been elucidated in the past few decades.

Inflammation is the primary pathologic feature of periodontal disease, and bacterial plaque is the essential etiologic factor responsible for inducing the host inflammatory response. However, it is host susceptibility and ability of the host defense to respond appropriately to the bacterial challenge that results in differences in the disease severity from one individual to another. Conversely, recent evidence suggests the presence of chronic inflammatory periodontal disease may significantly affect systemic health conditions such as coronary heart disease (CHD), stroke, or adverse pregnancy outcomes.

Consequently, the relationship between periodontal disease and systemic disease (periodontal medicine) is a two-way road, with systemic host factors acting locally to reduce resistance to periodontal destruction and the local bacterial challenge generating widespread effects with the potential to induce adverse systemic outcomes.

CRP has been shown to predict cardiovascular mortality in recent studies, and elevated CRP levels have been observed in middle-aged patients with periodontitis. Combination of chronic infections like periodontitis with elevated CRP is associated with higher chronic heart diseases.[3,4]

CRP is used as one of the markers of choice in monitoring the acute phase response because the markers increase to a relatively high concentration compared to basal concentration.[1]

Serial CRP measurement can be used as a diagnostic tool for finding clinical infections, monitoring effects of treatment, outcome, and early detection of relapse of the disease, and hence can be a useful diagnostic aid in determining disease progression.[2]

C-reactive Protein

Tillet and Francis (1930) discovered the presence of CRP in the serum of patients with pneumonia, but it was not actually isolated until 1941. The name is derived due to the ability of the CRP to react with C-polysaccharide isolated from pneumococcal cell walls. It is a member of pentraxin family of proteins. They are ligands for leukocyte Fcy receptors. The CRP gene is located on first chromosome. CRP is synthesized by hepatocytes and is classified as an acute phase protein on the basis of its increase in plasma concentration during infection and inflammation and is a golden marker of inflammation.[4] Pepys and Baltz (1983) suggested that CRP is synthesized by the liver in response to diverse inflammatory stimuli, including heat, trauma, infection, and hypoxia.[5]

Functions of CRP

A major function of CRP, a component of innate immune system, is its ability to bind phosphocholine and recognize some foreign pathogens as well as phospholipids of damaged cells. It can activate complement system when bound to one of its ligands and can also bind to phagocytic cells, an observation suggesting that it can initiate the elimination of targeted cells by its interaction with both humoral and cellular effector systems of inflammation. Other proinflammatory effects of CRP include induction of inflammatory cytokines and tissue factor in monocytes. It is thought to assist in
CRP has the ability to prevent the adhesion of neutrophils to endothelial cells by decreasing the surface expression of L-selectin, inhibit the generation of superoxide by neutrophils, and stimulate the synthesis of interleukin-1 (IL-1) receptor antagonist by mononuclear cells.[2]

CRP has also been reported to stimulate tissue factor production by human peripheral blood monocytes and has a procoagulant effect. It has also been reported that CRP recruits monocytes by receptor-mediated chemotaxis into the arterial wall. It colocalizes with foam cells in atherosclerotic lesions.[6,7]

**Circulating CRP Concentrations**

CRP is a direct and quantitative measure of the acute phase reaction. The plasma levels of CRP in most healthy subjects is usually 1 mg/L, with the normal being defined as <10 mg/L. Plasma levels increase within 4-6 h after initial tissue injury and continue to increase several hundredfold within 24-48 h. CRP remains elevated during the acute phase response and returns to normal with restoration of tissue structure and function. The rise in CRP is exponential, doubling every 8-9 h. The half-life is less than 24 h.[8] The amount of CRP produced by the body varies from person to person, and this is affected by an individual’s genetic makeup (accounting for almost half of the variation in CRP levels between different people) and lifestyle.

After stimulation of the hepatocytes by cytokines, levels of CRP in the blood start to increase within 6 h. These concentrations can increase up to 1000-fold or even more. Smoking and obesity are positively correlated with CRP levels, whereas weight loss and cessation of smoking decrease CRP values.[4]

The clearance rate of CRP is constant, therefore the level of CRP in the blood is regulated solely by synthesis.[9] A single high CRP value must be followed by re-sampling when it is above 1.75 mg/L for men, above 1.00 mg/L for no oral contraceptives (OC)-using women, and above 2.00 mg/L for OC-using women.[10] Elevated CRP levels reflect certain low-grade infections associated with CHD, periodontitis, and infections caused by cytomegalovirus and *Chlamydia pneumoniae*.[11,12]

Early laboratory methods were only qualitative in nature until the late 1970s when significant advances in isolating CRP and measuring to the picogram range were made. Most clinical laboratories now use laser nephelometric assay because of its ease of use, speed, and reproducibility. Various analytical methods are available of CRP determination, such as enzyme-linked immunosorbent assay (ELISA), immunoturbidometry, rapid immunodiffusion, and visual agglutination.[13]

People with normal body mass index showed twofold difference in average CRP between those who had periodontal disease and those who did not, but the difference decreased with increasing body mass index and was negligible among severely obese people.[11] Interleukin-6 (IL-6) and CRP represent the most sensitive markers used to evaluate the inflammatory status of an individual.[7,14]

**Risk Factors**

Established risk factors for “high-normal” values of CRP within the general population include older age, cigarette smoking, chronic bacterial infections, and chronic bronchial inflammation. Viral infections tend to give lower CRP level than bacterial infection.[6]

Higher CRP levels tend to be found in individuals who smoke, have high blood pressure, are overweight, and do not exercise, whereas lean, athletic individuals tend to have lower CRP levels.[1]

Large amounts of CRP are produced by hepatocytes in response to circulating cytokines, such as tumor necrosis factor (TNF)-α and IL-1, produced at the site of tissue destruction. This CRP production by
hepatocytes occurs at the expense of albumin and other constitutive proteins, a process labeled “reprioritization” of hepatic protein synthesis. However, competing demands for protein synthesis in cases of acute, overwhelming inflammation can lead to anomalous short-term changes in acute-phase reactant.[6]

Napoli et al.[6] showed elevated levels of CRP in conditions such as acute stroke, surgery, and cancer.

**Relationship among CRP, Periodontal Disease, and Cardiovascular Disease**

Localized infections resulting in increased inflammation and tissue loss in the periodontium elicit systemic host changes manifested by an increase in acute phase reactants.[15]

Several inflammatory mediators are elevated in peripheral blood in subjects with periodontal disease, suggesting that periodontal inflammation either contributes directly to the elevation of the concentration of these substances in peripheral blood or signals distant organs (e.g. the liver) to produce them. These proteins may have deleterious effects on other target organs (e.g. heart, brain) by modulating disease processes such as atherosclerosis.[16]

Periodontal diseases are associated with an increase in CRP levels. This is significant because CRP is a widely accepted measure of the level of systemic inflammation, and increases in CRP levels are associated with an increased risk of atherosclerosis. In patients with both atherosclerosis and periodontal disease, CRP levels were elevated above the level seen with only one disease the other. Periodontal disease also may lead to transient increase in circulating levels of IL-1β, TNF-α, and prostaglandin E₂ (PGE₂). This may be the first step in the contribution of periodontal diseases to systemic inflammation.[17]

Elevated levels of CRP, IL-6, and neutrophils in patients with periodontitis may occur when bacteria and bacterial products, and cytokines enter the circulatauion.[18]

The total volume of inflamed periodontal tissue may also play a role and there is tendency for higher CRP levels in generalized periodontitis compared to localized periodontitis. It has been established that the extent of bacteremia is directly related to the severity of the periodontal inflammation. Subsequently, the systemically dispersed bacteria and lipopolysaccharide (LPS), as well as cytokines from the periodontal lesion, may stimulate hepatocytes and circulating leukocytes to produce CRP and IL-6, respectively.[19]

Dentate people with extensive periodontal disease had an increase of approximately one-third in mean CRP and a doubling in the prevalence of elevated CRP, compared with periodontally healthy people.[5]

Periodontal disease may be linked to systemic inflammation through two main mechanisms.[17] One pathway of the model proposes that periodontal disease occurs as a joint response to local pathogens and to an underlying hyperinflammatory trait, which also causes elevation of systemic inflammatory mediators. However, an additional synergistic mechanism is proposed in which local periodontal infection creates an elevated systemic inflammatory response that potentiates the increase in CRP caused by systemic risk factors.[5]

The presence of periodontal pathogens *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus*, and *Bacteroides forsythus* in subgingival samples was positively associated with elevated CRP levels.[3]

CRP and fibrinogen affects coagulation, platelet activation, and aggregation. The LPS and inflammatory cytokines that are present in periodontal disease may increase the expression of leukocyte
adhesion molecules such as intercellular adhesion molecules or vascular cell adhesion molecules, or by endothelial cells, which in turn is associated with atheroma formation.[20]

CRP localizes with complement in human heart during myocardial infection, suggesting that it binds to diseased muscle tissue, fixes complement, and hence triggers complement-mediated inflammation that contributes to atheroma formation. Periodontal infections may be associated with an increased risk of atherosclerotic processes and strokes, in part via the association of periodontal infections with elevated levels of CRP.[18,21]

Intraoral source of infection can create a systemic inflammatory response, therefore placing “apparently healthy” patients at increased risk of cardiovascular disease; such an association could also represent a mechanism underlying recent epidemiological findings that oral diseases appear to be risk factors for cardiovascular disease.[18]

Moderate increase in CRP (i.e. >2.11 mg/L) in healthy population was a risk factor for myocardial infarction and stroke.[20]

CRP, IL-6, and neutrophils may contribute in part to the mechanism for the observed associations between chronic infections and cardiovascular diseases. CRP may activate complements in damaged blood vessel wall. IL-6 has pro-inflammatory properties and procoagulant effects; these properties may contribute to the pathogenesis of coronary syndromes. Furthermore, IL-6 stimulates the production of CRP by hepatocytes. The elevated levels of neutrophils affect blood rheology; they may adhere to endothelial membranes and release harmful oxygen radicals and proteolytic enzymes, and in this way also contribute to increase inflammatory activity in atherosclerotic lesions.[22]

The clinical relevance of much smaller increase in CRP has been highlighted recently in epidemiological studies demonstrating that individuals with “high-normal” values of CRP have increased risks for cardiovascular disease. So, moderate elevation of CRP in apparently healthy individual is a risk factor for cardiovascular disease.[5,22]

LPS and other bacterial components can activate an impressive cascade of inflammatory cytokines that play a role in atherosclerotic heart disease, either through a direct action on the vessel wall or by inducing the liver to produce acute phase proteins.[19,23]

Combination of chronic infection and elevated CRP level is associated with a significantly higher CHD risk than either of these factors alone.[11]

CRP level was an independent predictor of cardiovascular mortality in older women.[22]

CRP enhances the expression of tissue factory by monocytes and is thus procoagulant. It also induces complement activation, leading to an increased inflammatory response that could increase the likelihood of lethal arrhythmias or the volume of ischemic tissue. CRP production by the liver is also stimulated by interleukin and promotes leukocyte adhesion that results in enhanced recruitment of monocytes to atherosclerotic plaques, thus supporting thrombus formation.[24]

Periodontal diseases are associated with an increase in CRP levels.[24,25] This is significant because CRP is a widely accepted measure of the level of systemic inflammation and increases in CRP levels are associated with an increased risk of atherosclerosis (ACS). In patients with both ACS and periodontal disease, CRP levels were elevated above the level seen with only one disease or the other.[26] Periodontal disease also may lead to transient increase in circulating levels of IL-1β, TNF-α, and prostaglandinE₂(PGE₂). This may be the first step in the contribution of periodontal diseases to systemic inflammation.[17]
Conclusion

CRP, the classical marker of acute phase response, is an indicator of a variety of pathological processes including infection, tissue damage, and chronic inflammatory disease. As the goal of modern health care continues to shift from an attitude of treatment to one of prevention, investigations will increasingly be directed toward elucidating predisposing factors that lead to atherosclerosis and developing appropriate early intervention. Periodontal diseases may represent one such factor. Periodontitis itself is endemic in many countries, despite the fact that treatment modalities have proven successful over the long term and preventive measures are well understood. Periodontal diseases, like atherosclerosis, are an inflammatory disease. Herein may lie the most plausible link between the two diseases, in that periodontal disease may be contributing to a heightened systemic inflammatory state that, in turn, contributes to the progression or exacerbation of atherosclerosis. It will be incumbent on all dental professionals to take appropriate measures to both counsel patients in the prevention of periodontal diseases and, where necessary, arrange treatment for affected individuals to receive appropriate care in a specialist setting.

Footnotes

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