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Review Article

# Relationship between C-reactive protein and periodontal disease: A new tale of an old molecule

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ABSTRACT

Oral fluids are a substrate for a new generation of non-invasive diagnostic tools through the development of ultra- and high-sensitive detection systems and the fact that they contain many serum analytes that reflect normal function or disease status. Within the oral cavity C-reactive protein (CRP) has been detected in both gingival crevicular fluid (GCF) and saliva, and is considered to be an important biomarker for systemic disease. We review the biological properties of CRP, the association between CRP and periodontal disease, and the possibility that CRP may be a potent therapeutic target. A systematic search for data related to the association between CRP and periodontal disease was performed to recognize studies on animals and human (PUBMED, MEDLINE, COCHRANE, and Google search).



## 1. Introduction

Periodontal disease, caused mainly by bacteria, is characterized by inflammation and destruction of the attachment apparatus of the teeth.[1] Studies indicate that the periodontal lesion is not strictly a localized process but may lead to systemic alterations in the immune function. Periodontitis has been proposed as having an aetiological or modulating role in cardiovascular disease and adverse pregnancy outcome.[2] The diffusion of plaque derived antigens beyond the local lesion into the systemic circulation presumably accounts for this.[3] Several mechanisms have been proposed to explain or support such theories. One of these is based around the potential for the inflammatory phenomenon of periodontitis to have effects by the systemic dissemination of locally produced mediators such as C-reactive protein (CRP), interleukins–1beta (IL-1β) and –6 (IL-6) and tumor necrosis factor-alpha (TNF-$\alpha$).[2] Traditionally, CRP was thought to be produced exclusively by the liver, but recent research suggests localised production in neurons, smooth muscle cells, macrophages of atherosclerotic plaques, epithelial cells, and adipose tissue. This then leads to the question of what is the source of CRP in oral fluids – is it local from the periodontal or oral tissues, or delivered by the serum as a result of systemic inflammation? If systemic, then GCF levels could be used to replace blood tests as an easy measure of systemic CRP to evaluate risk/prognosis in other diseases. If local, then this may be indicative of active inflammation in periodontal tissues, with the potential to act as a marker of disease activity. A systematic search of literature was carried out to identify relevant studies (original article and controlled trials) by using keywords like acute phase reactants, C-reactive protein, cardiovascular disease, periodontal disease in PUBMED, MEDLINE, COCHRANE, and Google databases. Animal models as well as human trials were included in this search. In addition, we searched the reference list of all relevant articles.

## 2. What is CRP

C-reactive protein is an acute phase reactant which is released by the body in response to inflammatory stimuli

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or acute injury and is an essential response of the body to injury.[4] CRP, which has a half-life of 19 hrs. is a serum protein synthesized in liver during an inflammatory challenge[5] and is usually present as a trace element of plasma (0 to 0.6mg/dl). CRP concentration increases in the blood with inflammation or tissue destruction and returns to normal levels with the termination of the process.[5] CRP is an important marker of current disease activity and an elevated serum levels of CRP is a substantiation of active tissue–damaging process.[4] CRP plays an important protective role in recognizing foreign pathogens and initiate their elimination, most likely activating the classic pathway of complement system via C-activation.[6] Several studies have been carried out comparing the CRP levels in assessing the disease activity of various systemic inflammatory disorders and in diagnosing and treatment of systemic infections. Elevated CRP levels have been found in conditions like rheumatoid arthritis, ankylosing spondilitis, wegener's granulomatosis, polyarteritis nodosa, Behçet's syndrome, neonatal septicemia, systemic lupus erythematosus, post operative infection, thromboembolic complications after major surgery, ulcerative colitis, and myocardial infarction.[4]

### 2.1. Historical background

The discovery of CRP was reported in 1930 by Tillet and Francis.[4] They were investigating serological reactions in pneumonia with various extracts of pneumococci and observed that a non-specific somatic polysaccharide fraction, which they designated fraction C, was precipitated by the sera of acutely ill patients. After the crisis the capacity of the patients sera to precipitate C polysaccharide (CPS) rapidly disappeared, and the C-reactive material was not found in sera from normal healthy individuals.

Avery (1941)[4] and his collaborators characterized the C-reactive material as a protein which required calcium ions for its reaction with CPS (C-polysaccharide) and introduced the term "acute phase" to refer to serum from patients acutely ill with infectious disease and containing the C-reactive protein.

Lofstrom (1944)[4] independently described a non-specific capsular-swelling reaction of some strains of pneumococci when mixed with acute-phase sera and subsequently showed that the substance responsible was CRP. He detected CRP in non-infectious as well as infectious conditions; and the acute – phase reaction, in which the concentration of certain plasma proteins increases, is now recognized as a general and non-specific response to most forms of infective and non-infective inflammatory processes, cellular and / or tissue necrosis, and malignant neoplasia semi-quantitative assays for serum CRP were widely used for many years to provide an objective index of the acute-phase response and therefore of disease activity in rheumatological and other conditions. The dramatic changes in CRP concentration which occur in disease suggest that it may have important physiological and / or pathophysiological functions.

### 2.2. Synthesis, structure and binding properties of CRP

CRP is synthesized by hepatocytes and is normally present as a trace constituent of the plasma. The rate of CRP synthesis and secretion increases within hours of an acute injury or the onset of inflammation, probably under the influence of humoral mediators, such as leukocyte endogenous mediators. The serum CRP concentration may reach peak levels of as much as 300 $\mu$g/ml within 24-48 hours.[4] Human CRP is found in plasma as a non-glycosylated cyclic pentamer consisting of identical 21,000 dalton non-covalently bound subunits. In primates and rabbits the concentration of CRP in plasma increases 100 to 1000 fold after tissue injury or inflammation. This increase in CRP concentration exceeds by several orders of magnitude the increase noted for other acute phase serum proteins, such as haptoglobin, fibrinogen, $\alpha$1-antitrypsin, $\alpha$1-antichymotrypsin, $\alpha$1-acid glycoprotein, $C_3$ (the third complement (C) component), and ceruloplasmin. Only the increase in serum amyloid A protein (SAA), after tissue injury is comparable to that for CRP.[7] Immunohistochemical examination of rabbit liver and biosynthetic studies of primary tissue cultures indicate that liver is the major, if not only, site of CRP synthesis. The in vivo rate of catabolism of radiolabeled CRP is rapid and not significantly different in normal animals and in animals stimulated with endotoxin or turpentine, supporting the conclusion that the acute phase increase in serum CRP is due to an increased rate of synthesis. Induction of CRP synthesis may be mediated by blood-borne factors, similar or identical with IL-1, a product of mononuclear phagocytes that induces SAA synthesis.[7]

The induction of CRP synthesis after tissue injury serves as an excellent model for studies of eukaryotic gene control due to the following reasons:[7]

1. The increase in CRP synthesis is quantitatively impressive i.e., the CRP levels in human plasma under "resting" conditions is about 1to 2$\mu$g/ml. Within hours after tissue injury, plasma levels exceeding 100 $\mu$g/ml are observed.
2. The protein has been purified to homogeneity; its complete amino acid sequence is known and some of its biologic activities have been elucidated.
3. CRP cDNA clones have been isolated and are available for studies of the structure and expression of the CRP gene.[7]

### 2.3. Structural biology and host defence function

Czalai A.J., et al (1999)[8] described human CRP as a calcium ($Ca^{2+}$) binding acute phase protein with binding

specificity for phosphocholine. Recent crystallographic and mutagenesis studies have provided a solid understanding of the structural biology of the protein; while experiments using transgenic mice have confirmed its host defense function. The protein is composed of five protomers which are identical in nature and each contains 187 amino acids, with a single intrachain disulfide bond and without carbohydrate modification. It is in a cyclic symmetry and in a disc-like configuration. In each protomer, on one face there is a binding site for phosphocholine which consists of a hydrophobic pocket that accommodates the methyl groups of phosphocholine and two $Ca^{2+}$ ions that ligate the phosphate group. On the converse face is a deep cleft created by segments of the N and C termini and delineated by an alpha–helix.[8] (Figure 1)

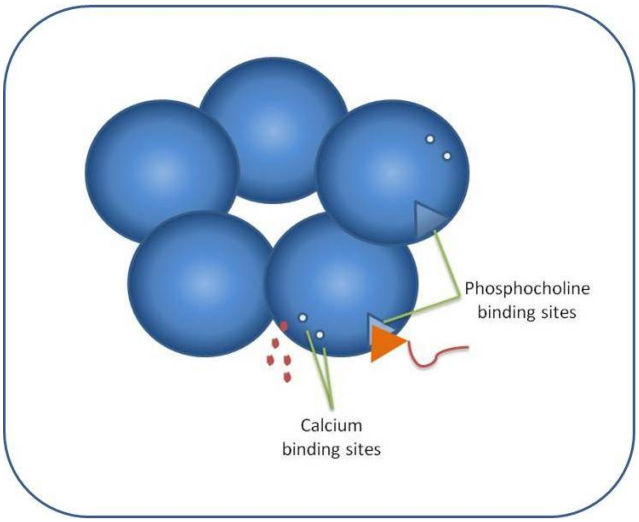


**Fig. 1:** Pentameter structure of CRP

### *2.4. The Physiologic Structure of Human CRP and its Complex with Phosphocholine*

The circulating human CRP concentration rises promptly and widely in a cytokine-mediated response to infection, inflammation and tissue injury. CRP is a classical acute phase reactant, its serum values are usually measured, to detect and screen human diseases. CRP is known to have pathogenic effects and of particular interest is the recent findings of relationship linking increased CRP production and coronary atherothrombotic events.[9] Nonetheless, CRP possibly has vital host defence, scavenging and metabolic functions by virtue of its ability of calcium dependent binding to exogenous and autologous molecules containing phosphocholine (PC) and then activating the classical complement pathway.

### *2.5. Proteins Related to C-Reactive protein and synthesis*

The production of acute phase proteins has been shown to be mediated largely by cytokines and by glucocorticoid hormones to a lesser extent. The majority of the acute-phase proteins are glycoproteins, which take part in an array of roles in the homeostatic feedback to injury. The acute phase proteins have been found to have a vital function in the inhibition of extracellular proteases, blood clotting, fibrinolysis, modulation of immune cell function and the clearance and neutralization of injurious components from the circulation.[10] The serum concentration of a number of those proteins rises promptly during infection and concentrations can swell 2 to 100 fold and stay high during infection.[10] Acute phase proteins can be separated into two groups: Type I and Type II:[10] The acute phase proteins in humans vary considerably in the degree of their surge after inception of injury.

**Type I:** Comprises of C-reactive protein, serum amyloid A, $\alpha$1-acid glycoprotein and complement $C_3$. They are induced and modulated by IL-1 like cytokines which are proinflammatory in nature such as IL-1 and tumor necrosis factor.

**Type II:** Comprises of haptoglobin, fibrinogen, $\alpha$1-antitrypsin, $\alpha$2-macroglobulin and $\alpha$1- antichymotrypsin. They are induced by the IL-6 like cytokines.[10] Oncostatin M and IL-6, which are $\alpha$-helical cytokines; are the most dynamic inducers of acute phase proteins. The IL-6 mediated synthesis of hepatic proteins can also be extensively controlled by other cytokines and by insulin and the counter regulatory hormones like dexamethasone, glucagon, and epinephrine. Generally the induction of type I acute phase proteins occurs by synergistic action of IL-6 kike cytokines with IL-1 like cytokines. This event is speculated to be mainly regulated by IL-6 acting on the hepatocyte and promoting transcriptional activation of the acute-phase protein genes.

The co-mutual interaction between IL-6 and functionally related other inflammatory cytokines, in addition to the hypothalamo-pituitary adrenal axis, serve as a separate part of the intricate mesh of regulatory neuroendocrino immunological interactions. The level of IL-1, tumor necrosis factor and IL-6 in the peripheral blood is diminished by glucocorticosteroids through transcriptional and posttranscriptional routes and protract their impact on the target cells by elevating the receptor expression.[10]

### *2.6. Functional properties of C-Reactive protein*

CRP precipitates soluble ligands and agglutinates particulate ligands. Once complexed, via either its calcium dependent or its polycation binding sites, it becomes a potent activator of the classical complement pathway starting with $C_{1q}$. Complement activation proceeds as

efficiently as with an IgG antibody and leads to fixation of $C_{4b}$ and $C_{3b}$, which can mediate the important complement dependent adherence reactions, and to fixation of the terminal complex $C_{5b}$-$C_9$, causing lysis if the ligand is on a cell surface. Complement split fragments, active in the fluid phase, are also generated. CRP, like antibodies, can thus bind to ligands, opsonise materials for phagocytosis, and initiate cell-damaging and inflammatory reactions.[4,11] Other activities which have been ascribed to CRP include selective binding to T-lymphocytes and modification of some of their functions, suppression of platelet aggregation and activation reactions, and enhancement of the activity and motility of phagocytic cells. CRP complexed in a suitable way may bind to lymphocytes bearing Fc($\gamma$) receptors (including B, T and non-B, non-T cells) both in vivo and in vitro, but the functional significance of this is not known.[4,11]

### *2.7. Regulation of complement activation by CRP*

Complement activation by CRP is constrained to $C_1$, $C_4$ and $C_3$ with little utilization of $C_{5-9}$. CRP binds to microbial polysaccharides and further binds to ligands uncovered on damaged cells. Classical complement pathway activation occurs by binding of CRP to those substrates leading to their uptake by phagocytic cells. Reduction of deposition and generation of $C_{5b-9}$ by the alternative pathway and depositions of $C_{3b}$ and lysis by the lectin pathway occurs by surface bound CRP. These actions of CRP are the consequence of employment of factor H resulting in regulation of $C_{3b}$ on bacteria or erythrocytes. Activation of the complement system by CRP may help curb the inflammatory response by helping in opsonization with minimal production of $C_{5a}$ and $C_{5b-9}$.[12]

### *2.8. Regulation of phagocytic leucocyte activities by CRP*

CRP was classified by Mortensen R.F. and Zhong W. (2000)[13] as an effector of innate host resistance because of its ability to activate the classical complement cascade. It occurs via specific CRP receptors (CRP-R) that of late have been recognized as Fc gamma RI and Fc gamma RII on human phagocytic leucocytes. Recent research is also suggestive of an anti-inflammatory role for CRP as it prevents chemotaxis and the respiratory burst of neutrophils and also modulates endotoxin shock.

However CRP appears to be a multifunctional protein with its ability to exert both effector functions for innate host resistance, as well as existing specific anti-inflammatory effects.[13] CRP activates cells of the monocyte / macrophage lineage, signifying disparity in regulation of these two leucocyte populations at the signalling level.

### *2.9. The role of C-Reactive protein in Vivo: A hypothesis*

The role of CRP in vivo is not known, although under some circumstances it can cause inflammation. CRP may play a part in the pathogenesis of the many inflammatory conditions in which its circulating concentration is elevated. Probably the normal function of CRP is generally beneficial to the organism as a whole, and this may be by acting as an early broad-spectrum recognition mechanism for the products of pathogenic microorganisms. On the other hand increased CRP production is a feature of non-infective as well as infective diseases, and CRP binds to a wide range of autogenous products– lipids and phospholipids, polycations and polyanions – all of which are constituents of cells and likely to be abnormally exposed in or released from damaged tissues. In vivo-binding of CRP to necrotic cells has been described and may contribute to resolution and repair. The main role of CRP is to recognize in the plasma the potentially toxic autogenous materials released from damaged tissues, to bind to them, and thereby to detoxify them and / or facilitate their clearance.[11]

## 3. CRP and Periodontitis

The character of subgingival microbiota in the instigation and development of periodontitis is broadly acknowledged. Periodontal pathogens involve local and systemic inflammatory and immune responses. The local inflammatory response to these pathogens or their products is delineated by infiltration of inflammatory cells including polymorphonuclear neutrophils (PMN), macrophages, lymphocytes, and plasma cells in the periodontal tissues. Cytokines are involved in destruction of both periodontal connective tissue and alveolar bone and can also trigger a systemic acute phase response. Activated macrophages liberate cytokines, and some individuals react to microbial challenge with an unusually elevated release of such inflammatory cytokines as PGE2, IL-1 and TNF-$\alpha$.[14] Recent research has also shown that C-reactive proteins (CRP) serum levels are elevated in patients with periodontal disease.[14]

A number of studies have suggested a relationship between periodontitis and atherosclerosis. There is mounting evidence that chronic infections as well as inflammatory mechanisms play a considerable role in atherogenesis and cardiovascular diseases (CVD). Direct and indirect host-mediated effects of infectious agents could be liable for the relationship between infections in general and periodontitis specifically, and atherosclerosis.[14] However, the mechanism by which CRP plays a role in cardiovascular diseases is not clear. CRP may trigger the complement system and be involved in the development of foam cells in atheromas.[14] Recent studies have suggested that even a moderate increase in CRP levels, such as those

found in patients with periodontal disease, may predict a risk for cardiovascular diseases and atherosclerosis.

## 4. Critical Review of Literature

A recent meta-analysis of studies up to 2007 found only modest evidence that periodontal therapy lowered serum CRP levels with a weighted mean difference of 0.50 mg/L, P<0.00001 (95% CI: 0.08-0.93), based on four studies (D'Aiuto et al 2005, Seinost et al 2005, D'Aiuto et al 2006, Tonetti et al 2007),[15–18] and although all studies showed a favourable effect from treatment, it was concluded that there was no conclusive evidence due to the scarcity of studies.[19]

Overall, serum CRP exhibits a tendency to be lowered in periodontitis patients responding best to treatment, those with highest CRP at baseline, and those without other systemic conditions that can increase systemic CRP. Furthermore, it may take up to 6 months for periodontal treatment to have a significant effect on systemic CRP. There is a possible dose-response relationship between the extent of resolution o periodontal infection and the level of reduction in systemic inflammatory markers.[20]

However, the relationship between periodontal disease and CRP is complex, with no correlation between the severity of periodontal disease and CRP at baseline.[21] Other factors seem to play a significant role in the overall level of CRP, such as the underlying genotype of the patient. The magnitude of serum CRP increase following non-surgical periodontal treatment of systemically healthy subjects with severe periodontitis was significantly influenced by the presence of 34 homozygosity for the +1444T allele of the CRP gene (CRP (+1444C>T) polymorphism) on day 1 (21.10±4.81 mg/L vs 12.37 ± 1.61 mg/L, P = 0.02) and day 7 (4.89 ± 0.74 mg/L vs 3.08 ± 2.00 mg/L, P < 0.01), even after adjusting for cardiovascular risk factors and baseline and peak IL-6 concentrations.[22]

Importantly, the actual magnitude of contribution of periodontitis to systemic CRP in any individual is likely to be variable, influenced by the degree of periodontal inflammation, the concurrence of other systemic conditions and the underlying genetic predisposition to systemic inflammation. Indeed, previous studies have shown that a CRP genotype significantly influences serum CRP at baseline in systemically healthy patients and significantly influences stimulated CRP level in both systemically healthy patients and those with cardiovascular disease, even after accounting for age, sex, BMI, smoking, diabetes, and IL-6 levels.[23]

Several studies have indicated that periodontal therapy is successful in reducing serum CRP in only a subset of patients, usually those with the highest serum CRP[21,24] or inflammatory burden as measured by periodontal parameters[25] at baseline, or those responding best to periodontal treatment.[26] Furthermore, improvements are more likely to be seen in patients without other conditions known to increase CRP, such as smoking, and obesity.[27]

It may be that periodontitis contributes to increased serum CRP only in some, but not all patients,[24] and that periodontal treatment will therefore only be effective in reducing serum CRP in this subset. Similarly the magnitude of increased serum CRP as a result of periodontitis is likely to be variable between individuals. In a recent study, 45 patients were examined and divided into the following three groups: healthy, gingivitis, and chronic periodontitis group based on gingival index, probing pocket depth, and clinical attachment level. Using enzyme-linked immunosorbent assay, gingival crevicular fluid and serum samples were quantified for C-reactive protein and was found that the mean C-reactive protein concentration in gingival crevicular fluid and serum was found to be highest in periodontitis group, and least in healthy group.[28] Patients with elevated serum CRP levels are considered at high risk of future cardiovascular events.[29]

However, despite the improvements in serum CRP levels achieved by periodontal therapy there is currently no evidence that periodontal treatment will reduce the incidence of cardiovascular events. If CRP is a valid therapeutic target, and periodontal therapy an important modifier of serum CRP levels, then one would expect a reduction in serum CRP to reduce the risk of cardiovascular events. The actual importance of periodontal therapy in any given individual is likely to be substantially modified by concurrent inflammatory conditions, smoking, baseline serum CRP levels, and the effectiveness of periodontal therapy.

## 5. Conclusion

CRP has an extensive array of functions that makes it a potential contributor to disease and as a result a compelling therapeutic target. There is certainly a relationship between both periodontal disease and systemic disease with CRP, which is an important one, as highlighted by recent consensus recommendations.[30] Patients with moderate to severe periodontitis ought to be informed that there may be an elevated risk for atherosclerotic CVD related with periodontitis, and that systemic assessment of patients with periodontitis must take account of systemic CRP levels. However, the character of this relationship is ambiguous and periodontal therapy may be only one facet of CRP reduction in periodontitis patients at risk of CVD, but so far there are no means to identify which patients are expected to gain largely from intervention. In addition, there is no concrete evidence that periodontal therapy can in fact decrease cardiovascular events.

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.

## 6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

## 7. Source of Funding

None.

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