Role of C-Reactive Protein in Periodontal Disease – A Review

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ABSTRACT

CRP is an acute-phase reactant that is produced in response to diverse inflammatory stimuli including heat, trauma, infection, and hypoxia. Serum CRP levels provide useful information for the diagnosis, monitoring and therapy of the inflammatory process and associated disease.

CRP is a valuable inflammatory biomarker in various clinical conditions. Elevated levels of serum CRP are also found in subjects with cardiovascular diseases. CRP has been associated with adverse pregnancy outcomes, including preterm delivery, preeclampsia and intrauterine growth restriction. Recommendations by American Heart Association states that patients should be educated about oral health as no one is systemically healthy without possessing good oral health.

Keywords: C-Reactive Protein, Periodontal Disease

INTRODUCTION

One of the major disease affecting the of supporting tissues of the teeth is periodontitis.[1] This condition occurs in response to a predominantly gram-negative bacterial infection originating from dental plaque.[2] Subgingival biofilms present a continual renewing reservoir of lipopolysaccharide (LPS) and gram-negative bacteria with ready access to the periodontal tissues. Gram-negative micro-organism and LPS secreted by them serve as systemic challenges by inducing major vascular responses, including inflammatory cell infiltrate in the vessel walls, vascular fatty degeneration, vascular smooth muscle proliferation, and intravascular coagulation.[3]

Oral infections produce significant increases in systemic inflammatory responses by two ways; (i) bacteria from the oral cavity directly exacerbating the cardiovascular disease or altering systemic risk factors for cardiovascular disease; (ii) the host inflammatory macromolecules circulating in the blood are increased by the chronic periodontal infection foci and translocated bacteria in to the circulation, thus exacerbating the cardiovascular disease.[4]

ACUTE PHASE RESPONSE AND ACUTE PHASE PROTEINS

The acute-phase proteins are defined as proteins whose serum concentration is altered at least 25% in response to inflammation and include proteins of complement, coagulation and fibrinolytic systems: antiproteases; transport protein; inflammatory mediators and others.[5]

The representation of acute phase response takes place as an early and unspecific but highly complex reaction of the animal organism to a variety of injuries i.e. bacterial, viral or parasitic infection, mechanical or thermal trauma, ischemic necrosis or malignant growth.[6]

PLASMA PROTEINS IN THE ACUTE PHASE RESPONSE[7]

Plasma proteins can be broadly classified into two types, based on their plasma concentration.

A. Proteins whose plasma concentration increases with acute phase response:[7]

i. Compliment system: C3, C4, C9, Factor B, C1 inhibitor, C4b-binding protein, and Mannose binding lectin.
ii. Coagulation and fibrinolytic system: Fibrinogen, Plasminogen, Tissue plasminogen activator, Urokinase, Protein S, Vitronectin, Plasminogen-activator inhibitor.
iii. Antiprotease: α 1- Protease inhibitor, pancreatic secretory trypsin inhibitor, Inter-α- trypsin inhibitors.
iv. Transport proteins: Ceruloplasmin, Haptoglobin, Hemopexin.
v. Participants in inflammatory responses: Interleukin-1-receptor antagonist, Secreted phospholipase A2, Granulocyte colony-stimulating factor, Lipopolysaccharide-binding protein.
vi. Others: C-reactive protein, Serum amyloid A, Acid glycoprotein, Fibronectin, Ferritin, Angiotensinogen.

B. Proteins whose plasma concentration decreases with acute phase response:[7]

i. Albumin
ii. Transferrin
iii. Transthyretin
iv. Alpha-fetoprotein
v. Thyroxine-binding globulin
vi. Insulin-like growth factor I
vii. Factor XII

C- REACTIVE PROTEIN

C-reactive protein (CRP) and the acute phase response were first discovered by Tillett and Francis 1930, as precipitation was observed with addition of pneumococcal C-polysaccharide to serum of a patient with acute pneumonia in Oswald Avery's laboratory. This reactive material was also detected by these investigators in serum of patients with acute rheumatic fever, bacterial endocarditis, and staphylococcal osteomyelitis. CRP is an acute-phase protein produced by various inflammatory stimuli

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such as trauma, infection and hypoxia. C-reactive protein levels guide decisions regarding diagnosis, monitoring and therapy for various inflammatory reactions and linked diseases.[8]

CRP is a plasma protein, pentameric in nature, that participates in systemic response to inflammation. Its homologes are formed in vertebrates and many invertibrates. it has extremely high sensitivity but very poor specificity as it is generated in response to many forms of injury. It is a pattern recongnition molecule that binds to specific molecules configuration formed on the surface of pathogen.[9] It is regulated by interleukin-6 (IL- 6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). These in turn cause systemic changes including hepatic release of a range of plasma proteins, activation of complement proteins and various metabolic changes.[10]

Periodontal pathogens affect the immune system and promote local and systemic inflammatory responses. Persistent localized infection may influence the systemic levels of inflammatory mediators. Recent trials have indicated that treatment of periodontal infections, whether by intensive mechanical therapy, drug therapy, or extraction, can significantly lower serum levels of CRP.[9,11]

STRUCTURE AND PHYLOGENY OF CRP

CRP belongs to the pentraxin family exhibits calcium dependent reactivity with widely distributed ligands. Human CRP (M_r 115,135) consists of five identical noncovalently associated 23KDa protomers arranged symmetrically around a central pole.[12]

Each protomer consists of a typical "lectin fold," that is composed of a double-layered β sheet with flattened jellyroll topology. The ligand binding site, composed of loops with two calcium ions bound 4 Å apart by protein side-chains, is located on the concave face. The other face carries a single α helix (Figure 1).[13]

LIGANDS

Volanakis and Kaplan (1971) identified the specific ligand for CRP in the pneumococcal C-(capsular) polysaccharide as phosphocholine, part of the techoic acid of the pneumococcal cell wall. The most well characterized ligand of CRP is phosphocholine (PC). This interaction requires calcium. Studies showed that CRP bind chromatin through interactions with the histones and naked DNA cannot be binded by CRP. CRP binds the histones H1 and H2A most strongly, with considerably less binding to H2B, H3 and H4. The binding of CRP to chromatin has been reported to cause its solubilization in the presence of complement.[12]

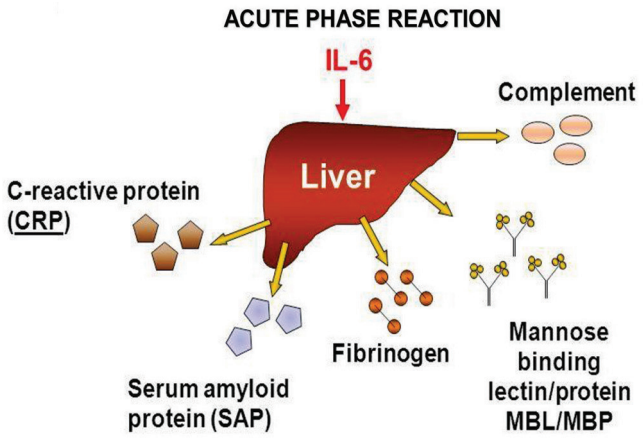

Figure-1: Acute phase reaction

LIGAND BINDING AND BIOLOGICAL ROLE OF CRP

Human CRP binds with highest affinity to phosphocholine residues, but it also binds to a variety of other autologous and extrinsic ligands thus aggregating or precipitating the cellular or molecular structures that bear ligands. Ligands, that are autologous in nature include damaged cell membranes, apoptotic cells, native and modified plasma lipoproteins, small nuclear ribonucleoprotein particles, a number of different phospholipids and other related components. Whereas, the ligands that are extrinsic in nature include many phospholipids, glycans and other constituents of microorganisms, such as capsular and somatic components of bacteria, parasites, fungi, and other plant products. On aggregating or binding to macromolecular ligands, human CRP is identified by C1q, potently activating the classical complement pathway. CRP engages the main adhesion molecule of complement system that is C3, and that terminal membrane attack complex i.e. C5–C9. Bound CRP may produce secondary binding sites for factor H and thereby regulate alternative-pathway amplification and C5 convertases.[13]

Phosphocholine is a structural component of many prokaryotes and is almost universally present in eukaryotes, and a substantial proportion of germline-encoded, highly conserved natural antibodies resemble CRP in specifically recognizing phosphocholine. Thus the capacity to bind these residues may be important for both host defense and handling of autologous constituents including necrotic and apoptotic cells.[13]

PROPERTIES AND FUNCTIONS OF C- REACTIVE PROTEIN

1. CRP when bound to bacteria can activate the complement to enhance opsonisation and clearance of the bacteria prior to the production of specific IgM or IgG. This process of protein coating to enhance phagocytosis is similar to opsonization by antibodies.[14]
2. CRP induces activation of the classical complement pathway and act as scavenger for chromatin fragments.[14]
3. CRP bound to bacteria or cells, can interact with the natural killer cells and with the monocytes and may increase the tumoricidal activity of these cells.[14]
4. CRP modulates macrophage function.[14]
5. CRP induce the synthesis of IL-1α, IL-1β, TNFα and IL-6 in human peripheral blood mononuclear cells and human alveolar macrophages.[14]

C REACTIVE PROTEIN: FROM PENTAMERIC TO MONOMERIC

CRP demonstrates two different conformational forms: the native pentameric (pCRP) and monomeric isoform (mCRP), which possess distinct antigenic, electrophoretic, and biological features.[15]

GENERATION OF mCRP

The two main mechanisms in vivo may be summarized as follows.

Local expression: numerous studies[17] reported the presence of mCRP mRNA in various extrahepatic tissues, including adipocytes, inflammatory cells within atheromatous plaques and smooth muscle cells.

Local dissociation: pCRP undergoes dissociation in to mCRP in membranes of apoptotic cells and activated platelets in atherosclerotic plaques, representing an important interface between innate and adaptive immunity, atherogenesis and thrombosis.[17] In a basic step, mCRP is formed as CRP subunit, though the native pentameric conformation is still retained. $mCRP_m$ is associated with enhanced complement fixation. This molecule rapidly detaches from cell membrane and finally dissociated in solution into mCRPs, the final and most important form of mCRP. This second stage is associated with more powerful atherogenic properties.[18]

REGULATION AND SYNTHESIS OF C- REACTIVE PROTEIN

The predominant region for synthesis of CRP is liver. CRP is synthesized as a response to proinflammatory cytokines and its synthesis is regulated primarily and mainly by IL-6 by promoting de novo synthesis of CRP via up-regulation of C/EBPβ and C/EBPδ, key transcription factors in this process. Along with IL-6, the other inflammtory markers that increases the transcription rate of CRP is IL-1 and TNF.[19]

Serum CRP levels is also closely associated with signaling by proinflammatory cytokines which released by visceral adipose tissue. Indeed, both hypoadiponectinemia and hyperleptinemia, two adipokine disturbances common in subjects with obesity and insulin resistance, have been linked to increased hepatic production of CRP, as well as augmented in situ synthesis of CRP in vascular endothelial cells in hyperleptinemia.[20]

After synthesis of CRP, it's released in circulation, thus serum CRP levels tend to increase significantly 6 to 8 hours after initial stimulation, peaking at 24 to 48 hours, with a half-life of approximately 19 hours.[10] Numerous studies have focused on identifying other extrahepatic sources of CRP production that include, synthesis of CRP in coronary smooth muscle cells in response to inflammatory cytokines. In endothelial cell activation, locally produced serum CRP has a important role.[21]

NORMAL LEVELS OF CRP

Normal levels of CRP being in ng/ml quantities, may increase to hundred of µg/ml within 72hrs after tissue injury. CRP, presents as a trace protein in overtly normal and healthy person, the median value being 0.8 mg/l, with an interquartile range of 0.3 to 1.7 mg/l. CRP plays a key role in the host's defense against infection.[10]

During a major CRP response elicited by e.g. bacterial infection, up to a 10,000-fold increase in circulating CRP levels due to de novo hepatic synthesis can be seen. The rise is generally proportional to the degree of tissue damage.[2]

CONDITIONS OR DISEASES WHERE C-REACTIVE PROTEIN IS ELEVATED[22]

A. Acute inflammation:

- Bacterial infection
- Pneumococcal pneumonia
- Acute rheumatic fever
- Bacterial endocarditis
- Staphylococcal osteomyelitis

B. Chronic inflammation:

- Systemic lupus erythematosis
- Rheumatic arthritis
- Reiter's syndrome, psoriatic arthriopathy, arthritis following jejuno-ileal bypass
- Polyarteritis nodosa, disseminated systemic vasculitis, cutaneous vasculitis
- Polymyalgia rheumatica
- Crohn's disease
- Ulcerative colitis
- Dermomyositis
- Osteoarthritis
- Neoplastic diseases
- Smokers
- Obesity
- Diabetes

C. Tissue injury:

- Tissue injury and surgery
- Acute myocardial ischemia

CRP AND CHRONIC PERIODONTITIS

Periodontal diseases involve chronic inflammatory processes resulting from interaction of selected gram negative bacterial species with the host defense in disease susceptible individuals. The host responds to the microbial challenge, with a high inflammatory response with increased levels of cytokines like IL-1, IL-6, TNF-α. These mediators promote activation of the acute phase reactants resulting in elevated serum levels of CRP, α1-acid glycoprotein, ceruloplasmin, serum amyloid A.[23]

CRP AND AGGRESSIVE PERIODONTITIS

Aggressive periodontitis (AgP) generally affects systemically healthy individuals less than 30 years old, although patients may be older. Aggressive periodontitis may be universally distinguished from chronic periodontitis by the age of onset, the rapid rate of disease progression, the nature and composition of the associated subgingival microflora, alterations in the systemic host immune response, and a familial aggregation of diseased individuals. There is little information on the relationship between AgP and systemic conditions.[24]

Trang N. Salzberg et al[25] 2006 demonstrated that patients with AgP demonstrate elevated serum concentrations of CRP. It was reported that periodontitis had an impact on systemic markers of inflammation in a relatively young subject group. It was also noted that patients did not require generalized severe disease to demonstrate elevated CRP concentrations.

ROLE OF C-REACTIVE PROTEIN AND PERIODONTAL DISEASE IN SYSTEMIC HEALTH

There is an abundance of evidence that periodontitis, especially severe periodontitis in early life, significantly enhances risk for certain systemic diseases like coronary heart disease, risk of death from heart attack, atherosclerosis and stroke, and preterm labor and low birth weight infants.

Periodontitis may relate with susceptibility to systemic diseases in 3 ways[26]

SHARED RISK FACTORS

Factors that place individuals at high risk for periodontitis may also place them at high risk for systemic diseases such as cardiovascular disease. Among the environmental risk factors and indicators shared by periodontitis and systemic diseases, such as cardiovascular disease, are tobacco smoking, stress, aging, race/ethnicity, male gender, and history of Periodontitis. It seems likely that the polymorphisms in the IL-lß and TNF-α gene family are likely to be associated with cardiovascular disease as well as with periodontitis.[26]

SUBGINGIVAL BIOFILMS

A reservoir of Gram-Negative bacteria in subgingival biofilms constitutes an enormous and continuing bacterial load. A sample harvested from one pocket with a single pass of curette may yield up to 10^7 to 10^8 bacteria. All major periodontal pathogens are Gram-negative and they continuously shed vesicles rich in LPS. Systemic challenge with Gram-negative bacteria or LPS induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration, and intravascular coagulation.[26]

THE PERIODONTIUM

Proinflammatory cytokines, TNF-α, IL-lß, and IFN-γ, as well as PGE2, reach high concentrations in the tissues in periodontitis. Proinflammatory cytokines and prostaglandins accumulate in the tissues in active severe periodontitis at extraordinary levels as high as 1 to 3 µmol/L.[27] Therefore periodontitis affected tissues may serve as a reservoir of cytokines and prostaglandins which can enter in the circulation and induce systemic effects.[26]

ASSOCIATION BETWEEN CRP AND PERIODONTAL DISEASE WITH CARDIOVASCULAR DISEASE AND ATHEROSCLEROSIS

A recent joint consensus conference of the American Heart Association (AHA) and the Center for Diseases Control (CDC) identified three different risk categories based on serum CRP levels. Based on the observations, subjects with CRP concentrations less than 1 mg/l are considered to be at low risk, whereas those with concentrations in the 1–3 mg/l range are assigned a medium risk level and those with more than 3 mg/l in serum CRP are considered to be at high risk for future cardiovascular disease and events.[28]

CRP stimulates leucocyte–endothelium interactions via the modulation of endothelium-derived molecules and chemokines in various cultured endothelium cells and decreases endothelial nitric oxide synthase (eNOS) mRNA protein as well as its bioactivity. More recently, the endothelial glycocalyx, get damaged by CRP. This increases the sensitivity of endothelium for pro-atherogenic insults. Thus C-reactive protein is called a pro-atherogenic biomarker for the entire range of cardiovascular disease, ranging from fatty streak formation to clinical events.[29]

CRP could induce atherosclerosis in various ways: a) oxygen radicals, and b) adhesion molecules.[19]

a) Oxygen Radicals

CRP activates complement platelets and induces expression of cytokines. Activated complement platelet-activating factor and cytokines stimulate leukocytes to release oxygen radicals. CRP also enhances the generation of oxygen free radicals by monocytes and neutrophils directly.

b) Adhesion Molecules

Cell adhesion molecules are involved in atherogenesis. CRP induces expression of adhesion molecules in the endothelial cells along with the generation of MCP-1 oxygen radicals, that would increases the expression of adhesion molecules. Expression of adhesion molecules by arterial endothelial cells is modulated by free radicals and oxidative stress and suppressed by antioxidants.

ASSOCIATION BETWEEN CRP AND PERIODONTAL DISEASE WITH DIABETES

Periodontal disease is considered as the sixth greatest complication of diabetes (Löe, 1993).[30] Prolonged exposure to hyperglycemic condition results in decreased fibroblast proliferation, decreased collagen synthesis, enhanced collagen glycosylation and cross linkage resulting in defective collagen metabolism and normal collagen is replaced with highly polymerized and cross linked collagen. Vascular basement membrane thickening and narrowing of the lumina of the capillaries and pre-capillary arterioles result in reduced oxygen consumption and oxidation of glucose. These vascular changes lead to deficient nutrients supply to the surrounding tissues and also hindered elimination of waste products, which deteriorate the gingival health, specially in diabetic patients.[30] Individuals with poorly controlled diabetes present with increased gingival bleeding, increased probing depths, increased attachment loss, increased alveolar bone loss, increased tooth loss, sessile or pedunculated gingival polyps, enlarged gingiva and tendency towards multiple abscess formation.[31]

ASSOCIATION BETWEEN CRP AND PERIODONTAL DISEASE WITH PRETERM LOW BIRTH WEIGHT

CRP has been associated with adverse pregnancy outcomes, including preterm delivery, preterm low birth weight, preeclampsia, and intrauterine growth restriction.[14] Preterm infants are at elevated risk for death, neuro-development disabilities, cognitive impairment, and behavioral disorders. Therefore, CRP might be a plausible mediator of the association between periodontitis and adverse pregnancy outcomes. Elevated CRP could amplify the inflammatory response through complement activation, tissue damage, and induction of inflammatory cytokines in the monocytes and therefore may mediate the relationship between periodontitis and adverse pregnancy outcomes.[32]

Potential mechanisms which explain the relationship between periodontal disease (PD) and preterm low birth weight (PTLBW) infant delivery was that periodontal infection serves as a chronic reservoir of lipopolysaccharide (LPS) which are responsible for the production of interleukin-1beta (1L-1β), prostaglandin E2 (PGE2) and tumour necrosis factor alpha (TNFα) and CRP that are in turn associated with preterm parturition and fetotoxicity.[14]

EFFECT OF PERIODONTAL THERAPY ON SERUM CRP LEVEL

Recent trials have indicated that treatment of periodontal

infections, whether by intensive mechanical therapy, drug therapy or extraction, can significantly lower serum levels of CRP. D'Aiuto et al.[33] conducted a study to observed a median decrease in serum CRP level after completion of periodontal therapy and found that control of periodontal disease can be obseved with non-surgical periodontal therapy, along with decrease in the serum mediators and markers of acute phase response. Since CRP is an acute phase protein, once the cause for elevation of CRP is eliminated, CRP levels fall drastically.

Goyal L et al.[34] and Noack B et al.[35] also shown a positive association between chronic periodontal infections and elevated CRP levels. Following the periodontal treatment, as bacterial load is significantly reduced; antibody titers and avidity to the specific pathogens are improved. Due to these changes, local inflammation is progressively reduced, and clinical parameters like probing pocket depths, bleeding on probing are significantly improved.[36]

With contrast to the above study, Ide et al.[37] observed in their study that the circulating acute phase protein levels reduced with periodontal therapy, but failed to observe a reduction in serum CRP levels along with non-surgical periodontal therapy. Reason behind, why CRP remains elevated after nonsurgical periodontal therapy, is that SRP (scaling and root planing), alone is insufficient to control or prevent periodontal infection in all types of periodontitis patients and elimination of all the pathogens from deep inaccessible pockets is not possible by only nonsurgical intervention because removal of deposits and pathogens from these inaccessible area may require surgical intervention and/or the use of antimicrobial drug treatment.

EVIDENCE THAT PERIODONTAL TREATMENT IMPROVES BIOMARKERS AND CVD OUTCOMES

As most of the chronic diseases, periodontitis shares most of its putative and established risk factors with CVD, including age, gender, socioeconomic status, diabetes, obesity, smoking and hypertension.[38] Periodontal therapy, remove which primarily involves the mechanical disruption of the dental biofilm of the diseased dentition. The main consistent finding after periodontal therapy was a reduction of serum levels of CRP (stable measure of systemic inflammation) and an improvement of measures of endothelial function (which represents a surrogate marker of CVD).[39]

Indeed, intensive nonsurgical periodontal therapy produced an acute inflammatory response that resolved within 1 month and a marked reduction of blood markers of inflammation was observed during the subsequent 6 months.[11] Moreover, periodontal treatment often comprises surgical corrective sessions following the non surgical phase of treatment. It is plausible to believe that a localized periodontal surgery including mucoperiosteal flap elevation and possibly bone surgery might also act as a sharp inflammatory stimulus, thus producing a sustained host response.[40]

CONCLUSION

CRP is a important biomarker of inflammation in various clinical stages. However, being non-specific, its use is limited. There are evidence that periodontitis elicits a mild acute-phase response with the elevation of serum CRP levels. The elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions and potentially increasing the risk for cardiovascular events. Elevated levels of serum CRP are also found in subjects with cardiovascular diseases. CRP has been associated with adverse pregnancy outcomes, including preterm delivery, preeclampsia and intrauterine growth restriction. Recommendations by American Heart Association states that patients should be educated about oral health as no one is systemically healthy without possessing good oral health.

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