

## Review Article

## C-Reactive Protein and its applications in Oral and Maxillofacial Surgery- An Overview

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**Abstract:** C-reactive protein (CRP) was discovered by Tillet and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C polysaccharide of pneumococcus. C-reactive protein (CRP) is an acute phase protein which reflects a measure of the acute phase response. CRP, which is present in only small amounts in healthy individuals, is involved in several processes of the unspecific immunologic defense. The serum levels of CRP raises with infection making it a positive acute phase reactant. This review mainly highlights the role of CRP in the field of Oral and maxillofacial surgery, It provides a knowledge based framework for interpretation and analysis of clinical observations of CRP in relation to infection and other pathologies in orofacial region.

**Keywords:** C-reactive protein(CRP), inflammation.

### INTRODUCTION

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.

The conventional measures to estimate infections such as evaluation of WBC count and ESR are valuable in determining state of patient at testing time. However, the predictability of these is limited [1]. A better knowledge of the inflammatory cascade has given new insights and provided several mediators that in conjunction with the clinical manifestations, can be useful as markers of infection [2]. One such mediator is C-reactive protein (CRP) and is probably the most widely used marker.

C-reactive protein (CRP) is a ring-shaped, pentameric protein found in blood plasma. It is an acute phase protein which was discovered in 1930, in pneumococcal pneumonia patients [1]. C-reactive protein (CRP) is a well established biochemical marker

of inflammation, and has also been shown to be involved in several functions of immune system [3, 4].

In normal healthy individuals, CRP is present only in small amounts and is involved in the process of innate immune system with functions such as activation of complement system, antigen clearance and regulation of phagocytosis by activation of neutrophils [1, 5, 6]. In severe infections or inflammatory reactions, striking rise in serum concentration of CRP is seen up to 1,000-fold within few hours of clinical symptoms [6].

The serum levels of CRP raises with infection making it a positive acute phase reactant with a very short half-life of 5–7 h [1, 6]. Thus, advantage of having short half lives makes serum CRP levels as sensitive indicators of infection [5, 6].

Fascial space infections of odontogenic origin can lead to life threatening situations, owing to the anatomical connectivity of potential spaces to one another. Potentially fatal complications may become inevitable making constant observation and monitoring of such patients a necessity.

Serial CRP measurement can be used as a tool for early diagnosis of clinical infections, to monitor the

effects of treatment, outcome, and early detection of relapse of the disease, and hence can be a useful aid in determining progression of a disease [2]. Several studies have shown that CRP could be useful in infection diagnosis [7], as well as in monitoring the response to antibiotic therapy [8, 9].

### C- Reactive protein

The discovery of C- Reactive protein(CRP) in 1930 is attributed to Tillet and Francis, it is so named because it reacts with the somatic C polysaccharide of *Streptococcus pneumonia* [10]. CRP was initially considered to be a pathogenic secretion, as its levels were elevated in people with a variety of illnesses including cancer, however, the discovery that it is synthesised in the liver demonstrated it to be a native protein.

CRP is an acute phase reactant, a sensitive marker of inflammation and tissue damage [11]. It has a short half life. The normal range for CRP is < 2 mg/L in normal healthy individuals, however with illnesses such as rheumatoid arthritis or sepsis, its concentrations can increase up to 300 mg/L. CRP belongs to the pentraxin family of ligand-binding and calcium-dependent plasma proteins. Increase in CRP levels is associated with a broad range of infections, immune-mediated inflammatory diseases, trauma, and malignancies. The levels of CRP may increase up to 50 to 100 mg/L in case of acute infections. However it is of significance that, under all physiologic and pathologic conditions, Plasma half life of CRP remains constant. The plasma levels of CRP rapidly rise and fall after introduction and cessation of stimulus respectively.

### SYNTHESIS AND METABOLISM

The synthesis of CRP primarily occurs in hepatocytes, in response to cytokines such as interleukin 6. In some models, induction of CRP requires both interleukin 6 and either interleukin-1 or TNF- $\alpha$  [12]. IL 6- dependent hepatic biosynthesis is the main source for CRP. Glucocorticoids enhance the stimulatory effects of cytokines on the production of acute phase proteins [13]. Insulin, on the other hand, decreases their effects on the production of some acute phase proteins [14]. Efficiency of secretion of CRP is enhanced significantly during acute-phase response.

Following an acute stimulus the plasma concentration of CRP rises within 6 hrs, and may double every 8 hrs thereafter, reaching a peak at around 50 hrs [15]. Similarly on cessation of stimulus, the plasma CRP concentration declines rapidly in exponential manner, the half life of the molecule in circulation being 5-7hrs [16].

### CONDITIONS OR DISEASE STATES WHERE C- REACTIVE PROTEIN IS ELEVATED [17]

#### A. Acute inflammation:

- Bacterial infection

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

#### B. Chronic inflammation:

- Systemic lupus erythematosus
- Rheumatic arthritis
- Reiter's syndrome, psoriatic arthropathy, 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

### Regulation of CRP

The gene for CRP is located on short arm of chromosome 1, and about 35 to 40% of the variability of baseline CRP concentrations among different healthy individuals is mediated by genetic polymorphisms in the CRP gene [18,19]. Apart from fulminant liver failure, there are no other pathologies and very few drugs (e.g. statins, niacin, fibrates) that will reduce the CRP concentrations, unless they also affect the underlying acute-phase stimulus such as antibiotics for infection or corticosteroids for an inflammatory disease [20]. On the other hand, obesity, smoking, diabetes mellitus, lack of exercise, pregnancy and hormonal therapy (estrogens or progesterones) are associated with a mildly elevated CRP concentration.

Extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes [21, 22]. The mechanisms regulating synthesis at these sites are unknown, and it is unlikely that they substantially influence plasma levels of CRP.

CRP concentration does not have any diurnal variations and is unaffected by diet, therefore indicating it can be estimated using a non-fasting blood sample.

### Functions of CRP

An important 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.

Phosphocholine is found in a number of bacterial species and is a constituent of sphingomyelin and phosphatidylcholine in eukaryotic membranes.

However, the head groups of these phospholipids are inaccessible to CRP in normal cells, so that CRP can bind to these molecules only in damaged and apoptotic cells [23-25]. In addition to phosphocholine, CRP can bind to a wide variety of other ligands, including phosphoethanolamine, chromatin, histones, fibronectin, small nuclear ribonucleoproteins, laminin, and polycations (11, 19). Ligand-bound or aggregated CRP efficiently activates the classical complement pathway through direct interaction with C1q. There is evidence that CRP can interact with the immunoglobulin receptors Fc<sub>RI</sub> and Fc<sub>RII</sub> as well, eliciting a response from phagocytic cells. The ability to recognize pathogens with subsequent recruitment and activation of complement, as well as effects on phagocytic cells, constitute important components of the first line of host defense.

### **Role of C-reactive protein in Oral and Maxillofacial Surgery**

Infections or other causes of tissue injury result in a complex set of systemic and metabolic reactions, which presents as 'The acute phase response'. Apart from other physiological, metabolic, and biochemical changes, the acute phase response is associated with alterations in the hepatic synthesis and serum levels of some proteins. Thus, while the levels of positive acute phase proteins like CRP, complement 3, serum amyloid A, alpha-1, and glycoprotein, etc., increase due to stimulation of hepatic synthesis, visceral transport proteins (negative acute phase proteins) like albumin, transferrin, thyroxin binding prealbumin (TBPA), and retinol binding proteins (RBP), etc., decrease due to depression of their hepatic production [26, 27].

In healthy individuals, CRP, is present in only small amounts and is involved in several processes of the non specific immunologic defense. A rapid and significant rise in the serum concentration of CRP is often seen in severe infections or inflammatory reactions. This suggests to the possibility, that rise of CRP levels may serve as a definitive aid in the early diagnosis of septicemia.

Patients with odontogenic fascial space infections are at increased risk of complications like upper airway obstruction, descending mediastinitis, thrombosis of jugular vein, venous septic emboli, rupture of carotid artery, adult respiratory distress syndrome, pericarditis, septic shock and disseminated intra-vascular coagulopathy, therefore, mandating vigilant scrutiny and monitoring of such patients. The CRP concentration is a good marker of infection diagnosis, and that it performs better than body temperature and White cell count(WCC). The combination of CRP and temperature measurements further increases the specificity for the diagnosis of infection [28]. Thus, based on these properties of the markers attempt has been made to use them in patients

with fascial space infections for early diagnosis and to guide antibiotic therapy.

Sabel KG and Wadsworth C [6] conducted study on the early diagnosis of acute infections and emphasized that CRP can be used for early stage detection of infection. They also concluded that antibiotics usually can be withdrawn if the clinical condition of the patient was satisfactory, and if the CRP levels not above normal limits.

Franz *et al.* described that combination of positive IL-8 and/or CRP >10 mg/l in neonates with suspected bacterial infection is feasible (with 96% sensitivity) and cost effective in reducing antibiotic therapy [29]. Pourcyrus *et al.* suggested that it would be appropriate to discontinue antibiotic therapy if three serial CRP measurements were normal [30].

Sharma A *et al.*, [31] In a prospective study concluded that CRP can be a useful marker for determining severity of infection, to assess the efficacy of treatment regime and also determine the duration of hospital stay for patients with fascial space infections of odontogenic origin. It was also concluded that prealbumin has an extra advantage of being a sensitive marker for nutritional status of the patient.

It was Rudolf Virchow In 1863, who postulated the induction hypothesis. It stated that cancer originated at site of chronic inflammation. Chronic inflammation is associated with the risk of cancer. For instance, human immunodeficiency virus, viral hepatitis B, and human papilloma virus are well known for their association with an increased risk of cancer .

Khandavilli SD *et al.*, [32] in a prospective study evaluated if elevated preoperative levels of serum CRP could predict the prognosis of patients treated with primary surgery for oral squamous cell carcinoma. It was concluded that that a raised preoperative CRP was associated with worse overall survival. Tumour size and stage when combined with CRP levels increases the predictive power of this indicator.

Kruse *et al.*, [33] in a prospective study investigated the significance of preoperative C-reactive protein (CRP) levels as a parameter for development of lymph node metastases or recurrence. It was concluded that there does not appear to be a positive association between preoperative CRP levels and development of recurrence or metastases.

It is still unclear whether CRP levels are elevated before the biological onset of cancer or if an elevated CRP level is also a risk factor for the development of cancer. Some authors have observed an association between elevated serum CRP levels in some cancers, like colorectal [34,35] and lung. On the other hand, some researchers doubt that CRP can be regarded

as a prognostic marker [36]. However, raised CRP concentrations have been demonstrated to be an indicator of a poorer prognosis for squamous cell carcinoma (SCC) in patients with esophageal cancer [37, 38].

## CONCLUSION

CRP is an acute phase protein and biomarker of infection. It is very useful in the diagnosis of infection as well as in the assessment of its response to antibiotic therapy. The duration of antibiotic usage, need for intensive care, and length of hospital stay becomes more rationale if these measurements are incorporated in clinical decisions. CRP is a nonspecific marker of inflammation, and additional studies of specific cytokines that regulate acute-phase response are necessary to elucidate the mechanisms by which inflammation influences the risk of cancer.

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