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C-Reactive Protein

Moneer Faraj and Nihaya Salem

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1. Introduction

C- reactive protein (CRP) was so named because it was first discovered as a substance in the serum of patients with acute inflammation that reacted with the C- (capsular) polysaccharide of pneumococcus [1].

Discovered by *Tillett* and *Francis* in 1930[2], it was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer [3], however, the discovery of hepatic synthesis demonstrated that it is a native protein [4][5][6][7].

CRP is phylogenetically a highly conserved plasma protein, with homolog in vertebrates and many invertebrates that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a character that has long been employed for clinical purposes. CRP is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. Its rapid increase in synthesis within hours after tissue injury or infection suggests that it contributes to host defense and that it is part of the innate immune response [8].

2. Molecular structure of CRP

Entrez Gene summary for CRP the protein encoded by this gene belongs to the pentaxin family. It is involved in several host defense related functions based on its ability to recognize foreign pathogens and damaged cells of the host and to initiate their elimination by interacting with humoral and cellular effector systems in the blood. Consequently, the level of this protein in plasma increases greatly during acute phase response to tissue injury, infection, or other inflammatory stimuli[12]. It is induced by IL1/interleukin-1 and IL6/interleukin-6

UniProtKB/Swiss-Prot: CRP_HUMAN, P02741

Size: 224 amino acids; 25039 Da

Cofactor: Binds 2 calcium ions per subunit

Subunit: Homopentamer. Pentaxin (or pentraxin) have a discoid arrangement of 5 non-covalently bound subunits

Subcellular location: Secreted

Mass spectrometry: Mass=23028; Method=MALDI; Range=19-224; Source=Ref.15;

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Function: Displays several functions associated with host defense it promotes agglutination, bacterial capsular swelling, phagocytosis (CRP initiates the activation of the complement cascade and binds Fc gamma RI (CD64) and Fc gamma RIIA (CD32a) on phagocytes to activate phagocytic responses) and complement fixation through its calcium-dependent binding to phosphorylcholine. It can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells [13].

The CRP Entrez gene cytogenetic band located on the first chromosome: 1q21-q23

Ensemble cytogenetic band: 1q23.2

HGNC cytogenetic band: 1q21-q23.

CRP is a 224-residue protein with a monomer molar mass of 25106 Da. The protein is an annular pentameric disc in shape [14][15].

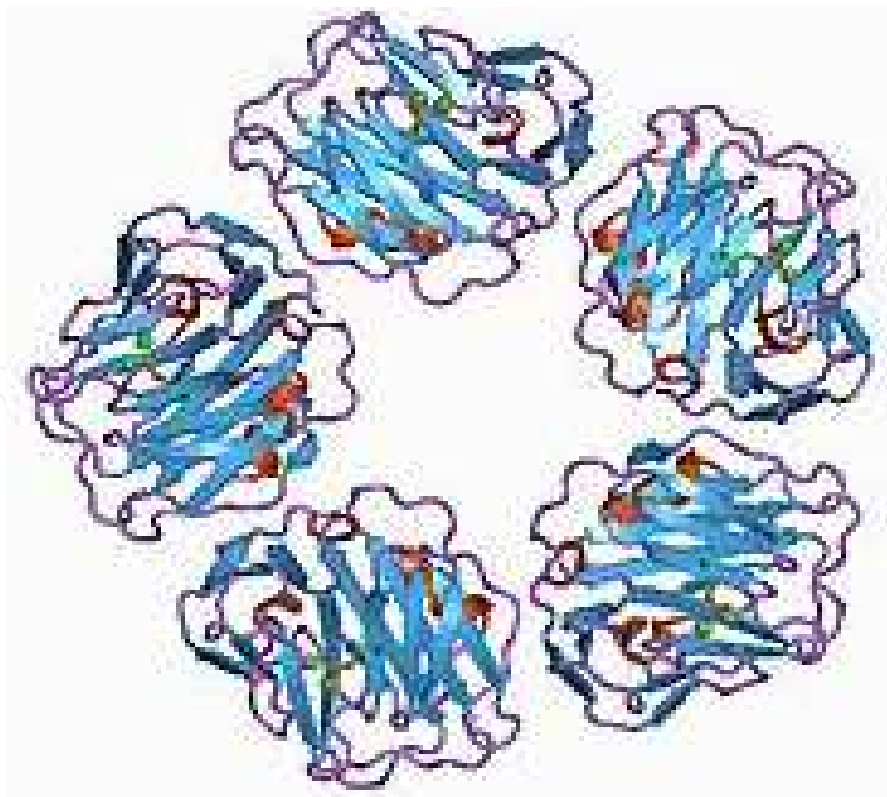


Figure 1. Pentameric structure of CRP viewed down the 5-fold symmetry axis. The effector face of the molecule is on the top, while the calcium- and PCh-binding sites are on the opposite 'recognition' face [1]

3. Methodology and clinical applications

CRP is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production

Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments.

Blood, usually collected in a serum-separating tube, is analyzed in a medical laboratory or at the point of care. Various analytical methods are available for CRP determination, such as ELISA (Enzyme-linked immunosorbent assay). ELISA can perform other forms of ligand binding assays instead of strictly "immuno" assays, though the name carried the original "immuno" because of the common use and history of development of this method. The technique essentially requires any ligating reagent that can be immobilized on the solid phase along with a detection reagent that will bind specifically and use an enzyme to generate a signal that can be properly quantified. In between the washes only the ligand and its specific binding counterparts remain specifically bound or "immunosorbed" by antigen-antibody interactions to the solid phase, while the nonspecific or unbound components are washed away. Unlike other spectrophotometric wet lab assay formats where the same reaction well (e.g. a cuvette) can be reused after washing, the ELISA plates have the reaction products immunosorbed on the solid phase which is part of the plate and thus are not easily reusable [19], immunoturbidimetry (Immunoturbidimetric Method. This reagent is intended for the in vitro quantitative determination of CRP concentration in serum or plasma on automated clinical chemistry analyzers) [20], rapid immunodiffusion (is a diagnostic test which involves diffusion through a substance such as agar. Two commonly known forms are Ouchterlony double immunodiffusion and radial immunodiffusion) [21], and visual agglutination [22][23] (quantitative slide method and semi quantitative diluted method)

There are two different tests for CRP. The standard test measures a much wider range of CRP levels but is less sensitive in the lower ranges. The high-sensitivity CRP (hs-CRP) test can more accurately detect lower concentrations of the protein (it is more sensitive), which makes it more useful than the CRP test in predicting a *healthy* person's risk for cardiovascular disease [24].

(hs-CRP) test measures using laser nephelometry. The test gives results in 25 minutes with sensitivity down to 0.04 mg/L [26]. hs-CRP usually is ordered as one of several tests in a cardiovascular risk profile, often along with tests for cholesterol and triglycerides. Some experts say that the best way to predict risk is to combine a good marker for inflammation, like hs-CRP, along with the lipid profile [27].

CRP is one of several proteins that are often referred to as acute phase reactants and is used to monitor changes in inflammation associated with many infectious and autoimmune diseases [28].

We should be healthy at the time of the sample collection, without any recent illnesses, infections, inflammation, or other tissue injuries. Since the hs-CRP and CRP tests measure the same molecule, people with chronic inflammation, such as those with arthritis, should

not have hs-CRP levels measured. Their CRP levels will be very high due to the arthritis often too high to be measured or meaningful using the hs-CRP test [29].

Normal concentration in healthy human serum is usually lower than 4.9 mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, active inflammation, bacterial infection, severe bacterial infections, tissue injury (postoperation), trauma and burns.

CRP is a more sensitive and accurate reflection of the acute phase response than the ESR[30] another blood test often ordered in conjunction with CRP (erythrocyte sedimentation rate or sed rate known as ESR) both CRP and ESR give similar information about non-specific inflammation.

CRP appears and disappears more quickly than changes in ESR. Therefore, your CRP level may drop to normal following successful treatment [31], whereas ESR may remain elevated for a longer period.

The half-life of CRP is constant. Therefore, CRP level is mainly determined by the rate of production (and hence the severity of the precipitating cause). In the first 24 h, ESR may be normal and CRP elevated [32]. CRP and ESR have been used to diagnose postoperative infections after spinal surgery. We did a prospective study in Baghdad [33]. The aim of the study was to determine the duration of the physiological rise in the serum CRP without the development of infection following lumbar laminectomy. Forty patients (19 women, 21 men) mean age 44.2, age range 27-60 yrs were included in the study.

All patients underwent laminectomy. Additional clinical data relevant to the study included body temperature, duration of surgery & blood transfusion.

The indication of surgery established several days to weeks before the surgical procedure. Pathologic findings included:

- 27 lumbar spinal canal stenosis
- 2 reoperation for stenosis
- 1 spinal canal hydrated cyst
- 10 lumbar disc herniation.

Preoperatively, a single – shot antibiotic prophylaxis with cefotaxime 1 gram was given to all cases. All patients were operated under general anesthesia. Duration of surgery varied from 60-180 min. (average 80.5 min.). Before surgery no patient received steroids. Blood samples were taken on the day of surgery and on each consecutive day after surgery for 10 days.

The parameters taken were CRP, ESR, Total white blood cell count. On 1st post operative day the CRP started to increase in 34 patients (range 12- 96, average 27). In the 2nd and 3rd post operative day all the patients had high CRP with an average of 39 & 38 respectively. This increase was highly significant ($P < 0.001$). A dramatic decline in the CRP level was noticed to start in the 5th post operative day (average 27), then gradual

reduction was noticed until a normal ranges at day 9th post operatively (average 4.8) as shown in figure -2.

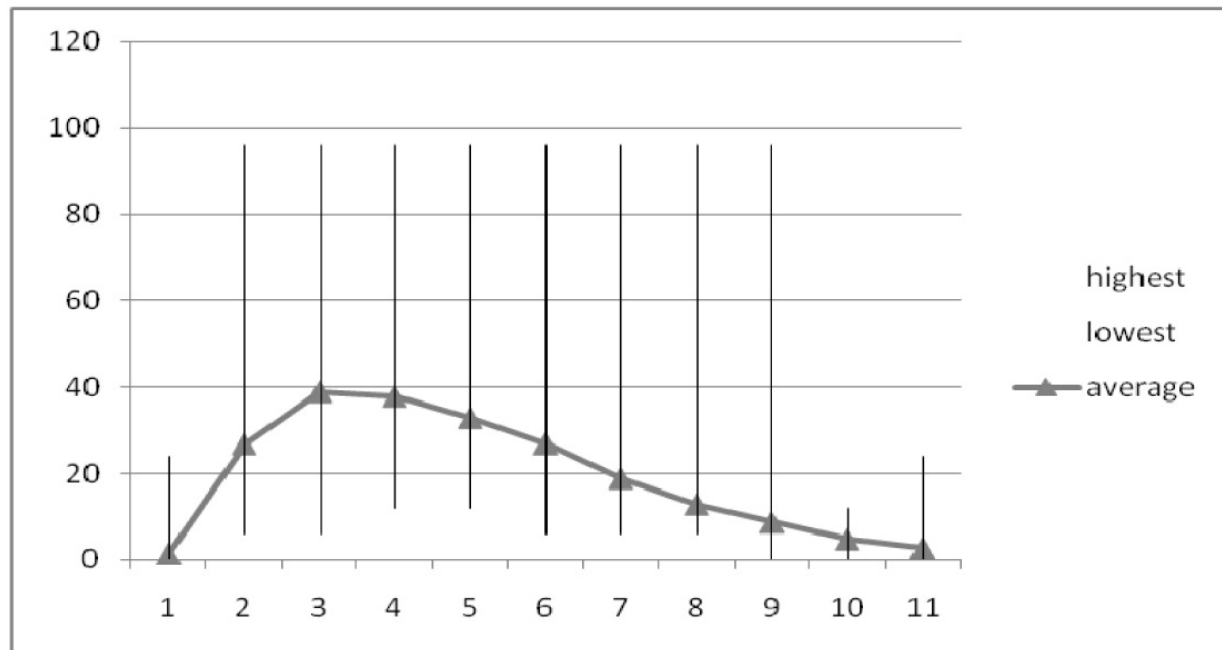


Figure 2. The CRP level of all patients from day one which is here is the operation day to day 11, the average values plotted together [34]

Increased CRP values during the first 5 post-operative days did not indicate that an infection is ongoing. An infection should be considered with prolonged CRP elevation (more than 5 days) as noticed is one of our patients or when a second rise occurs. Although we did not use steroids or non steroidal anti inflammatory drugs post operatively, but these medications seems to effect on the level of CRP. *Munoz m. et al* [35] revealed that pre-operative treatment with *naproxane* and *famotidine* was well tolerated and reduced the acute phase response after instrumented spinal surgery. In this study we could not find any correlation of the raised CRP level they age , sex , ESR , WBC count , body temperature duration of surgery blood transfusion[36] with exception of *Orrego LM et al*[37] who noticed that more complex surgical procedure had higher CRP level and explained due to the amount of tissue trauma. *Sugimorik et al* [38] showed no correlation between the high CRP concentration and the level, type of lumbar disc herneation or the preoperative clinical data. *Thelander et al* [39] noticed that peak levels were not related to bleeding, transfusion, operation time, administered drugs, age or sex However, it has not been demonstrated if resolution of the signs and symptoms of postoperative spinal wound infections in patients who are being treated with intravenous antibiotics correlates with these markers. CRP is a sensitive marker of pneumonia. A persistently high or rising CRP level suggests antibiotic treatment failure or the development of an infective complication. These results suggest that CRP, rather than $\text{TNF-}\alpha$ or IL-6, may have a role as a clinical marker in pneumonia [40]. Most recently CRP has made headlines as it relates to heart disease an association between

minor CRP elevation and future major cardiovascular events has been recognized, leading to the recommendation by the Centers for Disease Control and the American Heart Association that patients at intermediate risk of coronary heart disease might benefit from measurement of CRP. It is yet to be determined if CRP serves as a marker of heart disease or whether it plays apart in causing atherosclerotic disease (hardening the arteries)[41]. CRP has been shown to have a close relationship with vascular diseases. CRP is a powerful independent risk factor for atherosclerosis and atherosclerosis-related diseases (Lusic et al., 2006 [42]; Verma et al., 2006)[43]. Elevated high-sensitivity CRP (hsCRP) has been measured in the blood of patients with essential hypertension (Li et al., 2005) [44] or abdominal aortic aneurysms (Vainas et al., 2003 [45]; Tambyraja et al., 2007 [46]) with enhanced systemic or local arterial strain. Elevated serum hsCRP independently correlates with blood pressure (Sung et al., 2003)[47], arterial stiffness (Kim et al., 2007) [48], and aneurysmal size (Vainas et al., 2003) [49]. Although several investigations have demonstrated that aneurysmal tissues and diseased coronary artery venous bypass grafts (Jabs et al., 2003)[50] produce CRP, little is known about its mechanism. Blood vessels are dynamically subjected to mechanical strain in the forms of stretch and shear stress that result from blood pressure and blood flow. Mechanical strain on the vessel wall can increase from 15 to 30% in hypertensive individuals (Safar et al., 1981[51]; Shaw and Xu, 2003)[52][53].

CRP testing is not precise enough to diagnose specific diseases but serves more as a general indicator that more testing may be needed if inflammation or infection is found. The CRP test is therefore useful in assessing patients with the following list[54]:

- Swelling and bleeding of the intestines (inflammatory bowel disease).
- Painful swelling of the tissues that line the joints (rheumatoid arthritis).
- Diseases of the immune system, such as lupus.
- Pelvic inflammatory disease (PID)
- Painful swelling of the blood vessels in the head and neck (giant cell arteritis).
- Cancer of the lymph nodes (lymphoma).
- Infection of a bone (osteomyelitis).
- Connective tissue disease
- Heart attack
- Infections
- Pneumococcal pneumonia
- Rheumatic fever
- Tuberculosis

4. Factors that effects on high levels of CRP

Many doctors will prescribe taking non steroidal anti-inflammatory drugs ((NSAIDs like aspirin, ibuprofen, and naproxen) or statins may reduce CRP levels in blood. Both anti-inflammatory drugs and statins may help to reduce the inflammation, thus reducing CRP. However, there are natural treatments that can help reduce inflammation in the blood.

Following are some of the natural treatments for lowering C - reactive protein levels and inflammation in the blood:

Fish Oil Omega 3 Fatty Acids Doctors and nutritionists have recommended Omega 3's for years, and recently fish oil has been the most recommended source for Omega 3 Fatty Acids. Fish oil contains two of the most therapeutic Omega 3 Fatty Acids the DHA and EPA. These two fatty acids are the most readily absorbed by the body (much more so than the ALA found in flax seed oil), and can help reduce inflammation in the blood among other benefits.

Ginger - Ginger root extract has long been used in Asian cooking, and has been used for centuries as a digestive aid and motion sickness cure, and more recently to lower cholesterol. Ginger can also help reduce inflammation, as it relaxes the muscles surrounding blood vessels and facilitates blood flow throughout the body.

MSM - Methyl Sulfonyl Methane, commonly known as MSM, is a naturally occurring sulfur compound found in some vegetables. MSM is found in many arthritis formulas, and has strong anti-inflammatory properties.

These three nutrients may help reduce CRP levels in your blood. All three are important for maintaining heart health as well as general health and wellbeing [55].

There was a study found a significant effect of treatment for 2 months with 1000 mg/day vitamin C on plasma CRP, in non diseased moderately overweight nonsmokers with baseline CRP ≥ 1.0 mg/L. The magnitude of the effect was similar to that of statins. There was no significant effect of vitamin E. These data represent the largest study to date on the effects of vitamins C and E on CRP and extend our previous findings in overweight active and passive smokers. They indicate that vitamin C should be further investigated for its potential for reducing chronic inflammation and its consequences. And they identify a threshold concentration above which there is a potential for reduction in CRP. Future studies to determine whether vitamin C can reduce some of the inflammation-related adverse consequences of obesity should be considered. Such trials should focus on individuals with elevations (≥ 1.0 mg/L) in CRP, because studies with low-risk persons are less likely to show an effect, resulted in misleading outcomes. If persons with lower CRP levels must be included, separate randomization of those with CRP ≥ 1.0 mg/L would justify separate examination of this subgroup, assuming adequate power in this stratum. In addition, if the potential independent effect of vitamin C is to be determined, it would be necessary to exclude persons who are taking other anti-inflammatory drugs (except low-dose aspirin for heart disease prevention) and to exclude users of multiple vitamins (something which has not been done in most large antioxidant trials), because multiple vitamins alone can raise plasma ascorbic acid levels substantially and make the control group insufficiently different from the active treatment group. Finally, it may be prudent to evaluate vitamin C alone, unpaired with vitamin E, as we found a weaker CRP-lowering effect with the combination than with vitamin C alone in our previous trial [56].

5. C - reactive protein concentrations in cerebral spinal fluid in gram-positive and gram-negative bacterial meningitis

Several reports have shown an ability of CRP to discriminate between patients with bacterial meningitis and patients with aseptic (viral) meningitis. Although a recent Meta-analysis suggested that a negative CRP test in either cerebrospinal fluid (CSF) or serum can be used with a very high probability to rule out bacterial meningitis, a more recent report suggested that serum concentrations are a better screening tool for this differential diagnosis.

The substantial increase in CSF CRP, as well as the trend of an increased CSF/blood ratio of CRP, suggests that infection with gram-negative bacteria enhances permeability of CRP through the blood-brain barrier. It is possible that these findings reflect the ability of the endotoxin lipopolysaccharide-s, present in gram-negative but not in gram-positive bacteria, to affect the permeability of the blood-brain barrier [57][58]. CSF nitric oxide (NO) may be involved in this mechanism because its concentration in CSF is higher in gram-negative meningitis. This possibility is supported by the higher potency of gram-negative bacteria to promote macrophage NO production [59], the enhanced production of NO in the CSF of septic meningitis [60], and the role of NO in permeability changes of the blood-brain barrier in LPS-induced experimental meningitis [61].

Another interesting potential explanation for the present observation is that lipopolysaccharide-s produced by gram-negative bacteria could induce local CRP synthesis in the central nervous system. CRP can be produced in neurons [62], and lipopolysaccharide-s can induce CRP in extrahepatic sites [63]. This may also explain the increase, albeit nonsignificant, in serum CRP in the gram-negative cases. There is currently no single test to diagnose the etiology of meningitis promptly and accurately. Given its high sensitivity and easy measurability, CRP may be a useful supplement for rapid diagnosis and categorization of bacterial meningitis.

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Moneer Faraj and Nihaya Salem

Department of Neurosurgery, Hospital of Neurosciences, Baghdad, Iraq

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