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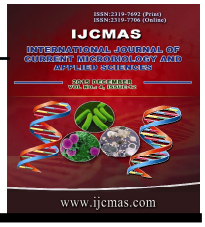

Case Study

C-Reactive Protein - A critical Review

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A B S T R A C T

Fifty cases were screened for CRP those who are having various ailments including high blood pressure, diabetic mellitus with polyneuropathy, oral cavity infection and hepato-spleenomegaly of different aetiologies. In this hospital (Sree Narayana Medical Trust, Varkala) we have screened the serum samples by latex agglutination test. It is a specific test. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (Erythrocyte Sedimentation Rate). CRP appears and disappears more quickly than changes in ESR. There for your CRP level may drop to normal following successful treatment, whereas ESR may remain elevated for a longer period. CRP levels will be very high in the arthritis, increased serum CRP concentrations are positively associated with the risk of future coronary events such as coronary artery dices cerebrovascular dices, peripheral arterial dices. The use of CRP for these purposes requires the use of hs CRP assay that have detection limits less than 0.3mg/L. Several automated immunoturbidimetric and immunonephelometric assays are commercially available and are capable of sensitive and precise measurements at low concentrations of CRP. hs CRP to be a stronger predications of risk than LDL cholesterol.

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 (en.wikipedia.org).

Discovered by Tillett and Francis in 1930, it was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer (Pepys and Hirschfield, 2003), however, the discovery of hepatic synthesis demonstrated that it is a native protein (en.wikipedia.org; Peter J. Kennelly *et al.*, 2009; Matthew R. Pincus *et al.*, 2007; John J. Ratey *et al.*, 2008).

CRP is phylogenetically a highly conserved plasma protein, with homolog invertebrates 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 (www.jbc.org).

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 (http://ghr.nlm.nih.gov/gene/CRP). It is induced by IL1/interleukin-1 and IL6//interleukin-6 Size: 224 amino acids; 25039Da Subunit: Homopentamer. Pentaxin (orpentraxin) 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; Mass spectrometry: Mass = 22930; Method = MALDI; Range = 19–223; Source = Ref.15;.

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 (www.uniprot.org).

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 (www.genecards.org; Wolford and Hanson, 2003).

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 immune sorbent 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.

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 (Clyne and

Olshaker, 1999). hs-CRP test measures using laser nephelometry. The test gives results in 25 minutes with sensitivity down to 0.04mg/L (en.wikipedia.org). 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 (labtestsonline.org).

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 (www.ncbi.nlm.nih.gov).

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 (labtestsonline.org).

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 (post operation), trauma and burns.

CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (en.wikipedia.org) 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 (boneandspine.com), 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 24h, ESR may be normal and CRP elevated (en.wikipedia.org). CRP and ESR have been used to diagnose postoperative infections after spinal surgery.

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 nonsteroidal anti-inflammatory drugs postoperatively, but these medications seems to effect on the level of CRP. Munozm *et al.* (2004) 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 (http://www.scopemed.org) with exception of Orrego *et al.* (2005) who noticed that more complex surgical procedure had higher CRP level and explained due to the amount of tissue trauma. Sugimorik *et al.* (2003) showed no correlation between the high CRP concentration and the level, type of lumbar disc herneation or the preoperative clinical data. Thelander *et al.* (1992) 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 TNF-α or IL-6, may have a role as a clinical marker in pneumonia (http://chestjournal.chestpubs.org). 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) (www.jbc.org). 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; Verma *et al.,* 2006). Elevated high-sensitivity CRP (hsCRP) has been measured in the blood of patients with essential hypertension (Li *et al.,* 2005) or abdominal aortic aneurysms (Vainas *et al.,* 2003; Tambyraja *et al.,* 2007) with enhanced systemic or local arterial strain. Elevated serum hsCRP independently correlates with blood pressure (Sung *et al.,* 2003), arterial stiffness (Kim *et al.,* 2007), and aneurysmal size (Vainas *et al.,* 2003). Although several investigations have demonstrated that aneurysmal tissues and diseased coronary artery venous bypass grafts (Jabs *et al.,* 2003) 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; Shaw and Xu, 2003).

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 (www.creactiveprotein.net):

- 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 lymphnodes (lymphoma).
- Infection of a bone (osteomyelitis).
- Connective tissue disease
- Heart attack
- Infections
- Pneumococcal pneumonia
- Rheumatic fever
- Tuberculosis

Factors that effects on high levels of CRP

Many doctors will prescribe taking nonsteroidal 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 (http://www.healthy-heart-guide.com/crp-blood-test.html).

There was a study found a significant effect of treatment for 2 months with 1000mg/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.

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 CSFCRP, 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 lipopolysaccharides, present in gram-negative but not in gram-positive bacteria, to affect the permeability of the blood-brain barrier (www.clinchem.org; Wispelwey *et al.,* 1988). 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 (Jungi *et al.,* 1999), the enhanced production of NO in the CSF of septic meningitis (Tsukahara *et al.,* 1998), and the role of NO in permeability changes of the blood-brain barrier in LPS-induced experimental meningitis (Boje, 1996).

Another interesting potential explanation for the present observation is that lipopolysaccharides produced by gram-negative bacteria could induce local CRP synthesis in the central nervous system. CRP can be produced in neurons (Yasojima *et al.*, 2000), and lipopolysaccharides can induce CRP in extra hepatic sites (Introna *et al.*, 1996). 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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