International Journal of Advanced Science and Technology
Vol. 29, No. 12s, (2020), pp. 512-519

Clinical Applicability Of C Reactive Protein Testing – A Review Of Current Research

Dr. Santhoshini Vaijinath[1*], Dr. Sangeetha S[2]
[1]*Assistant Professor, Department of Microbiology*
[2]*Professor, Department of Microbiology*

Abstract

C-reactive protein (CRP) is a plasmatic protein of the pentraxin family and is often proposed as the solution of various clinical predicament. This is a protein of the acute phase, synthesised by hepatocytes. Its production is stimulated mainly by interleukin 6, interleukin 1 β, and tumour necrosis factor α in response to infection or tissue inflammation. Since its identification in 1930, C reactive protein has been studied as a screening device for inflammation, a marker for disease activity, and as a diagnostic adjunct. This review will largely focus on our current understanding of the CRP measurement as a diagnostic tool for finding clinical infections, monitoring effects of treatment, outcome, and early detection of relapse of the disease, and hence can be a useful as a diagnostic aid in determining disease progression.

KEYWORDS : *CRP; Acute phase reactant; Diagnostic utility; biomarker.*

INDRODUCTION

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 [1].1 An acute phase protein has been defined as the one whose plasma concentration increases (positive acute phase proteins) or decreases (negative acute phase proteins) by at least 25% during inflammatory disorders. Other acute phase proteins include transport proteins (haptoglobin, ceruloplasmin, gamma 1-trypsin inhibitor, etc.), coagulation proteins (fibrinogen, prothrombin, etc.), and complement components (C3, C4, C5, etc.) [2].

Tillet and Francis (1930) discovered the presence of CRP in the serum of patients with acute inflammation, but it was not actually isolated until 1941. The name is derived due to the ability of the CRP to react with C-polysaccharide isolated from pneumococcal cell walls. It is a member of pentraxin family of proteins [3]. They are ligands for leukocyte Fcγ receptors. The CRP gene is located on first chromosome. CRP is synthesized by hepatocytes and is classified as an acute phase protein on the basis of its increase in plasma concentration during infection and inflammation and is a golden marker of inflammation [4].Pepys and Baltz (1983) suggested that CRP is synthesized by the liver in response to diverse inflammatory stimuli, including heat, trauma, infection, and hypoxia [5].

serum CRP is a useful and rapidly available adjunct to clinical assessment in diagnosis and exclusion of bacterial infection in the early neonatal period, has encouraged us to withhold or discontinue antibiotics and also has a role in monitoring response to treatment[6].

CRP levels are of value in 6 clinical situations[7]:

- ✓ monitoring the response to antibiotic treatment in patients with known bacterial infections,

- ✓ in obstetric patients with premature rupture of membranes, a rise in CRP can give early warning of intrauterine infections,
- ✓ differentiation between active disease and infections in patients with systemic lupus and ulcerative colitis where the level of response to active disease has been previously established,
- ✓ as a measure of disease activity and response to disease-modifying drugs in rheumatoid arthritis,
- ✓ early detection of complications in postoperative patients,
- ✓ in differentiating between infection and graft-versus-host-disease in bone marrow transplant patients.

In this scenario, it is necessary to consider the diverse perspectives outlined worldwide and assess opinions for and against this controversial protein, in order to ultimately analyze the inclusion of its routine determination as part of the diagnostic work-up in patients.

C-REACTIVE PROTEIN (CRP) :

The definition of C-reactive protein (or CRP), according to the National Institutes of Health, is "a protein made by your liver that is sent into your bloodstream in response to inflammation." This molecule is a member of the pentraxin family of proteins. It is secreted mostly by cells in the liver in response to a variety of inflammatory cytokines and can rise very quickly. This happens when the body senses a threat, including an injury or recognition of foreign molecules in the body. To a lesser extent, CRP is released by muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. Levels of this protein can increase up to 1,000-fold at sites of infection or inflammation. Emerging research shows that CRP plays important roles in inflammatory processes including by altering pathways involved in apoptosis, phagocytosis, nitric oxide release and production of cytokines [8].

Mechanism

A gene on chromosome 1q21-q23 that encodes C reactive protein. It is involved in host immune defence due to its ability to recognize foreign pathogens and damaged host cells and trigger their elimination by interacting with humoral and cellular effector systems. Plasma CRP is markedly increased during the acute-phase response to tissue injury, infection or other inflammatory stimuli[9]. The aim of this response is to reduce tissue damage, isolate and destroy foreign organisms and start the rebuilding process.

Normal CRP Value

Serum CRP level is 1.0 mg/L in healthy young adults. The average value of CRP in healthy adults increases to 2.0 mg /L as they age. C-reactive protein value is slightly higher in women than men. The units of some centers are in mg/dL [10].

PRODUCTION OF CRP:

CRP is one of many plasma proteins and is a sensitive systemic marker of inflammation. It is synthesised by the liver in response to microbial infection, tissue injury, and autoimmune disorders in the acute phase of the response[11]. This phase of the response comprises non-specific physiological and biochemical reactions to most forms of tissue damage, infection, inflammation, and malignant neoplasia. The synthesis of proteins is rapidly upregulated, principally in hepatocytes, under the direct control of cytokines that originate at the site of pathology. CRP can also be expressed by smooth muscle cells in coronary arteries after exposure to inflammatory cytokines[12].

FUNCTIONS OF CRP :

A major 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. It can activate complement system when bound to one of its ligands and can also bind to phagocytic cells, an observation suggesting that it can initiate the elimination of targeted cells by its interaction with both humoral and cellular effector systems of inflammation[13]. Other proinflammatory effects of CRP include induction of inflammatory cytokines and tissue factor in monocytes. It is thought to assist in complement binding to foreign and damaged cells and affect the humoral response to disease[14].

CRP has the ability to prevent the adhesion of neutrophils to endothelial cells by decreasing the surface expression of L-selectin, inhibit the generation of superoxide by neutrophils, and stimulate the synthesis of interleukin-1 (IL-1) receptor antagonist by mononuclear cells [15]. CRP has also been reported to stimulate tissue factor production by human peripheral blood monocytes and has a procoagulant effect. It has also been reported that CRP recruits monocytes by receptor-mediated chemotaxis into the arterial wall. It colocalizes with foam cells in atherosclerotic lesions [16].

CAUSES [17] :

Infections: CRP value increases in bacterial and viral infections. It increases up to 100 mg/L in viral infections and it goes above 100mg/L in bacterial infections.

Inflammatory diseases: Diseases like familial Mediterranean fever (FMF), rheumatoid arthritis, systemic lupus erythematosus (SLE)

Necrosis: Death of damaged cells or tissues due to various reasons is called necrosis. CRP level increases in cases such as heart attack, acute pancreatitis.

Trauma: It increases after surgery, burns and fractures in the body.

Cancer: It increases in many cancers, including lymphoma and sarcomas.

SYMPTOMS [17] :

Fever, local heat increase, weakness, redness, Swelling and pain

RISK FACTORS :

Established risk factors for “high-normal” values of CRP within the general population include older age, cigarette smoking, chronic bacterial infections, and chronic bronchial inflammation. Viral infections tend to give lower CRP level than bacterial infection [18].

Higher CRP levels tend to be found in individuals who smoke, have high blood pressure, are overweight, and do not exercise, whereas lean, athletic individuals tend to have lower CRP levels [19].

Large amounts of CRP are produced by hepatocytes in response to circulating cytokines, such as tumor necrosis factor (TNF)-α and IL-1, produced at the site of tissue destruction. This CRP production by hepatocytes occurs at the expense of albumin and other constitutive proteins, a process labeled "reprioritization" of hepatic protein synthesis. However, competing demands for protein synthesis in cases of acute, overwhelming inflammation can lead to anomalous short-term changes in acute-phase reactant [20].

Napoli *et al*. showed elevated levels of CRP in conditions such as acute stroke, surgery, and cancer [21].

C-REACTIVE PROTEIN TEST :

It is important to recognize that CRP, similar to other markers of inflammation, can be elevated because of any inflammatory process or infection and, thus, its interpretation needs careful assessment of the entire clinical picture by the ordering physician. Other inflammatory processes, such as active arthritis, trauma, or infections, can raise the c-reactive protein level independently.

Because of the these variables and fluctuations, it is also recommended by the U.S. Centers for Disease Control and Prevention (CDC) to measure fasting and non-fasting c-reactive protein levels ideally two weeks apart, and to use the average of these two results for a more accurate interpretation if the CRP level is used as a screening tool for cardiovascular disease. It measures the level of C-reactive protein (CRP) in your blood. This type of test can be performed in both adults and children, and even babies to check for signs of illnesses[22].

Commen test for inflammation and infection

Nowadays, the CRP test is a routine blood test done to measure general levels of inflammation and infection in the body, determine their severity, and monitor response to treatment. With the discovery of an association between CRP and risk of cardiovascular events, some researchers have recommended its use to assess risk of cardiovascular disease as well as to guide and gauge response to treatment with statins [23].

CRP AND INFECTION :

CRP is an important factor in determining the etiology of infection. The level of CRP can be significantly higher in bacterial infections. It can distinguish between bacteria and virus infections.

C-reactive protein is a marker for inflammation, and its levels increase during bacterial infection [24]. Kingsley and Jones stated that CRP increases during infection in response to monocytic mediators such as IL-1 and IL-6 and that it has a stable decay rate. It is thought that most of the interaction between CRP and the immune response to pathogens involves the binding of CRP to PCh and the activation of the classical complement pathway [25]. Mold et al. showed that CRP provides mice with protection against infection by the gram-positive pathogen Streptococcus pneumoniae by binding to a PCh determinant of the pathogen cell wall and activating the complement pathway. Mice pretreated with 200 µg CRP before being infected showed an increase in percentage survival across all pathogen doses tested. The study concluded that the ability of CRP to protect against infection lies in its ability to bind to pneumococcal polysaccharide C in the bacterial cell wall [26].

Szalai et al. showed that CRP can confer protective benefits against Salmonella enterica serovar Typhimurium, a gram-negative pathogen that provides a model of typhoid fever in mice. By using

transgenic mice expressing human CRP, the study found that CRP offered protection against a low dose of Typhimurium and increased resistance to a fatal infection with a low dose of Typhimurium. Szalai et al. concluded that CRP increases the early clearance of intravenously injected bacteria from the blood and reduces dissemination of bacteria to the liver and spleen during the initial stages of infection, thus allowing the mice to survive infection[27].

Marnell et al. reviewed the protective role CRP against Haemophilus influenza infection in both transgenic and wild-type mice treated by passive inoculation[28]. CRP was shown to bind the pneumococcal C-polysaccharide of bacteria and opsonize them for phagocytosis. This process did not require the use of the Fcγ receptors, suggesting that CRP is not primarily protective by direct opsonization but more likely through activation of complement and subsequent opsonophagocytosis.

Kingsley and Jones tested whether CRP could be used to distinguish different types of infections. They discovered that mean CRP levels in a spreading infection were higher than those in other colonized, critically colonized, and locally infected groups. All cases of infection showed an increase in CRP levels compared to non-infected controls, but CRP levels could not distinguish between the infection types, showing that it is infection in general that causes CRP levels to increase, rather than the type of infection[28]. This was also noted by Healy and Freedman who showed that CRP levels can be used only as a method of detecting infection, rather than distinguishing it.

C-reactive protein can mediate host responses to Staphylococcus aureus including some protective function against infection and an increase in phagocytosis of this pathogen. Povoa et al. stated that the normal CRP level for the healthy population is about 0.08 mg/dL, and this increases to more than 8.7 mg/dL during chronic S. aureus infection. Thus, CRP can be used as an indicator of infection, alongside a body temperature of more than 38.2°C [29]. Patterson and Mora observed that enhanced resistance to intraarticular infection with S. aureus in chickens was associated with an increase in serum CRP and that isolated preparations of the protein produced antibacterial activity[30]. Mulholland and Cluff discovered that endotoxin-induced changes in resistance to local infection with S. aureus in rabbits were correlated with the circulating levels of leukocytes in the blood. The study showed that induced resistance was paralleled by an increase in CRP and leukocytes[31]. This was collaborated by Patterson et al. who found an association between CRP and non-specific resistance to infection, including S. aureus and showed that CRP was acting upon the polysaccharide bacterial cell wall. Black et al. stated that CRP enhances the in vitro phagocytosis of many microorganisms (including S. aureus) by leukocytes. Their work confirmed this finding even in the absence of complement, suggesting that the enhancement of phagocytosis by CRP is due to the interactions with Fcγ receptors[32].

In summary, evidence shows that CRP is not only a marker of infection and inflammation but that CRP also has a protective role against bacterial infections , principally through the activation of complement and subsequent opsonization of pathogens.

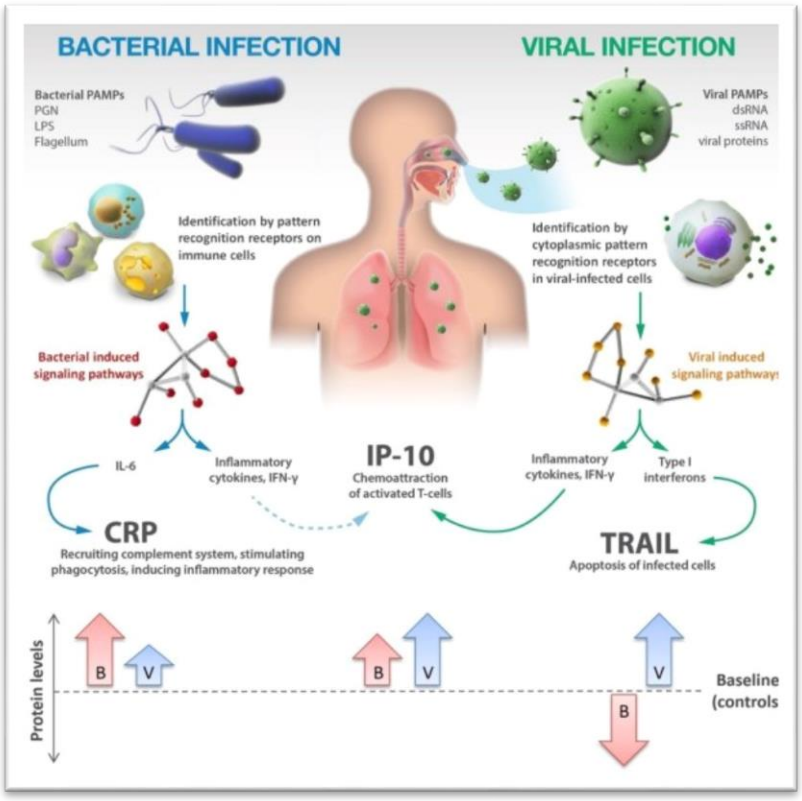

Figure : Relationship between CRP and infection

FUTURE TARGET FOR CRP THERAPY IN HUMAN DISEASE :

We have long speculated that CRP may have significant proinflammatory effects, and that, by binding to ligands exposed on cells or other autologous structures as a result of infection, inflammation, ischemia, and other pathologies, and triggering complement activation, it may exacerbate tissue damage, leading to more severe disease[33]. The rat myocardial infarction model provided the first direct evidence of these processes in vivo, but they are not necessarily confined to cardiovascular disease. The excellent correlation of circulating CRP concentrations with the severity, extent, and progression of many different pathologies, and the prognostic significance of these associations, are consistent with CRP not just being a marker of disease but also contributing to pathogenesis. A definitive way to test this concept will be the use of novel drugs that specifically block CRP binding and its proinflammatory effects in vivo[34]. If these compounds are effective, they may find very broad applicability. Such drugs would be a powerful tool for determining whether increased CRP production merely reflects atherosclerosis or does indeed participate in its pathogenesis and complications, and they could also have cardioprotective effects in acute myocardial infarction. Knowledge of the structure and function of CRP — including its three-dimensional structure alone and complexed with ligands-coupled with experience in developing an inhibitor of the related protein SAP establishes an excellent platform for drug design [35].

CONCLUSION :

CRP, the classical marker of acute phase response, is an indicator of a variety of pathological processes including infection, tissue damage, and chronic inflammatory disease.The research of this review indicate

that measurement of the CRP level is useful to determine the disease status, monitor the treatment course and evaluate the prognosis of various disease in clinical practice. The availability of CRP measurement in clinical practice would be important for clinical examination. This article provides information about knowledge-based framework for interpretation and analysis of clinical observations of CRP in relation to cardiovascular and other diseases. We also review the properties of CRP, its possible role in pathogenesis of disease, and our own observations that identify it as a possible therapeutic target.

REFERENCES

1. Hussain T.M, Kim D.H. C-reactive protein and erythrocyte sedimentation rate in orthopaedics. Spring. 2002;15:13–16.
2. Gabay C, Kusher I. Acute - Phase Proteins and Other Systemic Responses to Inflammation. N Engl J Med. 1999;340:448–454.
3. Russell R. Atherosclerosis-An Inflammatory Disease. N Engl J Med. 1999;340:115–126.
4. Pepys M.B, Gideon M. Hirschfield - C-reative protein: A critical update. J Clin Invest. 2003;111:1805–1812.
5. Zambson J.J, Reynolds J.S, Chen P, Genco R.J, Slots J, Thomas E.R. Microbiology of Periodontal Disease. In: Slots J, Taubman JE, editors. USA: St. Louis; 1985. pp. 32–40.
6. Ramamoorthy R.D, Nallasamy V, Reddy R, Esther N, Maruthappan Y. A review of C-reactive protein: A diagnostic indicator in periodontal medicine. J Pharm Bioallied Sci. 2012;4(2): S422–S426.
7. Nystrom T. C- reactive protein: A marker or player ? Clin Sci. 2007;113:79–81.
8. Chalmers J.D, Singanayagam A, Hill A.T. C-Reactive Protein is an independent predictor of severity in community - acquired pneumonia. Am J Med. 2008;121:219–225.
9. Ahmadi-Abhari S, Luben R.N, Wareham N.J, et al. . Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. Eur J Epidemiol. 2013;28:541–550.
10. Li W, Xiong L, Fan L, et al. . Association of baseline, longitudinal serum high-sensitive C-reactive protein and its change with mortality in peritoneal dialysis patients. BMC Nephrol. 2017;18:211-215.
11. Chandy S, Joseph K, Sankaranarayanan A, et al. . Evaluation of C-reactive protein and fibrinogen in patients with chronic and aggressive periodontitis: a clinico-biochemical study. J Clin Diagn Res. 2017;11:ZC41–ZC45.
12. Caixeta A, Stone G.W, Mehran R, et al. Predictive value of C-reactive protein on 30-day and 1-year mortality in acute coronary syndromes: an analysis from the ACUITY trial. Journal of Thrombosis and Thrombolysis. 2011;31(2):154–164.
13. Ong K.L, Allison M.A, Cheung B.M, et al. Trends in C-reactive protein levels in US adults From 1999 to 2010. American Journal of Epidemiology. 2010;177:1430–1442.
14. Eppy S, Nainggolan L, Rumende C.M. The differences between interleukin-6 and c-reactive protein levels among adult patients of dengue infection with and without plasma leakage. Acta Med Indones. 2016;48(1):3–9.
15. Duraan A, Gonzalez A, Delgado L, Mosquera J, Valero N. Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. J Med Virol. 2016;88(2):351–355.
16. Althaus T, Greer R.C, Swe M.M, et al. Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial. Lancet Glob Health. 2019;7(1):e119–ee31.
17. Mortensen R.F. C-reactive protein, inflammation, and innate immunity. Immunol Res. 2001;24:163-176.
18. Hosford-Donovan A, Nilsson A, Wahlin-Larsson B, Kadi F. Observational and mechanistic links between C-reactive protein and blood pressure in elderly women. Maturitas. 2016;89:52- 57.

19. Nilsson K, Gustafson L, Hultberg B. C-reactive protein: Vascular risk marker in elderly patients with mental illness. Dement Geriatr Cogn Disord. 2008;26:251-256.
20. Bermúdez V, Cabrera m, Mendoza L, et al. High-sensitivity C-Reactive Protein epidemiological behavior in adult individuals from Maracaibo, Venezuela. Revista Latinoamericana de Hipertension. 2013;8(1):22–29.
21. Lane T, Wassef N, Pooole S, Mistry Y, et al. Infusion of pharmaceutical-grade natural human C-reactive protein is not proinflammatory in healthy adult human volunteers.Circ Res. 2014;114:672–676.
22. Ridker P.M. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003;107:363–369.
23. Mortensen R.F. C-reactive protein, inflammation, and innate immunity. Immunol Res. 2001;24(2):163–176.
24. Healy B, Freedman A. Infections. Br Med J. 2006;332(7545):838–841.
25. Kingsley A, Jones V. Diagnosing wound infection: the use of C-reactive protein. Wounds UK. 2008;4(4):32–46.
26. Mold C, Nakayama S, Holzer T.J, Gewurz H, Du Clos T.W. C-reactive protein is protective against Streptococcus pneumoniae infection in mice. J Exp Med. 1981;154(5):1703–1708.
27. Szalai A.J, VanCott J.L, McGhee J.R, Volanakis J.E, Benjamin W.H. Human C-reactive protein is protective against fatal Salmonella enterica serovar typhimurium infection in transgenic mice. Infect Immun. 2000;68(10):5652–5656.
28. Marnell L, Mold C, Du Clos T.W. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol. 2005;117(2):104–111.
29. Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P, et al. C-reactive protein as a marker of infection in critically ill patients. Clin Microbiol Infect. 2005;11(2):101–108.
30. Patterson L.T, Mora E.C. The C-reactive protein response and disease resistance in the domestic fowl. Tex Rep Biol Med. 1965;23:600–606.
31. Mulholland J.H, Cluff L.E. The effect of endotoxin upon susceptibility to infection. The role of the granulocyte. In: Landy M, Braun W, editors. Bacterial Endotoxins. New Brunswick, NJ: Rutgers University Press. 1964. p. 211–229.
32. Patterson L, Harper J, Higginbotham R. Association of C-reactive protein and circulating leukocytes with resistance to Staphylococcus aureus infection in endotoxin-treated mice and rabbits. J Bacteriol. 1968;95:1375–1382.
33. Shinohara S, Sugaya M, Onitsuka T, Machida K, Matsuo M, Tanaka F. Prognostic Impact of Postoperative C-reactive Protein for Non-small Cell Lung Cancer Following Lobectomy. Anticancer Res. 2018;38(5):3193–3198.
34. Kraus V.B, Jordan J.M. Serum C-Reactive Protein (CRP), target for therapy or trouble? Biomarker Insights. 2006;1:77–80.
35. Oh J, Teoh H, Leiter L.A. Should C-reactive protein be a target of therapy? Diabetes Care. 2011;34(2):S155–S160.