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A PERSPECTIVE ON HIGH SENSITIVITY C-REACTIVE PROTEIN (hs-CRP)

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ABSTRACT

C-reactive protein (CRP), an acute phase reactant synthesized mainly by the liver, belongs to the pentraxin family of proteins. It helps in immune regulation by assisting in the recognition of damaged host cells and foreign pathogens, and their removal. Immunoassays for CRP with greater sensitivity (hence called high sensitivity CRP or hs-CRP) than those previously in routine use, have revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events besides indicating a link with a host of other communicable and non-communicable diseases. Compelling data exists to suggest that plasma hs-CRP should be included in the routine laboratory tests for risk evaluation and stratification in diverse clinical conditions.

KEY WORDS: C-reactive protein, hs-CRP, acute-phase reactant, disease, risk.

INTRODUCTION

The first reaction of the body to immunological stress is the innate, non-specific response preceding specific immune reactions. The acute phase response is a prominent systemic reaction of the organism to local or systemic disturbances in its homeostasis caused by infection, tissue injury, trauma or surgery, neoplastic growth or immunological disorders.[1] At the site of invasion by a microorganism and the place of tissue injury, a number of responses of the tissue itself are initiated. Pro-inflammatory cytokines are released, and the vascular system and inflammatory cells are activated.[1] Of the cytokines, the most notable are the interleukins (IL1, IL6 and IL8), TNFα, C-reactive protein (CRP), mannose-binding

protein, complement factors, ferritin, ceruloplasmin, serum amyloid A and haptoglobin. These are known as positive acute-phase reactants (Table 1).[2] The liver responds by producing a large number of acute-phase reactants. Some act to destroy or inhibit growth of microbes. At the same time, the production of a number of other proteins is reduced; these are, therefore, referred to as negative acute-phase reactants. Examples include albumin, transferrin, transthyretin, retinol-binding protein, antithrombin, transcortin etc. The decrease of such proteins may be used as markers of inflammation. "Negative" acute-phase proteins decrease in inflammation. The physiological role of decreased synthesis of such proteins is generally to save amino acids for producing "positive" acute-phase proteins more efficiently.[2] The present review focuses on CRP.

Table 1. Acute-phase response proteins.

Group	Individual proteins
***Positive* acute phase reactants**	
Major acute-phase reactants	Serum amyloid A, C-reactive protein, serum amyloid P component
Complement proteins	C2, C3, C4, C5, C9, B, C1 inhibitor, C4 binding protein
Coagulation proteins	Fibrinogen, von Willebrand factor
Proteinase inhibitors	α_1-Antitrypsin, α_1-antichymotrypsin, α_2-antiplasmin, heparin cofactor II, plasminogen activator inhibitor I
Metal-binding proteins	Haptoglobin, haemopexin, ceruloplasmin, manganese superoxide dismutase
Other proteins	α_1-Acid glycoprotein, haeme oxygenase, mannose-binding protein, leukocyte protein I, lipoprotein (a), lipopolysaccharide-binding protein
***Negative* acute phase reactants**	
	Albumin, pre-albumin, transferin, apoA1, apoAII, *Homo Sapien* glycoprotein, inter-α-trypsin inhibitor, histidine-rich glycoprotein

HISTORY

CRP is a member of the pentraxin family of proteins. It was the first pattern recognition receptor (PRR) to be identified.[3] It was so named because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide of Pneumococcus. 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. The later discovery of hepatic synthesis demonstrated that it is a native protein.[4]

REGULATION OF CRP EXPRESSION

The CRP gene, located on the short arm of chromosome 1 (1q21-q23), contains only one intron, which separates the region encoding the signal peptide from that encoding the mature protein. Induction of CRP in hepatocytes is principally regulated at the transcriptional level by the cytokine interleukin-6 (IL-6), an effect which can be enhanced by interleukin-1β (IL-1β). Extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes. The mechanisms regulating synthesis at these sites are unknown, and it is unlikely that they substantially influence plasma levels of CRP.[5]

STRUCTURE

CRP is an acute-phase protein featuring a homopentameric structure and Ca^{2+}-binding specificity for phosphocholine (PCh). It is a nonglycosylated circulating member of the pentraxin family that belongs to the lectin fold superfamily. Pentraxins are a family of evolutionarily conserved pattern-recognition proteins that are made up of five identical subunits. Based on the primary structure of the subunit, the pentraxins are divided into two groups: short pentraxins and long pentraxins. CRP and serum amyloid P-component (SAP) are the two short pentraxins. The prototype protein of the long pentraxin group is pentraxin 3 (PTX3).[6, 7]

The human CRP molecule is composed of five nonglycosylated polypeptide subunits (protomers) that are noncovalently bound, arranged with cyclic pentameric symmetry and assembled around a central pore in a disc-like configuration (Fig.1).[6] Each subunit has a mass of 23,027 Da (containing 206 amino acid residues) and the whole human CRP molecule has a mass of 115,135 Da.[7]

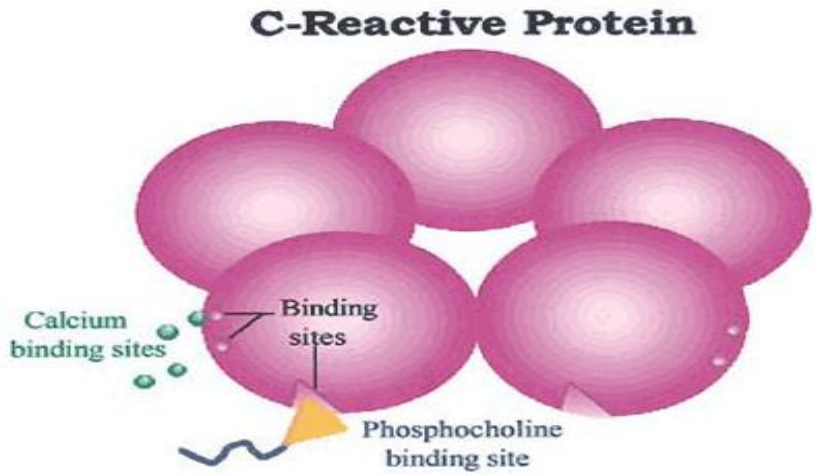

Figure 1. Structure of Human CRP.

FUNCTIONS

It assists in the recognition of damaged host cells and foreign pathogens, and their removal. When CRP binds to its ligand, it activates the complement system via the classical pathway and increases phagocytosis. While it is present in minute quantities in the plasma, after an acute inflammatory stimulation, it rises within a few hours. It peaks within 2-3 days. Its half-life is 19 hours. The increase in CRP levels is proportional to the inflammatory stimulus. With a greater stimulus, a higher and longer lasting level of CRP is measured. After the inflammatory stimulus is removed, the CRP levels quickly decrease. Acute-phase CRP reaction does not show diurnal variation, and is not affected by diet.[2]

NORMAL LEVELS

In healthy individuals, the plasma CRP level is generally below 0.2 mg/dl. Due to micro-traumas that occur during the day, this level can increase up to 1 mg/dl. While a value between 1-10 mg/dl is considered as mild, any value above 10 mg/dl is considered a very high increase.[2] In the mid 1990s, immunoassays for CRP with greater sensitivity (hence called high sensitivity CRP or hs-CRP) than those previously in routine use, revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events. These findings triggered widespread interest.[8]

Individuals with plasma hs-CRP values at the high end of the normal range have 1.5 to 4 times the risk of having acute coronary events as compared with hs-CRP values at the low end of the normal range.[3] The most recent American Heart Association (AHA) consensus statement recommended that hs-CRP be used as an emerging risk factor to further stratify patients who are at intermediate risk according to the Framingham global risk stratification tool- meaning they are calculated to have a 10% to 20% 10-year risk of having a cardiovascular event. The panel suggested the following cut points for hs-CRP levels[9]:

- low risk (<1.0 mg/L)
- average risk (1.0-3.0 mg/L)
- high risk (>3.0 mg/L)

A single test for hs-CRP) may not reflect an individual patient's basal hs-CRP level. Repeat measurement may be required to firmly establish an individual's basal hs-CRP concentration. The lowest of the measurements should be used as the predictive value. Elevated plasma hs-CRP occurs in the last half of pregnancy and is associated with the use of oral contraceptives besides many non-communicable diseases such as CAD, ischemic stroke, insulin resistance,

hypertension, metabolic syndrome and peripheral artery disease.[10, 11] Table 2 summarizes the major conditions associated with increased plasma hs-CRP.[8]

Table 2. Major conditions associated with increased plasma hs-CRP.

Major acute-phase response	
Infections	Bacterial, systemic/severe fungal, mycobacterial, viral
Allergic complications of infections	Rheumatoid fever, Erythema nodosum
Inflammatory disease	Rhematoid arthritis, Juvenile chronic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Systemic vasculitis, Polymyalgia rheumatica, Reiter disease, Crohn's disease, Familial Mediterranean fever
Necrosis	Myocardial infarction, Tumor embolization, Acute pancreatitis
Trauma	Surgery, Burns, Fractures
Malignancy	Lymphoma, Carcinoma, Sarcoma
Modest or absent acute-phase response	
	Systemic lupus erythematosus, Scleroderma, Dermatomyosistis, Ulcerative colitis, Leukemia, Graft-versus-host-disease

CLINICAL SIGNIFICANCE

Measurement of acute-phase proteins, especially C-reactive protein, is a useful marker of inflammation in both medical and veterinary clinical pathology. It correlates with the erythrocyte sedimentation rate (ESR), however not always directly. This is due to the ESR being largely dependent on elevation of fibrinogen, an acute phase reactant with a half-life of approximately one week. This protein will therefore remain higher for longer despite removal of the inflammatory stimuli. In contrast, C-reactive protein (with a half-life of 6-8 hours) rises rapidly and can quickly return to within the normal range if treatment is employed.[12] For example, in active systemic lupus erythematosus, one may find a raised ESR but normal C-reactive protein.[2] Key aspects of raised plasma hs-CRP in diverse clinical conditions are briefly discussed below.

Cardiovascular and metabolic disorders

hs-CRP may provide a novel method for detecting individuals at high risk of atherosclerotic plaque rupture. Recent studies demonstrate that hs-CRP is a strong independent predictor of future myocardial infarction and stroke among apparently healthy individuals, as well as is a potential risk predictor for future atherosclerosis and cardiovascular diseases (CVD).[13] A

study done on 50 consecutive patients who had paroxysmal atrial fibrillation and 50 control subjects without atrial fibrillation demonstrated that left ventricular mass, left ventricular end-systolic diameter, and left atrial diameter were predictors of elevated CRP and persistent atrial fibrillation.[14] Similarly, Psychari and colleagues,[15] after examining 90 patients with persistent and permanent atrial fibrillation, showed that CRP and interleukin IL-6 were positively related to left atrial diameter, and that a significant relationship existed between IL-6 levels and atrial fibrillation duration in relation to cardioversion. Lo and co-authors[16] showed that high baseline CRP levels were associated with an increased risk of postoperative atrial fibrillation. Gaudino and colleagues[17] showed that the promoter polymorphism –174G/C IL-6 gene influenced the inflammatory response to coronary artery bypass grafting (CABG) and was associated with postoperative atrial fibrillation. Another cohort study done showed that hs-CRP test results provided the best prediction of incident CVD events (myocardial infarction, stroke, revascularization, and CVD-related death) when used along with traditional risk factors (age, cholesterol, blood pressure, smoking and diabetes) and parental history of myocardial infarction before age 60 years.[18]

Indulekha *et al*[19] studied the association of adipokines, inflammatory and oxidative stress markers in subjects with the following phenotypes: metabolically healthy, non-obese (MHNO), metabolically healthy, obese (MHO), metabolically obese, non-obese (MONO), and metabolically obese, obese (MOO). Levels of hs-CRP (P=0.029), TNF-α (P=0.036), IL-6 (P=0.042), oxidized LDL (P=0.036), and MCP-1 (P=0.039) increased from the MHNO to MHO to MONO to MOO phenotypes. hs-CRP (β=0.112, P=0.020) and oxidized LDL (β=0.114, P=0.050) showed a positive association with systolic blood pressure even after adjusting for age and gender. The metabolically obese phenotype is characterized by altered adipokine and inflammatory profiles, which could make this phenotype at high risk for type 2 diabetes mellitus and cardiovascular diseases. Sen *et al*[20] reported that central macular thickness correlated positively with CRP and negatively with BMI, documenting a strong association of CRP with diabetes retinopathy. Heier *et al*[21] studied a population-based cohort representative of 314 children with type 1 diabetes in Norway. CRP showed the most pronounced difference between diabetes patients and controls and the strongest correlation with HbA1c. Another recent study[22] on 55 type 2 diabetic patients with diabetic foot infection showed that baseline levels of acute-phase reactants, especially CRP, WBC, ESR, appeared to be helpful in predicting amputation and length of stay in diabetic patients with acute foot ulceration. A study on 407 women and 362 non-Hispanic whites without diabetes

mellitus showed that CRP >0.5 mg/dl predicted metabolic syndrome.[23] hs-CRP is considered to be a better predictor of obesity 12 months later than is LDL-C/HDL-C.[24]
Studies in patients with ischemic stroke showed that hs-CRP is significantly higher in the clopidogrel resistance group than in the clopidogrel sensitive group. Further, on the basis of National Institutes of Health Stroke Scale (NIHSS) score, hs-CRP levels are significantly higher in the group with NIHSS >5 compared with the one with NIHSS ≤5, and age and hs-CRP levels are the independent prognostic factors of brainstem infarction.[25]

The use of oral contraceptives profoundly increases CRP levels, independent of the presence of diabetes.[21] Studies done in polycystic ovarian syndrome (PCOS) documented elevated levels of CRP besides insulin resistance, compared to their counterparts.[26] A significant and positive correlation was found between hs-CRP and body mass index ($r = 0.308$, $p < 0.01$) among Indian adolescent women with PCOS suggesting that hs-CRP levels may not *per se* be associated with PCOS, rather it could be related to fat mass in these subjects.[27]

A study by Chen *et al*[28] showed that elderly subjects with severe obstructive sleep apnoea (OSA) had a significantly higher risk of hypertension and a lower level of CRP. Among the subjects with ischemic stroke and severe OSA, the levels of CRP, IL-6, and total antioxidant capacity were positively correlated with the desaturation index (DI). Total antioxidant capacity was negatively correlated with mean arterial oxygen saturation (SaO_2). Regression analysis results indicated that the total antioxidant capacity remained significantly and negatively correlated with mean SaO_2 levels. Moreover, the CRP levels remained significantly correlated with the apnea-hypopnea index and DI after controlling for covariates.

Chronic kidney disease

Wanner *et al*[29] showed that CRP is 5- to 10-fold higher in haemodialysis patients than in healthy controls and clearly is multifactorial in origin. A number of endogenous factors [angiotensin II, lipopolysacharide, modified low-density lipoprotein, advanced glycation end-products, homocysteine, viral infections] are able to trigger a nuclear factor-kB-mediated inflammatory, interleukin-6-driven, response via the generation of oxygen free radicals (oxidative stress). In addition, exogenous factors (dialysate endotoxin, vascular access, cuprophane dialyser material) have been identified in clinical studies which are also responsible, at least in part, for high serum CRP levels. Binding of CRP to degraded low-

density lipoprotein enhances complement activation and induces the expression of tissue factor.

Chronic obstructive pulmonary disease

Studies done in patients with chronic obstructive pulmonary disease (COPD) showed the effect of CRP on activation of the complement system can serve as a factor in maintaining an inflammatory state in stable COPD and thereby contribute to the negative systemic effects associated with COPD. A link between systemic inflammation and comorbidity in COPD has been suggested, and elevated CRP levels in COPD patients with CVD, type 2 diabetes , and lung cancer have been reported.[30] Other authors have shown that frequent readmissions for acute exacerbations of COPD are an independent risk factor for increased mortality and use of health-care resources and serum hs-CRP-D is an independent predictor for the same.[31]

Periodontal disease

Bansal *et* al[32] showed that CRP appears in the serum of patients with some forms of inflammatory oral disease. The highest incidence of positive CRP tests and the strongest CRP test reactions were observed in patients with acute alveolar abscesses. Various studies have proved a positive association between the presence of chronic periodontitis and high serum CRP levels because it is biologically plausible that inflammatory mediators (IL-1, IL-6 and TNF-α) are released under conditions of periodontitis and stimulate the hepatocytes to produce CRP. Similarly, in the presence of chronic periodontitis, higher serum CRP levels are found. Acute bacterial infections have been reported in 80% to 85% of patients with CRP values >100 mg/L. 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.

Transplantation

CRP levels were analyzed after pre-transplant conditioning and variably combined in septic, focal or viral infections with graft-versus-host disease (GvHD) in 64 bone marrow recipients. The CRP levels after pretransplant conditioning were low. The peak levels of CRP were influenced independently by the type of infection, septic and viral infections were significantly different. It was concluded that GvHD and the type of infection were independent determinants of the CRP responses. Therefore, although not highly specific for sepsis, CRP remains a useful detector of sepsis in bone marrow transplantation.[33]

Cancer

Studies done in nasopharyngeal carcinoma showed elevated plasma hs-CRP. Patients with advanced-stage disease were segregated by high Epstein-Barr virus DNA levels and high hs-CRP level into a poorest-risk group, and participants with either high Epstein-Barr virus DNA but low hs-CRP level or high hs-CRP but low Epstein-Barr virus DNA values had poorer survival compared with the bottom values for both biomarkers.[34] Another study on urological cancer showed CRP to be a significant prognostic factor for metastasis and mortality. The prognosis for patients with elevated CRP concentration is poor.

The underlying inflammatory process related to cancer plays an important role in the progression of renal cell carcinoma. On the other hand, systemic inflammation may create a pro-tumor environment and portend a poor prognosis. Numerous studies have shown that CRP is a significant prognostic factor for renal cell carcinoma patients treated with surgery and/or systemic therapy. Dynamic changes in CRP levels can be used to monitor the disease course, such as the effect of treatment intervention or further progression.[35] In metastatic prostate cancer, Rocha *et al*[36] showed that men with higher CRP had significantly worse overall survival than those with lower CRP (hazard ratio [HR] = 1.42, $p < 0.001$, 95% confidence interval [CI] = 1.17-1.73). In trials of castration-sensitive men, high CRP yielded an HR = 1.92 ($p = 0.005$, 95% CI 1.22-3.03). In castration-resistant men, high CRP yielded HR = 1.35 ($p = 0.003$, 95% CI 1.11-1.65) suggesting a detrimental impact for CRP on overall survival. The authors suggested that prospective validation is justified to enhance prognostication and trial design, given the affordability, ready availability, and large dynamic range of CRP. Lumachi *et al*[37] showed a significant inverse relationship between survival and CRP level in colorectal cancer patients. They proposed that CRP is a sensitive and easily detectable serum marker that can be useful in patients with colorectal cancer, allowing their better clinical stratification.

CONCLUSION

Based on solid and consistent evidence, plasma hs-CRP should be included in the routine laboratory tests for risk evaluation and stratification in diverse clinical conditions such as myocardial infarction, stroke, revascularization, atrial fibrillation, diabetic retinopathy, diabetes mellitus, metabolic syndrome, COPD, OSA, PCOS, chronic kidney disease, periodontal disease, and various cancers.

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