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CLINICAL EFFECTIVENESS OF C-REACTIVE PROTEIN AS INFLAMMATION MARKER IN CARDIOVASCULAR DISEASE

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ABSTRACT

The acute phase response protein produced by hepatocytes, C-reactive protein (CRP) is a sensitive inflammatory marker associated with increased risk of cardiovascular disease in healthy individuals. CRP has been shown to have prognostic value in patients with acute coronary syndromes.Elevated levels ofCRP a sensitive predictive marker of cardiovascular disease and acutemyocardial infarction.CRP is present within most atherosclerotic plaques and in events of acute myocardial infraction lesions and its binding ability to lipoproteins and its capacity for pro-inflammatory complement activation. The paper reviews the diagnostic accuracy of CRP in cardiovascular events and its use to determine inflammatory status.

KEYWORDS: Coronary Heart Disease, CRP, Inflammatory Marker

INTRODUCTION

The protein present in the serum of patients with acute inflammation, this protein reacted with C-polysaccharide of *pneumococcus*. C- reactive protein (CRP) was discovered by Tillett 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([I,2].The acute phase response develops in a wide range of acute and chronic inflammatory conditions like bacterial, viral or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury or necrosis,however,discovery of hepatic synthesis demonstrated that it is a native protein[3-6].CRP is the prototype acute-phase protein synthesized in the liver and its release is stimulated by interleukin 6 (IL-6) and other pro inflammatory cytokines [7]. During the acute phase response, levels of CRP rapidly increase within 2 hours of acute insult, reaching a peak in 48 hours. With resolution of the acute phase response, CRP declines with relatively short half-life of 18 hours .Measuring CRP level is a screen for infectious and inflammatory diseases [2].Serum amyloid A is a related acute-phase marker that responds rapidly in similar circumstances[2].Elevated markers of inflammation, in particular CRP,are associated with an increased risk of future cardiovascular events in healthy subjects, in patients with stable or unstable coronary heart disease and acute myocardial infraction [8,9].High- sensitivity C-reactive protein(Hs-CRP) has been shown to have prognostic value in patients with acute coronary syndromes, however, the most promising use of Hs-CRP has been in primary prevention settings.Hs-C – reactive protein not only a marker of low grade chronic systemic inflammation but also may be directly involved in atherosclerosis [10].It can amplify the anti-inflammatory response through complement activation, tissue damage and activation of endothelial cells [11].However, as with other proposed predictors of the risk of cardiovascular events, the prognostic value of these markers of inflammation remain uncertain. For example, a widely held clinical view is that levels of markers of inflammation vary too greatly over time to allow accurate prediction of risk. Furthermore, few prospective studies have measured all these markers of inflammation in a single group of patients, so the relative usefulness of each marker cannot be easily evaluated. In addition, data supporting the hypotheses that markers of inflammation significantly

increase the predictive value of lipid screening are scant and are limited almost exclusively to data from studies of Hs-CRP in middle aged men [12, 13].Hs-CRP has lower diagnostic value in acute appendicitis, surgical patients and in suspected lower-respiratory tract infection [14-16].

HIGH SENSITIVITY C- REACTIVE PROTEIN (Hs-CRP)

The pentraxinfamily, named for its electron micrograph appearance, from the *Greek penta* (five) and *ragos*(berries),[17].comprises CRP and serum amyloid P component (SAP) in man, and is highly conserved in evolution, with homologous proteins throughout the vertebrates and even in the phylogenetically distant arthropod, *Limulus polyphemus,* the horseshoe crab [18]. SAP, named for its universal presence in amyloid deposits [19],is a constitutive, non-acute phase plasma protein glycoprotein in man and all other species studied, except the mouse, in which it is the major acute- phase protein [20].In contrast, mouse CRP is a trace protein, the concentration of which increases only modestly in the acute- phase response to a maximum of about 2 mg/l [21].No mouse CRP knockout has yet been made to our knowledge, and *in vivo*work on CRP [22].

Human CRP is a calcium-dependent ligand protein, which binds with highest affinity to phosphocholine (PC) residues, as well as a variety of other autologous and extrinsic ligands, and aggregates or precipitates the cellular, particulate or molecular structures bearing these ligands. Autologous glands include native and modified plasma lipoproteins, damaged cell membranes,[23,24], a number of different phospholipids and related compounds, small nuclear ribonucleoproteinparticles and apoptotic cells[25-28].Extrinsic ligands include glycan, phospholipid and other components of Micro-organisms ,such as capsular and somatic components of bacteria ,fungi and parasites, as well as plant products [28,29].When human CRP is ligand-bound, it is recognized by C I q and potently activates the classical complement pathway, engaging C 3, the main adhesion molecule of the complement system, and the terminal membrane attack complex, C5-C 9 [30,31]. Bound CRP may also provide secondary binding sites for factor H, and hereby regulate alternative pathway amplification and C 5 convertases[32].

The secondary effects of CRP that follow ligand binding resemble some of the key properties of antibodies, suggesting that under various circumstances CRP may contribute to host defense against infection, function as pro-inflammatory mediator, and participate in physiological and pathophysiological handling of autologous constituents. The impaired CRP response in active systemic lupuserythematosus (SLE) and the spontaneous anti-nuclear autoimmunity of SAP knockout mice are compatible with pentraxin functioning to prevent autoimmunity [33 34].

Role of CRP in Innate Immunity

The conversation of the structure of CRP and of its calcium-dependent specific binding of ligands containing PC are related substances, together with the lack of any known deficiency or protein polymorphism, suggest that this protein must have had survival value. Microbial infection is a major driving force of change during evolution, and CRP has many features compatible with a role in innate immunity. The innate immune system discriminates self from non-self-using a restricted number of pattern recognition receptors that recognize pathogen associated molecular patterns [35],and most micro-organisms that penetrate the body's external barriers are recognized and cleared by cells and molecules which exhibit these broad specifities .If infectious organisms evade these mechanisms, the specific antigen receptor-bearing lymphocytes of the adapted immune system come into play, and significant subsets of lymphocytes, even in the previously unexposed animals, express germ-line-encoded specificity for immunogenic epitopes of pathogens. The T –cell-independent naturalIgM antibodies produced by the progeny of these cells comprise a significant proportion of serum immunoglobulins at birth, sand can both protection against some viral and bacterial infections [36]. and play a role via

complement activation in enhancing specific adaptive T- cell-dependent antibody production [37,38].One important class of highly conserved natural antibodies expresses the so-called T 15 idiotype, binds to PC as does CPR, and CRP, protects against *Streptococcuspneumoniae* infection [39,40] PC is a component of many prokaryotes and is almost universally present in eukaryotes [41].In *Streptococcus pneumonia,* PC is present in the somatic ribitolteichoic acid component and is associated with sugar residues in a variety of other organisms, including *Streptococci,Clostridium,Bacillus*,and *H.influenzae* [42,43].

CRP IN CADIOVASCULAR DISEASE

Several studies have demonstrated a powerful predictive relationship between increased CRP production, even within the range previously considered to be normal, and atherothrombotic events [44].Circulating CRP values correlate closely with other markers of inflammation, some of which show similar, albeit generally less significant, predictive associations [45].However CRP itself is particularly interesting with respect to cardiovascular biology and pathology, because not only does it bind selectively to LDL [46],especially oxidized and enzyme-modified LDL as found in atheromatousplaques, but it is actually deposited in the majority of such plaques [47,48], and it has a range of-pro-inflammatory properties that could potentially contribute to pathogenesis, progression and complications of atheroma [49].

Tissue necrosis is a potent acute-phase stimulus, and following myocardial infarction, there is a major CRP response, the magnitude of which reflects the extent of myocardial necrosis [50].Furthermore, the peak CRP values at around 48h after the onset, powerfully predict outcome after myocardial infarction [50]..Importantly, CRP is deposited within all acute myocardial infarcts, and compelling experimental evidence now suggests that the CRP response not only reflects tissue damage in this context, but may also contribute significantly to the severity of ischemic myocardial injury [51,52].The production of CRP following myocardial necrosis is the typical acute phase response to cell death and inflammation, mediated by action of liver of the cytokines cascade.Especially IL-6, triggered bysuch events. However, the stimuli that trigger the low-grade up-regulation of CRP production that predicts coronary events in general population or the more substantial CRP values associated with poor prognosis in severe unstable angina [53,54] or after angioplasty are not clear [55].The association with future stoke as well as the outcome following stroke, along with the ability of CRP to powerfully predict outcome in chronic renal disease also require explanation[56,57].Heart study from Framingham did find an association between CRP and coronary calcification. The distinction between so called ‘ disease markers’ and ‘process markers’ is important, particularly with respect to inflammation, not least because our concepts of the underlying disease processes continue to evolve[58,59].

In a prospective study of apparently healthy postmenopausal women, four markers of inflammation –Hs-CRP, serum amyloid A, interleukin-6 and sICAM-1 – were found to be significant predictors of the risk of future cardiovascular events. In addition, measurement of these markers increased predictive value of models based only on standard lipid screening. Of the 12 plasma measures evaluated in the study, Hs-CRP was the most significant predictor of risk of cardiovascular events; when measured widely available, standardized commercial assay, this marker distinguished between women at high risk and those at low risk and those at low risk, even in the subgroup of women with LDL cholesterol levels below 130 mg per deciliter (mean, 104 mg per deciliter), the target considered safe in the current guidelines of National Cholesterol Education Program[60,61].In another findings, which indicate that Hs-CRP is a potent predictor of risk regardless of LDL cholesterol level, data from the Cholesterol and Recurrent Events trail indicate that use of pravastatin resulted in decreased levels of Hs-CRP in a manner largely independent of LDL cholesterol [62].According to Ridker*et al* [10], Hs-CRP has emerged as a strong independent risk factor for future cardiovascular events that add prognostic information at all levels of LDL cholesterol, at all levels of Framingham Risk Factor Score (RFS), and at all levels of

metabolic syndrome.Pearson *et al* (2003) suggested that levels of Hs-CRP of <1, 1to<3, and ≤3 mg /L be used to represent low, moderate, and high vascular risk [63].

Atherothrombosis of the coronary and cerebral vessels is understood to be a disorder of inflammation and innate immunity, as well as a disorder of lipid accumulation. From a vascular biology perspective, the process of cellular adhesion, monocyte and macrophage attachment and transmigration of immune cells across the endothelium are crucial steps in early atherogenesis and in the later stages of mature plaque rupture, particularly the transition of unstable plaque at the time of acute thrombosis[64].There is abundant clinical evidence demonstrating that many biomarkers of inflammation are elevated years in advance of first myocardial infarction (MI) or thrombotic stroke and that these same biomarkers are highly predictive of recurrent MI, recurrent stroke, diabetes, and cardiovascular death. In daily practice, the inflammatory biomarker is widest use ishs-CRP, when interpreted within the context of usual risk factors, levels of Hs-CRP [64].Hs-CRP evaluation has recently been endorsed by the Centers for Disease Control and Prevention and by the American Heart Association to be used in conjunction with lipid evaluation as part of global risk prediction [65].Hs-CRP is a marker of inflammation that predicts incident myocardial infarction,stroke,peripheral arterial disease, and sudden cardiac death among healthy individuals with no history of cardiovascular disease, and recurrent events and patients with acute or stable coronary syndromes [66].Cardiovascular disease (CVD) is a multifactorial in etiology. Traditional cardiovascular risk factors such as increased cholesterol concentrations, blood pressure, are used to assess CVD risk .Recently better understanding of the role of inflammation in the atherosclerosis has prompted many to propose the measurement of various inflammatory markers to a better identify those who are at increased risk. C-reactive protein is found in endothelial atherosclerotic lesions evidence suggest that it may play role in atherogenesis[67].

DIAGNOSTIC ROLE OF CRP IN OTHER DISEASES

Increased production of CRP may reflect inflammation elsewhere in the body, although there no strong correlation with serological evidence of the various chronic microbial infections, such as *Chlamydial pneumonia* and *Helicobacter pylori*, that have been putatively linked with coronary heart disease [66].Indeed, within what was until recently accepted as the reference range for circulating CRP concentration up to 5 or 10 mg/I higher values have now been found strongly associated with increased body mass index [68,69],and also with features of the insulin resistance or metabolic syndrome, up and including diabetes mellitus [70,71].

CRP in Acute Appendicitis

Serum C-reactive protein was measured in 56 patients hospitalized with a suspected diagnosis of acute appendicitis. It was concluded that an increased CRP levels to more than 2.5 mg/dl is not a definite indicator of acute appendicitis. However, if the CRP level in blood drawn 12 hours after the onset of symptoms is less than 2.5 mg/dl, acute appendicitis can be excluded [72].

CRP in Acute Surgical Patients

Serum CRP levels were measured retrospectively in 473 surgical patients who presented to the Royal Adelaide Hospital emergency department. This was correlated with patient outcomes, defined by the need for imaging tests and/ or surgical interventions.Thelength of hospitalstay and 30-day mortality. Spearman's rank correlation and one-way analysis of variance were used for statistical analysis. It was concluded that CRP has poor diagnostic and prognostic capabilities as a single initial measurement in acute surgical patients. Statistical analysis implies that CRP levels are unable to accurately predict outcomes of such patients [15].

CRP in Lower Respiratory Tract Infection

Excessive prescription of antibiotics in patients with lower respiratory tract infection (LRTI) is common in primary care and might be reduced by rapid point-of care (POC) C-reactive protein testing. Engel*et al* (2012) reviewed the available evidence for the role of POC, CRP measurement in (i) guiding antibiotic prescription,(ii) predicting a etiology,(iii) and (iv) diagnosis (pneumonia) in LRTI patients.

It was concluded that evidence for the benefits of POC, CRP measurement in LRTI patients in primary care is limited, contradictory and does not support its use to guide treatment decisions yet [16].Victor van et al (2005)investigated the diagnostic accuracy of CRP with chest radiograph to discriminate between bacterial and viral infections of LRTI. It was concluded that testing CRP is neither sufficiently sensitive to rule out nor radiograph and bacterial etiology of LRTI.The evidence not consistently and sufficiently supports wide use introduction of CRP prescription [73].

CRP in Patients with Malignancy and Connective Tissue Infection

Serum C-reactive protein levels were measured in 22 patients, 15 patients with malignancy and connective tissue disease. Results showed that CRP concentration has a significant association with a positive culture {p=0.0023) but there was no sufficient evidence for an association between the parameters and presence of leukocytosis .CRP testing has a 84.6% sensitivity, 66% specificity as well as 80 % positive predictive value and a negative predictive value of 85%.The results were comparable to published reports on the diagnostic value of CRP determination [74].

CRP VERSUS OTHER INFLAMMATORY AND INFECTION MARKERS

Amyloid, a human acute- phase protein, serum amyloid A, has been reported to potentiate the adhesiveness and chemo taxis of phagocytic cells and lymphocytes. There is also evidence that macrophages bear specific binding sites for serum amyloid A; serum amyloid A-rich, high density lipoproteins mediate the transfer of cholesterol to macrophages at sites of inflammation and serum amyloid A enhances low-density lipoprotein oxidation in arterial cells [75,76].

Giovanna et al (1994) measured CRP ,serum amyloid A protein ,creatine kinase and cardiac troponin T in 32 patients with chronic stable angina, 31 with severe unstable angina and 29 with acute myocardial infarction. It was concluded that elevation of CRP and serum amyloid A protein at the time of hospital admission predicts a poor outcome in patients with unstable angina and may reflect an important inflammatory component in the pathogenesis of this condition [77].

Procalcitonin, a calcitonin propertied normally produced in the C cells of the thyroid gland, has recently drawn attention as specific marker of systemic inflammatory response to infection. During systemic infection, extra thyroid tissues produce procalcitonin; the exact site of production during sepsis in uncertain, Procalcitonin levels increase dramatically in patients with sepsis, are detectable within 3 hours of induction onset (at **least 20 hours earlier than CRP**), have a much longer half –life than cytokines and are stable in serum or plasma at room temperature (**>90% in 12 hr**).Elevated procalcitonin levels (**>0.5 nm/mL**) in emergency department patients with suspected infectious disease indicate ongoing and potentially severe systemic infection with an increased risk of fatal outcome.

The specificity of procalcitonin threshold more than 0.5 ng/mL approaches 100%, but levels below this threshold do not rule out infection [78].Mark *et al*.,(1999) suggested that in critically ill children the admission procalcitonin concentration is a better marker of infection than CRP or leukocyte count. A procalcitonin concentration of 2 ng/mL might be useful in differentiating severe disease in infants' and children [79].

Propcalcitonin and CRP in Bacterialmeningitis

Several proteins have been examined for their usefulness in the diagnosis of bacterial meningitis. Specifically CRP detected either in the serum or CSF, and serum procalcitonin concentration have been elevated in patients with acute bacterial meningitis and may be useful in discriminating between bacterial and viral meningitis. In one study CRP was capable of distinguishing Gram stain-negative bacterial meningitis from viral meningitis on admission with sensitivity of 96%, a specificity of 93%, and negative predictive value of 99% [80]. In another study, a serum procalcitonin concentration of more than 0.2ng/mL had a sensitivity and specificity of up to 100% in the diagnosis of bacterial meningitis, although false negative results have been reported[81,82]..

CONCLUSIONS

CRP is a novel screening test for cardiovascular disease, bacterial meningitis and other infections. CRP is less valuable in acute appendicitis, surgical patients and in lower respiratory tract infections. Serum protein amyloid A is useful test in unstable angina .Procalcitonin levels are useful in systemic infections.

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