International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Online International Journal Available at http://www.cibtech.org/jms.htm
2013 Vol. 3 (3) September-December, pp.114-119/Balakrishnan et al.
Review Article

C REACTIVE PROTEIN AS A MARKER OF ASTHMA CONTROL

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ABSTRACT
CRP is a marker of inflammation and increased levels have been associated with aging, smoking, cardiovascular diseases, connective tissue disorders and chronic obstructive pulmonary disease (COPD). Asthma is defined as a state of chronic inflammation where various cellular elements are involved. It is reasonable to expect elevated CRP levels in this chronic inflammatory disease. Hs-CRP assays are capable of detecting low grade inflammation that is not possible by the standard CRP kits. Elevated CRP has been associated with acute exacerbation, deteriorating pulmonary function parameters and increased sputum eosinophil levels in asthma. We hope to explore the role of CRP in asthma in detail. Understanding the interplay between CRP and asthma may allow us to predict future exacerbation and better monitoring of asthma.

Key Words: *Asthma, CRP, Hs-CRP, Exacerbation, Inflammation*

INTRODUCTION

Asthma is a problem worldwide with estimated 300 million affected individuals contributing to a large morbidity and economic burden (GINA 2009). It is estimated that nearly 13 million persons have asthma in India.

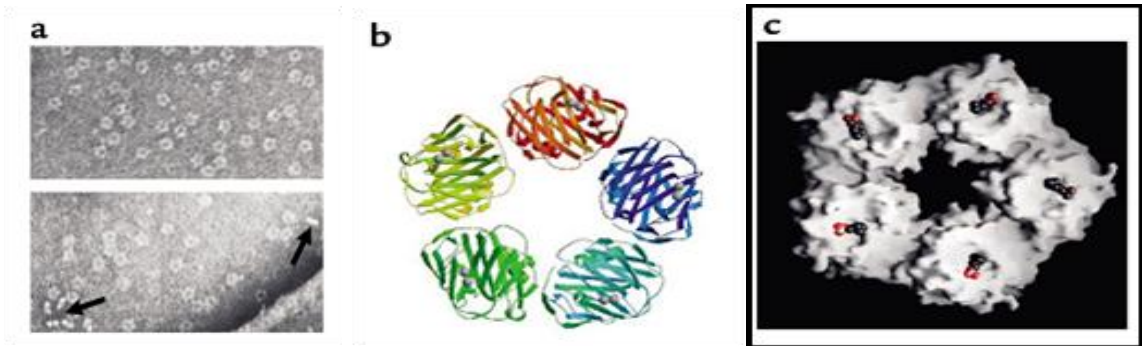

Figure 1: Molecular structure and morphology of human CRP
a) Negatively stained electron micrograph showing the typical pentameric disc-like structure face-on and side-on (arrows). (b) Ribbon diagram of the crystal structure, showing the lectin fold and the two calcium atoms (spheres) in the ligand-binding site of each protomer (Thompson *et al.*, 1999). (c) Space-filling model of the CRP molecule, showing a single phosphocholine molecule located in the ligand-binding site of each protomer (Thompson, 1999)

Though majority of patients of asthma can be controlled with inhaled medications, there are several patients who experience poor control of the disease with frequent exacerbations. These patients require early identification so that their medications may be stepped up so as to prevent severe asthma episodes which require hospitalization and intensive care support. Therefore there is the need to explore new markers that could help us to predict the kind of patient that requires more care, to predict when an

exacerbation is more likely and to monitor a patient with brittle disease. C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. It is this context that C reactive protein (CRP) is showing promise as a marker to predict those patients with poorly controlled asthma, brittle asthma and those who are prone to exacerbations and episodes of acute severe asthma.

CRP is a plasma protein which belongs to the pentraxin group and has been consistently used as a marker of inflammation, infection and tissue damage. It is synthesized by the liver and to a large extent its manufacturing is regulated by IL-6 (Gillman *et al.,* 2000). Monocytes, lymphocytes and neutrophils are also able to produce CRP (Baumann *et al.,* 1994). CRP could elicit macrophage activation through interaction with Fc receptors for antibodies (Wolbink *et al.,* 1996). CRP inhibits T- lymphocyte binding to antigen receptors (TCR). It has been demonstrated that CRP acts directly on monocytes and neutrophils through recognizing CRP-R receptors on their surface (Baumann *et al.,* 1994). The population of monocytes with specific surface antigenic determinants with an affinity to CRP has also been described by Müller *et al.,* (1986).

C-reactive protein (CRP) is one of the most characteristic markers of the inflammatory process. Its 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. The monitoring of CRP levels is a good diagnostic tool and is very useful in the assessment of early inflammation, as well as, in treatment monitoring and efficacy in acute-phase diseases (Ford *et al.,* 2003). Raised CRP levels have been associated with cardiovascular diseases, diabetes, obesity and ageing (Yudkin *et al.,* 1999). Smoking cessation has been linked with decreasing levels of CRP (Nakamura *et al.,* 2002). Measuring CRP level is a screen for infectious and inflammatory diseases. Rapid, marked increases in CRP occur with inflammation, infection, trauma and tissue necrosis, malignancies, and autoimmune disorders. Because there are a large number of disparate conditions that can increase CRP production, an elevated CRP level does not diagnose a specific disease. An elevated CRP level can provide support for the presence of an inflammatory disease

CRP may serve as a general scavenger protein and play an important role to recognize bacteria and damaged human cells and to mediate their elimination through opsonisation, phagocytosis, and cell-mediated cytotoxicity. The CRP can also activate the classical complement cascade by binding directly to the complement fragment C1q (Pepys *et al.,* 2003). High sensitivity CRP measurements enable detection of low levels of CRP which was not possible with the routine CRP kit. The standard assays for CRP have a lower detection limit of 3-8 mg/L and thus lack the sensitivity required to determine low-grade systemic inflammation levels (Ridker *et al.,* 2001). HS-CRP has a sensitivity of 0.04mg/LCRP values can never be diagnostic on their own and can only be interpreted at the bedside, in full knowledge of all other clinical and pathological results. However, they can then contribute powerfully to management, just as universal recording of the patient's temperature, an equally nonspecific parameter, is of great clinical utility (Mark *et al.,* 2003).

In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/l, and the 99th centile is 10 mg/l (Shine *et al.,* 1981). Higher levels are found in pregnancy. Following an acute-phase stimulus, values may increase from less than 50μg/l to more than 500 mg/l, that is, 10,000-fold. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate (Vigushin *et al.,* 1993) which thus directly reflects the intensity of the pathological process(es) stimulating CRP production. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR.

CRP and other Respiratory Diseases

CRP has been associated with decline in lung function. In a cohort study done in Denmark, it was found that higher levels of CRP at 20 yrs predicted the subsequent decline in lung function by age 29 yrs (Rasmussen *et al.,* 2009). This association was independent of smoking, BMI, cardiorespiratory fitness, AHR, asthma and serum ECP. The findings indicate that there is an association between systemic

inflammation and the decline in lung function that is not explained by asthma, smoking-related lung disease, poor fitness or obesity.

CRP has been studied extensively in chronic obstructive pulmonary disease(COPD). It was observed that CRP levels both in sputum and serum were higher in COPD patients as compared to healthy adults (Wu *et al.,* 2005). Moreover there was significant negative correlation between serum CRP and lung function indices. Broekhuizen *et al.,* (2006) observed that, irrespective of FEV1, COPD patients with a raised plasma level of CRP had more impaired energy metabolism, increased disability as defined by impaired exercise capacity, and more distress due to respiratory symptoms than patients with normal CRP levels. In addition CRP levels have been found to be predictor of future hospitalisation and death in COPD patients independent of smoking and lung function (Dahl *et al.,* 2007).

CRP levels have been found to be of value in diagnosing community acquired pneumonia (Vugt *et al.,* 2013). CRP levels were observed to be raised significantly in pneumonia patients as compared to acute exacerbation in COPD patients (Smith *et al.,* 1995). CRP levels were found to be important predictor of serious course in H1N1 influenza patients. Those with higher CRP values were associated with subsequent ICU admissions and mechanical ventilation (Zimmerman *et al.,* 2010).

CRP is also increased in obstructive sleep apnea (OSA). Patients with OSA have higher plasma CRP concentrations that increased corresponding to the severity of their apnea-hypopnea index score. Treatment of OSA with CPAP (continuous positive airway pressure) significantly alleviated the effect of OSA on CRP (Bateman *et al.,* 2004)

CRP and Asthma

Asthma is a chronic inflammatory disorders of the airways in which many cells and cellular elements play a role (GINA 2009). Not only local inflammation but also systemic inflammation is known to be associated with asthma. Therefore it is justified to expect CRP level which is a marker of inflammation to be raised in asthmatics as well.

The role of CRP in asthma has been studied by many and debates still remain about its correlation with severity and control. We conducted a study to evaluate high sensitivity CRP (hs-CRP) as a predictor of exacerbation in bronchial asthma by correlating it with exacerbation rate and FEV1. hs-CRP and FEV1 was assessed in 64 patients of severe bronchial asthma during remission. The number of exacerbations was assessed over 10 months (March to December). hs-CRP and FEV1 were repeated during exacerbations or at end of study.

A total of 53 exacerbations were observed in the study group (mean ± SD = 0.828 ± 0.79). hs-CRP level during remission (CRP_Rem) was 1.719 ± 1.43. There was partial positive correlation between CRP_Rem and exacerbations ($r=0.763$, $p<0.01$). hs-CRP levels was seen to rise (1.525 ± 1.90, $p<0.01$) and FEV1 decrease during exacerbations (0.735 ± 0.45, $p<0.01$). hs-CRP and FEV1 showed partial negative correlation during remission ($r=-0.5$, $p<0.01$) and during exacerbations ($r=-0.2$, $p>0.05$). Of the study population, in those with hs-CRP<1 during remission (n=29) there were 7 exacerbations (0.241 ± 0.43), CRP_Rem was 0.465 ± 0.28. In subjects with hs-CRP of 1-3 (n=20) 21 exacerbations were seen (1.05 ± 0.61), CRP_Rem was 1.94 ± 0.65. In those with hs-CRP>3 (n=15) there were 25 exacerbations (1.666 ± 0.62) with CRP_Rem of 3.847 ± 0.50.

We concluded that significant positive correlation of hs-CRP with exacerbation rates and significant negative correlation of hs-CRP and FEV1 are seen during remission. Thus hs-CRP levels during remission may be used as a marker for predicting future exacerbations in asthmatics (Menon *et al.,* 2008)

Kony *et al.,* (2004) in a population-based study showed associations of increased levels of serum hs-CRP with a high frequency of airway hyperresponsiveness and low forced expiratory volume in one second (FEV1) among subjects without heart disease. CRP has been inversely correlated with FEV_1.CRP has been demonstrated by Obaidi and colleagues to be higher in asthmatics as opposed to controls (Obaidi *et al.,* 2010). Furthermore it was observed that CRP levels were significantly higher during exacerbations than in stable asthmatic patients.

In a study done in Iran similar findings of high CRP levels in asthmatics with exacerbration as compared to controls were observed but the mean hs-CRP levels did not correlate with pulmonary function parameters, IgE or eosinophils (Razi *et al.,* 2012). Takemura *et al.,* (2006) observed that serum CRP levels were significantly raised in steroid naïve asthmatics as compared to controls but not in asthmatics on inhaled steroids. Among steroid-naive patients, serum hs-CRP levels significantly negatively correlated with indices of pulmonary function (forced expiratory volume in one second/forced vital capacity and forced mid-expiratory flow) and positively with sputum eosinophil count. No similar correlation was observed in patients on inhaled corticosteroid. It is most likely that CRP levels signals asthma exacerbation which is associated with rise in inflammation. Inhaled steroids suppress airway inflammation but do not have significant effect on systemic inflammation. Therefore the question arises can CRP predict local inflammation as well. In contrast Mojtaba *et al.,* (2011) and group did not find any significant correlation between CRP levels and FEV_1, FVC and FEV_1/FVC.

Elbehidy and colleagues observed that the levels of hs-CRP were significantly higher in patients with uncontrolled asthma than in the group with controlled disease (Elbeihidy *et al.,* 2010). Hs-CRP correlated negatively with FEV1% and positively with sputum eosinophil%. Hs-CRP correlated positively with neutrophil % in ICS treated asthmatics but it was highly significant in uncontrolled asthmatic group. Eosinophils play an active role in airway inflammation, bronchial hyper responsiveness and airway remodelling in asthma. The positive correlation of hs-CRP with sputum eosinophil further validates CRP as a marker for acute asthma.

Similar to the findings of Takemura *et al.,* (2006), Lama and colleagues observed that the serum CRP concentration was elevated in the ICS-naïve children with asthma while ICS-inhaling children had normal serum CRP concentration (Lama *et al.,* 2010). In another study by Kasayama *et al.,* (2008), it was revealed that the plasma CRP levels were significantly reduced in corticosteroid-naïve asthmatic patients treated with inhaled corticosteroid for 3 months. Hs-CRP has been particularly associated with non atopic asthma (Sahoo *et al.,* 2009). They observed that hs-CRP were higher in non atopic asthma patients as compared to asthmatics. There was positive correlation of hs-CRP with age in non atopic asthmatics where as there was no correlation in atopic asthmatics. Apart from the fact that aging is associated with rising CRP levels, hs-CRP did not show any correlation in atopics. Therefore removing aging as a confounding factor, it can be said that hs-CRP measurements may be particularly useful to monitor non atopic asthmatics.

It is thus suggested from the above discussion that there is sufficient evidence to suggest that CRP levels can be used to monitor inflammation in asthma. This knowledge can be used to predict asthma exacerbation and identify poor asthma control thereby providing better patient treatment and prevent life threatening exacerbations.

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