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A STUDY ON HIGHLY SENSITIVE C-REACTIVE PROTEIN (HS-CRP) IN INDIAN PATIENTS WITH BRONCHIAL ASTHMA

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ABSTRACT

C-reactive protein (CRP) is an acute phase protein synthesized in response to tissue damage or inflammation and reflects total systemic burden of inflammation in individuals. Introduction Asthma is an inflammatory disorder of the airways that involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes. The airway inflammation in asthma is persistent even though symptoms are episodic. The study was conducted on 100 consecutive patients diagnosed as having bronchial asthma and admitted in the Deccan College of Medical Sciences, Hyderabad, and Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry. The study suggests that there exists a certain degree of low-grade systemic inflammation in addition to the local bronchial inflammation in non-atopic asthmatics. Hence, hs-CRP may be used as a surrogate marker for the airway inflammation in non-atopic asthma patients. There is an association between airway inflammation in bronchial asthma and systemic inflammation.

Key words: C-reactive protein, High-sensitivity C-reactive protein, non-atopic asthma, Acute phase proteins.

INTRODUCTION

Asthma is a chronic inflammatory disease of large, small and medium airways with typical symptoms (cough, wheeze, breathlessness, chest tightness) and airway narrowing that is partially or completely reversible either spontaneously or by treatment associated with increased airway responsiveness to a variety of stimuli.[1] The prevalence of asthma increased steadily worldwide over the last several decades. Current estimates suggest that asthma affects 300 million people worldwide, with a predicted additional 100 million people to be affected by 2025 and approximately 250000-34500 people die per year from the disease [1].

Bronchial asthma is classified pathophisiologically into two types, atopic and non atopic asthma.[2] According to the level of control, asthma is classified into three types, well controlled asthma, partially controlled asthma and uncontrolled asthma.1 C-reactive protein (CRP) is a major inflammation sensitive plasma protein in humans. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine interleukin 6 (IL-6).[3] The measurement of CRP level in the blood is simple and has been used for decades in clinical practice to follow the progression of inflammatory processes.[4] Reduced lung function has been associated with various inflammation sensitive plasma proteins.[5-6]

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Reduced lung function has been associated with various inflammation sensitive plasma proteins. [5-6] Standard assays for CRP lack the sensitivity needed to determine the levels of inflammation and thus, clinical utility of standard CRP evaluation is extremely limited. Recent improvements have resulted in a new generation of highly sensitive assays that can detect the CRP at levels 100-fold lower than the earlier assays. [7] CRP determined using a highly sensitive assay is referred to as highly sensitive CRP (hs-CRP). Using hs-CRP, assessment of conditions indicative of chronic, low-grade inflammation is now possible. A positive association has been reported between raised hs-CRP levels and current asthma, respiratory impairment and bronchial hyper-reactivity in several studies. [5-8]

There is an association between increased hs-CRP levels and non-allergic asthma even when adjusted for body weight, but not so between hs-CRP and allergic asthma.3 An association has been reported between elevated hs-CRP levels and respiratory symptoms, such as wheeze, attack of breathlessness and nocturnal cough.3 The present study aims to evaluate the significance of hs-CRP in atopic and non-atopic asthma cases.

MATERIAL AND METHODS:

The study was conducted on 100 consecutive patients diagnosed as having bronchial asthma and admitted in the Deccan College of Medical Sciences, Hyderabad, and Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry. 25 non-asthmatics satisfying the exclusion criteria served as controls.

Patients were included if they had a clinical diagnosis of asthma and spirometry showing reversibility of more than and equal to 12% in forced expiratory volume in one second (FEV1), or at least 200 mL from baseline after inhalation of salbutamol (4×100 mcg) given by metered dose inhaler using a spacer device. Patients with upper or lower respiratory tract infection, trauma, collagen vascular disease, malignancy, ischemic heart disease, diabetes mellitus, hypertension and a body-mass index (BMI) more than 15, were excluded from the study. Elevated total immunoglobulin-E (IgE) and positive skin prick test was used to define the atopic status.

Informed consent was obtained from all the patients prior to enrolment. All the patients underwent a detailed symptom enquiry, physical examination and investigations including a complete blood count, sputum for Gram stain and pyogenic culture, chest radiograph (postero-anterior view), radiograph of the paranasal sinuses (Waters view), spirometry pre- and post-bronchodilator, serum total IgE, and skin prick test. The hs-CRP was measured in the peripheral venous blood samples in all the patients by a semi quantitative assay using Latex enhanced immunoturbidimetric test.

Statistical Analysis:

The data was analysed with Kruskal Wallis test and p values greater than 0.05 considered to be significant. Results were expressed as mean ± standard deviation (SD).

Table 1. Demographic profile of patients with bronchial asthma

Patient Characteristics	Atopic (N=91)	Non-atopic (N=9)
Age in years (mean)	35.3	32.8
Gender (Male : Female)	85 : 98	5 : 12
Smoking History		
Smokers	14	2
Ex-smokers	8	-
Non-smokers	69	15
Serum IgE level (mean)	1524.5	202.6

Table 2. Comparison of hs-CRP levels in study and control groups.

	Number of Patients	Mean±SD	95% Confidence Interval for Mean	
			Lower bound	Upper bound
Atopic asthma	91	2.9±2.1	2.6	3.2
Non-atopic asthma	9	8.3±2.5	7.1	9.6
Controls	50	1.9±1.2	1.5	2.2

RESULTS:

100 patients with bronchial asthma and 50 control subjects were enrolled in the study. Out of the 100 cases of bronchial asthma, 91 were atopic and 9 were non-atopic. The mean age of the patients in the atopic group was 35.3 years, while in the nonatopic group it was 32.8 years and in the control group it was 29.1 years. The demographic profile of the final cohort of 200 asthma patients is given in (T**able 1)**. A statistically significant increase in hs-CRP levels with age in atopic asthmatics ($p<0.001$). It was observed that asthmatic subjects had higher hs-CRP values than non-asthmatics **(Table 2).** Subjects with non-allergic asthma had higher hs-CRP levels ($p<0.001$) as compared to atopic asthmatics and control subjects.

DISCUSSION:

It is well known that CRP increases during infection and autoimmune disorders [9]. A positive relationship has been reported between elevated CRP levels and current asthma [10,11], respiratory impairment [12], and BHR [13]. In recent years, there have been some reports on the measurements of serum levels of Hs-CRP as a useful tool for the detection of systemic inflammation in asthma [14–16]. In asthma, the importance of airway inflammation has been well established. Beside the airway inflammation, systemic inflammation may exist in asthma.
The CRP is predominantly synthesized in the liver and is regulated by pro-inflammatory cytokines, primarily the tumour necrosis factor-alpha and interleukin-6 (IL-6). During an acute-phase response, there is a rapid increase in the production of CRP (≥10,000-fold), resulting in the release of elevated quantities into the circulation. The plasma half-life of CRP is approximately 19 hours. Although its function is still unclear, the CRP may serve as a general scavenger protein and play an important role in opsonisation, phagocytosis, and cell-mediated cytotoxicity. The CRP can also act as a potent proinflammatory agent and activates the classical complement cascade by binding directly to the complement fragment C1q. [17-18]

Standard assays for CRP lack the sensitivity needed to determine the levels of inflammation, and thus, clinical utility of standard CRP evaluation is extremely limited. Recent improvements have resulted in a new generation of highly sensitive assays that can detect the CRP at levels 100-fold lower than the earlier assays.[19] The CRP determined using a highly sensitive assay is referred to as highsensitivity-CRP (hs-CRP). Using hs-CRP, assessment of conditions indicative of chronic, low-grade inflammation is now possible. With the newer assays, the Centers for Disease Control and Prevention (CDC) has determined a value of 0.08-0.5 mg/L as a normal reference range for healthy persons.[20]
In the present study, most of the patients were in the 2nd to 4th decade of life. A previous study by Janson et al [21] had found ageing to be a confounding factor of elevated hs-CRP levels. This association between hs-CRP levels and age was not observed in non-atopic asthma patients and control subjects in our study. However, a weak but a statistically significant positive association between hs-CRP levels and age in atopic asthmatics was observed. The gender difference in CRP is controversial. Our study revealed that there is no statistical relation between sex and hs-CRP levels.

Subjects with atopic asthma (n=91) out-numbered non-atopic asthmatics (n=9) in our study which seems to be comparable with earlier studies that also reported that among asthmatics the majority belong to the atopic group. The present study confirms the results of the earlier studies which found that hs-CRP levels are related to smoking and that smoking is an independent confounding factor of elevated hs-CRP.[22] The relevance of high-sensitivity assays for the hs-CRP which is known to be a sensitive marker of low-grade systemic inflammation has not been fully studied in asthma.

Our study also concluded that non allergic asthma in particular is strongly associated with higher CRP levels, whereas allergic asthma is not.3 Our study also showed that non-atopic asthma is strongly associated with higher hs-CRP levels, whereas allergic asthma is not. The present study included a large number of atopic asthma patients as compared to the non-atopic asthma patients and such a comparison is likely to have its own fallacies which should be kept in mind whilst drawing study also concluded that non allergic asthma in particular is strongly associated with higher CRP levels, whereas allergic asthma is not. Our study also showed that non-atopic asthma is strongly associated with higher hs-CRP levels, whereas allergic asthma is not. The present study included a large number of atopic asthma patients as compared to the non-atopic asthma patients and such a comparison is likely to have its own fallacies which should be kept in mind whilst drawing conclusions.

CONCLUSION:

There is an association between airway inflammation in bronchial asthma and systemic inflammation. CRP is markedly increased in asthmatic patients, especially during exacerbation. Increases in CRP levels were associated with a steeper decrease in FEV1 and impaired other pulmonary function parameters. It is recommended to use serum CRP as a sensitive marker and a diagnostic tool for the detection and monitoring of airway inflammation in patients with bronchial asthma.

The non-atopic asthmatics, in addition to the local airway inflammation, some degree of systemic iflammation also exists, that may be detected using hs-CRP as a surrogate marker. We suggest that hs-CRP levels may be used as a systemic biomarker for the lung inflammation in non-atopic asthmatics as it can be easily measured as compared to exhaled biomarkers.

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