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Role of high sensitive C-reactive protein as a marker in assessing severity of asthma

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***Abstract*---**Increased serum high sensitive C-reactive protein (hs-CRP) in asthma and its association with disease severity has been investigated in many studies. This study aimed to determine serum hs-CRP status in asthma versus healthy controls and to examine its ability in predicting asthma control. This is a comparative-descriptive and observational study was carried out in the TB & Respiratory Medicine, N.C Medical College and Hospital over a period of 6 months. Total 70 patients (both old and newly diagnosed cases) were selected for the study for case group patients were on maintenance treatment including inhaled corticosteroids and bronchodilators according to the guideline treatment of asthma. In our present study, a total of 70 patients were included out of which 38 (57.4%) were males. In our study, most of the patients were 51-70 years i.e., 38 out of 70 (54.2%), followed by 31-50. The mean hs CRP of Case group patients are 4.31±1.46 and in control group patients 0.83±0.07. Pulmonary function test using Spirometer was s done in all the patients (case and control). The FEV1 values are compared against hsCRP values. Statistical significance is assessed using Spearman's correlation. Case group patients showing highly significant negative correlation of hsCRP with FEV1. These findings indicate that serum hs-CRP in asthma is higher than healthy control and increases with severity of asthma. Thus, serum hs-CRP measurement can be helpful in predicting asthma control and treatment response.

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Introduction

Systemic inflammation and reversible airflow narrowing is the dominant physiological feature of asthma. [1] Existence of inflammation is not limited to severe asthma, but even mild and moderate asthma are also associated with inflammation of the airway wall with abnormal accumulation of inflammatory cells and airway hyper-responsiveness. [2] Structural changes due to remodeling process result in irreversible airway narrowing and incompletely reversible airways' dilatation, bronchial hyper-responsiveness, airway edema, and hyper secretion. These changes are representative of severe inflammation and predispose patients to disease exacerbation and even death. [3] Existence of inflammatory process in asthma and its relationship with disease severity as well as deterioration of pulmonary function has been shown in several studies. [4] Inflammation plays an important role in the pathogenesis and progression of asthma, and thus, treatment of asthma is targeted to suppression of inflammatory process to achieve clinical response. [5]

Efficiency of treatment in asthma is based on clinical examination and pulmonary function test. Furthermore, suppression of inflammation with appropriate treatment is also associated with reduction of serum hs-CRP level. [6] These observations provide a rational for serum hs-CRP to be considered as a means for detection of systemic inflammation, response to treatment as well as for estimating asthma status. Response to treatment of asthma is evaluated by Asthma Control Test (ACT) [7] but variations in clinical features which constitute the components of the ACT criteria do not usually correlate with extent of pulmonary airway structural changes. This issue warrants an insured measurable mean for the evaluation of both severity of clinical features and inflammatory process. The ability of several bio markers has been tested for diagnosis, evaluation of treatment, or prognostic purposes in asthma as well as in chronic obstructive pulmonary disease (COPD). [8]

In patients with asthma the potential of serum CRP, SAA and fibrinogen in recognizing local or systemic inflammation has been shown [9] especially serum CRP which is a known parameter of inflammatory process, is sensitive to changes and readily accessible with low cost. In particular, the high-sensitive method of serum CRP measurement (hs-CRP) can detect minimal variations of serum CRP levels even in the range of normal limits, and thus can be considered as a sensitive marker for the identification of low grade systemic inflammation. The serum CRP has been used for evaluation of treatment in chronic pulmonary airway disease and other inflammatory conditions. [10] The reliability of hs-CRP as an inflammatory marker of asthma has been confirmed in correlation with sputum eosinophils. [11] Nonetheless, the ability of serum hs-CRP in predicting asthma control has not been investigated yet. For these reasons, the present case-control study was designed to determine the serum hs-CRP status in asthma versus healthy control and to examine the relationship between hs-CRP and asthma control determined by ACT criteria.

The aim of our investigation is survey the degrees of hsCRP in asthmatic patients, with the targets to assess the serum levels of hsCRP in asthmatic patients and to correlate the hsCRP in asthmatic patients with or without inhaled corticosteroids treatment, and to observe the relationship of hsCRP levels to clinical records of asthma.

Material and Methods

This is a comparative-descriptive and observational study was carried out in the TB & Respiratory Medicine, N.C Medical College and Hospital over a period of 6 months. Total 70 patients (both old and newly diagnosed cases) were selected for the study for case group patients were on maintenance treatment including inhaled corticosteroids and bronchodilators according to the guideline treatment of asthma [13].

Inclusion criteria

Patients of age 18 to 80 years, both male and female gender who are diagnosed with clinical symptoms of asthma with a criteria of Spiro metric analysis results showing a 15% increase and 200 ml increase in FEV 1 post bronchodilator.

Exclusion criteria

Patients with age less than 18 and more than 80 were excluded from the study. Further exclusion criteria include, current smokers, recent or current infection, history suggestive of any systemic inflammatory disease, obesity, coronary heart disease, diabetes, heart failure, history of venous thromboembolism, kidney disease, liver disease, malignancy and rheumatologic illness.

Normal volunteers

The normal volunteers recruited in to the investigation as controls based on the willingness and with a criterion that none of them had any past history of lung or hypersensitive ailment and were not utilizing any drug. At the time of recruitment, they all underwent full clinical examination, pulmonary function tests, and blood sampling. The control group volunteers had normal lung function tests (FEV1>83%) and normal IgE level. Those with high IgE were considered as atopic asthma.

Methods

Patients diagnosed with bronchial asthma present to pulmonary medicine OPD, those who satisfy the inclusion criteria were recruited into the study. In addition, the diagnostic work up which includes chest x ray, total and differential leukocyte count, and pulmonary function test. Blood samples were collected from such patients and also from controls and sent for high sensitivity CRP analysis the levels were noted.

Estimation of high-sensitivity C-reactive protein

Samples of peripheral venous blood were aspirated (2ml) and centrifuged, the serum was separated and subjected for the hsCRP estimation immune turbidimetry assay. Unlike cardiac conditions, there is no specific cutoff level or threshold level in bronchial asthma. There is a proportional documented increase in hsCRP levels in relationship to severity of bronchial asthma. The test gives results in 25 minutes with sensitivity down to 0.04 mg/L. The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as low risk (less than 1.0 mg/L), average risk (1.0 to 3.0 mg/L), and high risk (above 3.0 mg/L) was taken into account. [14]

Pulmonary function test

A Pulmonary function test was done to find out FEV1 and FEV1/forced vital capacity (FVC) using computerized Medikro Spiro Star spirometry systems. [15]

Statistical methods

Statistical analysis was done in all inclusion criteria subjects. The results were plotted in the Microsoft Office Excel worksheet and were analyzed. Statistical analysis was performed using SPSS version 25th. Descriptive statistics done were percentage analysis and cross tabulation analysis.

Result

In our present study, a total of 70 patients were included out of which 39 (55.7%) were males and 31 (44.3%) were females in case group (table-1).

Table 1: Distribution of gender

	Case		Control	
Gender	No. of patients	Percentage	No. of patients	Percentage
Male	39	55.7	41	58.6
Female	31	44.3	29	41.4
Total	70	100	70	100

Table 2: Distribution of different age groups of patients

	Case		Control	
Age	No. of patients	Percentage	No. of patients	Percentage
18-30 years	4	5.7	5	7.1
31-50 years	21	30.0	18	25.8
51-70 years	37	52.9	41	58.6
>71 years	8	11.4	6	8.5
Total	70	100	70	100

In table 2, in our study, most of the patients were 51-70 years i.e., 37 out of 70 (52.9%), followed by 31-50 years, i.e., 21 out of 70 (30.0%) in case group.

Table 3: Distribution of hsCRP of between two groups of patients

	Case (n=70)	Control (n=70)
	Mean ±SD	Mean ±SD
hsCRP	4.31±1.46	0.83±0.07

In table 3, the mean hs CRP of Case group patients are 4.31±1.46 and in control group patients 0.83±0.07.

Table 4: Distribution of Pulmonary function (FEV1) between two groups of patients

	Case (n=70)	Control (n=70)
	Mean ±SD	Mean ±SD
FEV1%	65.61±7.94	76.43±8.59
FVC	77.21±8.39	88.61±11.28

Table 5: Comparison of Pulmonary function and hsCRP using Spearman correlation

	Case (n=70)	
	r	p-value
FEV1%	-0.816	0.0004

In table 5, pulmonary function test using Spirometer was s done in all the patients (case and control). The FEV1 values are compared against hsCRP values. Statistical significance is assessed using Spearmann's correlation. Case group patients showing highly significant negative correlation of hsCRP with FEV1.

Discussion

In asthma, the importance of airway inflammation has been well established. Besides the airway inflammation, systemic inflammation may also exist in asthma. The relevance of high sensitivity assays for hs-CRP, which is known to be a sensitive marker of low-grade systemic inflammation, has not been fully studied in asthma. Studies have attempted to validate the use of hs-CRP as a surrogate marker of airway inflammation in bronchial asthma. [15]

The study by Takemura et al. cross sectionally examined the serum hs-CRP levels in steroid-naive and steroid-inhaling adult non-smoker patients with asthma and healthy controls. [16] Serum hs-CRP levels were significantly increased in case group as compared to controls. Recent population-based studies have shown increased levels of hs-CRP both in asthma and exacerbations of COPD and it was even detected in the stable statement of COPD. [17] The relationship between hs-CRP levels and the severity of asthma has been shown in two previous studies. [18]

Our study has revealed that there is a positive association between hs-CRP and the severity of asthma and a negative association between hs-CRP and ACT. But no association was found between the parameters of PFT and the levels of hs-CRP throughout asthmatic patients in our study. There was a positive correlation only within severe asthmatic patients in the study by Qian et al. [19] Regarding the previous studies, the relationship between levels of hs-CRP and the severity of asthma indicates that CRP is a pro inflammatory agent. Different pro inflammatory cytokines such as interleukin-1_ (IL-1_), IL-6, IL-8 and IL-18 have been synthesised by the activated proteins hs-CRP. These cytokines have increased due to asthmatic inflammation. [20] Severity of asthma correlates positively with the asthmatic inflammation. [21]

Significant differences in hs-CRP levels between subjects with severe asthma and controls without any respiratory symptoms have recently been demonstrated in one study. [22] In contrast, in a study by Takemura et al. [16] hs-CRP levels were only increased in steroid-naive patients compared with controls. [23] Also, serum hs-CRP levels in moderate asthmatic cases were significantly higher than in mild ones in our study.

A significant difference was determined between asthmatic subjects and controls in terms of PFT. But no significant relation was found between PFT and the levels of hs-CRP of the asthmatic patients in our study; similar to the previous reports by Qian et al. [19] Büyüköztürk et al. [24] and Ramirez et al. [25] On the contrary, there was positive correlation between the levels of RFT and hs-CRP according to the reports by Takemura et al. [16] Fujita et al. and Kim et al. [26]

Limitations of the study

The sample size was small and it was not a longitudinal study. In our study, we have shown the correlation between ACT and the levels of hs-CRP. The role of hs-CRP in evaluating asthma control advances the field in that way; the measurement of hs-CRP is simple, it is an easy applicable method, and is useful in the routine polyclinic follow-up. The hs-CRP can be used for assessing the control of the patient's symptoms, thus we suggested that hs-CRP may be a potential indirect marker of systemic inflammation that reflects both asthma severity and asthma control.

Conclusion

The clinical implications of this study can be summarised as follows: in the future, hs-CRP may be a good indicator of the dosage of inhaled corticosteroids in asthmatic patients due to its easy clinical use. The role of hs-CRP may also be important in evaluating the mortality of asthma similar to acute coronary syndrome. Further expanded longitudinal investigations are needed to examine the role of hs-CRP in both the severity and control of asthma.

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