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Original Article

A Study on the Association Between Highly Sensitive C-Reactive Protein in Patients with Non-Cystic Fibrosis Bronchiectasis: An Institutional Based Study

Charanpreet Singh Grover
Assistant Professor, Department of Chest and TB,
Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana, India.

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***Correspondence to:**
Dr. Charanpreet Singh Grover,
Assistant Professor,
Department of Chest and TB,
Gold Field Institute of Medical Sciences & Research, Faridabad,
Haryana, India.

ABSTRACT

Introduction: Cystic fibrosis reported to be the fatal autosomal recessive disorder globally which can affect 1 in 4500 individuals. Progressive respiratory impairment is thought to be the sole reason for the 95% of mortality due to cystic fibrosis. CRP has greater diagnostic sensitivity for inflammatory processes, but it has low specificity comparably. It can provide certain useful values when selecting candidates for therapy or investigating whether the treatment is effective once started. The availability of quantitative methods seems imperative when evaluating the CRP levels.

Materials and Methodology: 125 patients affected with bronchiectasis were enrolled for the study. Peripheral blood was drawn for the assessment of serum inflammatory markers. The blood samples were allowed to centrifuge at 3000 rpm at 4°c for 15 minutes and serum were stored at −70° c. A latex turbidimetric immunoassay with a sensitivity of 0.01 mg/L was used to calculate the circulating levels of hs-CRP.

Results: Following the initial assessment of hs-CRP, the patients were further divided into two groups according to their previous exacerbation-related hospitalizations: those with an hs-CRP level less than 4.26 mg/L (n = 38) and those with an hs-CRP level of 4.26 mg/L or higher (n = 37). The HRCT scores were significantly increased in the higher hs-CRP group compared with the lower group.

Conclusion: To conclude that, there was a good association between serum hs-CRP and HRCT scores especially in patients with stable non-CF bronchiectasis. Increased HRCT scores and decreased rest oxygenation saturation were relatively associated with increased levels of serum hs-CRP, which is suggestive of serum hs-CRP might be a useful biomarker which can directly reflects the degree of systemic inflammation in stable non-CF bronchiectasis. Therefore, further studies in this area of interest are still required in order to elucidate the clinical significance of the role of hs-CRP in the progression of bronchiectasis and treatment response, either in anti-inflammatory pharmacological therapy or in routine pulmonary rehabilitation programs.

KEYWORDS: Cystic Fibrosis, C-Reactive Protein, High Resolution Computed Tomography.

INTRODUCTION

The most commonly reported fatal autosomal recessive disorder is known to be Cystic fibrosis (CF). It predominantly affects approximately 1 in every 4500 new-born healthy infants and it follows a chronic course which involves several body systems generally. The major aetiology of morbidity and mortality caused by cystic fibrosis continues to be reportedly progressive respiratory impairment which accounts for about 95% of death rate.[1] Respiratory impairment arises due to the incapability of the muco-ciliary system to remove the thick, dehydrated secretions which in-turn increases bronchial obstruction, inflammation and recurrent infections which has the potency to damage the bronchial mucosal wall and finally results in bronchiectasis.

Individuals who are affected with this chronic disease commonly presents with acute superinfections or exacerbations due to the emergence of new pathogens, or could be due to an increase in habitual bacterial load, or due to the host inflammatory response (immunomodulation), each of which leads to deranged respiratory function and a poor & questionable prognosis.[2-4] No mechanisms or hypotheses has reached on the definition of a pulmonary exacerbation or on the diagnostic variables.[5] When there is absence of objective markers, commonly reported trials briefs a moderate-severe exacerbation as the major reason in which hospital admission and intravenous antibiotics are inevitable. No dedicated scoring systems have been designed for early and rapid detection of a pulmonary exacerbation, but the decrease in lung function parameters is usually sufficient in the clinical picture. Proper monitoring of these parameters in a dedicated unit and follow-up are the key elements for early diagnosis and initiation of available immediate therapy.[6]

A review study on the usefulness of blood bio-markers of pulmonary exacerbations in patients affected with cystic fibrosis shown that C-reactive protein (CRP) is the most commonly studied marker but some other markers (neutrophil elastase, anti-proteinase complex, interleukin 6, myeloperoxidase, lactoferrin, and calprotectin) seems promising too.[7] CRP has greater diagnostic sensitivity for inflammatory processes but it has low specificity comparably. It can provide certain useful values when selecting candidates for therapy or investigating whether the treatment is effective once started. The availability of quantitative methods seems imperative when evaluating the CRP levels. Various studies have assessed the value of CRP in the diagnosis of pulmonary exacerbation in patients with cystic fibrosis and in effective screening of the response of exacerbation to the treatment.[8] The results reveals that the CRP increases during exacerbations and decreases with treatment.

CRP is a pentraxin structure consisted of five 23 kDa subunits. It is highly stable and allows assessments to be made accurately in both fresh and frozen plasma, without requiring special collection protocols. Additionally, high-sensitivity assays for CRP have been standardized across many platforms. The long plasma half-life of CRP is calculated to be around 18 to 20 hours, has a stability over a long time and no circadian variation which makes it an accurate and sensitive marker of low-grade systemic inflammations.[9,10]

Hence, the aim of this study was to evaluate the relationship between hs-CRP and severity scores on HRCT and other clinical variables in some stable non-CF bronchiectasis patients.

MATERIALS AND METHODS

Seventy-five (75) patients affected with bronchiectasis were enrolled for the study purpose with proper written informed consent. The inclusion criteria include bronchiectasis documented on HRCT of chest, idiopathic aetiology of bronchiectasis, absence of other major pulmonary diagnoses and a steady state defined by the absence of changes in symptoms reported by the patient since the past 3 weeks. The exclusion criteria included in the study revealed bronchiectasis with defined aetiology, common variable immunodeficiency and use of antibiotics within the last three weeks. Patients with hepatic failure, malignancy or pregnancy were also excluded.

Peripheral blood was drawn for the assessment of serum inflammatory markers. The blood samples were allowed to centrifuge at 3000 rpm at 4°c for 15 minutes and serum were stored at −70° c. A latex turbidimetric immunoassay with a sensitivity of 0.01 mg/L was used to calculate the circulating levels of hs-CRP. The scoring system for HRCT was used and a score sheet was completed for each lobe of the lung in each individual.

Score	Grade
0	No bronchiectasis
1	Cylindrical bronchiectasis in a single lung segment
2	Cylindrical bronchiectasis >1 lung segment
3	Cystic bronchiectasis

Physical height was measured with a rigid stadiometer, and weight was measured by a calibrated digital scale. Body mass index (BMI) was calculated by dividing the weight (kilograms) by the height (meters squared), and then the quotient was converted into age- and sex adjusted percentiles based on population data from NHANES 2000.

Data were tabulated as mean ± SD and all statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). Independent Student *t*-tests or chi-square tests were performed to compare the clinical parameters if appropriate. For bivariate analysis, we clustered the participants using a cut-off point of serum hs-CRP of 4.26 mg/L, into two groups according to previous exacerbation-related history of hospitalizations. To compare hs-CRP with other clinical variables, we used age (years), BMI (kg/m2), FVC (L), FEV1 (L), FEV1/FVC, rest O2%, lowest O2%, ΔO2% and HRCT scores for correlation analysis. Correlations between data were analysed using Pearson's correlation tests. A p - value of less than 0.05 was considered statistically significant.

RESULTS

During the proposed study period, 130 patients with bronchiectasis were enrolled in the outpatient department and 80 patients were evaluated for this study as participants. Seventy-five patients who met the inclusion criteria were recruited in the study and their

demographic data are briefly shown in Table 1. Five patients with a serum hs-CRP level of more than 30 mg/L without any overt clinical symptoms or signs of infections at enrolment were excluded from the final analysis because of the uneven exacerbations and administration of oral antibiotics in the following weeks. Their serum hs-CRP levels were 45.63, 55.49, and 78.43 mg/L, respectively. Following the initial assessment of hs-CRP, the patients were further divided into two groups according to their previous exacerbation-related hospitalizations: those with an hs-CRP level less than 4.26 mg/L (n = 38) and those with an hs-CRP level of 4.26 mg/L or higher (n = 37). The characteristics and outcomes of the patients in two groups of with stable bronchiectasis are shown in Table 2. There were no statistical differences in age, sex distribution, smoking status, BMI, pulmonary function test and between the two groups. The HRCT scores were significantly increased in the higher hs-CRP group compared with the lower group which is shown in Table 3. Resting oxygenation saturation was reportedly decreased in the higher group than in the lower group, and there was a trend that patients with a lower hs-CRP had higher pulmonary functions (FVC and FEV1).

Table 1: Demographic data of the 75 stable bronchiectasis patients

Demographic data	Mean (SD)	95% interval
Age (years)	58.7	54.1 – 60.9
BMI (kg/m^2)	22.5	21.0 – 22.9
FVC (L)	2.3	1.8 – 2.4
FVC%	68.2	62.9 – 72.3
FEV_1	1.7	1.5 – 1.9
FEV_1%	63.3	57.3 – 68.8
Rest O_2 saturation	95.7	94.0 – 95.9
HRCT score	26.9	23.1 – 29.5
Hs – CRP (mg/L)	5.2	3.8 – 5.7

Table 2: Characteristics and outcomes of the 69 stable bronchiectasis patients.

Variables	Hs – CRP <4.26 N = 38	Hs – CRP≥4.26 N = 37	P – value
Age (years)	56.4 ± 13.8	59.2 ± 13.8	0.410
Gender (M/F)	22/16	23/14	0.823
BMI (kg/m^2)	56.0 ± 13.9	22.2±3.7	0.993
Smoking			
Never	31	30	0.868
Quit/current	7	7	
PFT			
FVC (L)	2.23±o.83	1.84±0.73	0.035
FVC (%)	72.6±16.6	61.3±21.2	0.016
FEV1 (L)	1.72±0.76	1.33±0.61	0.039
FEV1 (%)	67.8±21.6	56.8±23.7	0.047
FEV1/FVC (%)	72.9±11.2	70.8±10.6	0.422
HRCT scores	21.5±9.9	28.3±13.2	0.003
Bacterial colony			
Ps. Aeruginosa	6	14	0.118
Others	8	6	
Normal flora/ no growth	24	17	
Hospitalisation (times/year)			
<2	34	29	0.01
≥2	4	8	

Table 3: Correlations between hs-CRP, clinical variables, and HRCT score.

Variables	Hs – CRP (mg/L)	P - value
Age (years)	0.123	0.315
BMI (kg/m^2)	-0.096	0.443
FVC (L)	-0.162	0.189
FEV_1	-0.155	0.213
FEV_1/FVC	-0.058	0.639
Rest O_2 saturation %	-0.272	**0.027**
Lowest O_2 saturation %	-0.110	0.378
HRCT score	0.475	**<0.001**

DISCUSSION

The reported pathogenetic mechanism that leads to bronchiectasis is quite complex and still vague for better understanding.[1-5] The current ideology considers that idiopathic bronchiectasis, chronic bronchial infection and inflammation communicate with each other which can lead to progressive lung damage.[3] Bronchiectasis associated with airway obstruction has been studied more extensively in the recent times; But little is documented about the intensity of low-grade systemic inflammation. According to our experience and knowledge, this is the first study which very well describe the relationship between serum hs-CRP rather than traditional CRP and certain clinical variables including disease severity and HRCT in a group of patients with stable non-CF bronchiectasis. Our results revealed that hs-CRP had a good relationship with HRCT severity scores and may effectively serve as a chronic inflammatory marker in the stable phase of non-CF bronchiectasis patients, in spite of its broad clinical spectrum collectively. Progressive idiopathic bronchiectasis comprises of at least two subsets of patients.[2,3] One subset constitutes the huge majority of cases which deteriorates over decades with an increased frequency of exacerbations, sputum volume and extent of bronchiectasis. The other subset is commonly those with single-lobe involvement and can be asymptomatic between exacerbations or without overt exacerbations and does not deteriorate even after decades. No study has still evaluated the severity and disease activity of idiopathic bronchiectasis, since two long-term studies have already assessed the factors influencing mortality rate.[11,12]

C-reactive protein is majorly produced in the liver and IL-1, IL-6 and TNF-α have been identified as the prompt regulators of its production.[13,14] More sensitive immune assays for CRP (high-sensitivity CRP, hs-CRP) have become readily available thus making relatable measurement and comparison of low CRP levels present in blood. These sensitive assays have revealed the relationship between hs-CRP levels and the development & progression of coronary heart disease.[15,16] and osteoarthritis.[17] Additionally, the significant association between hs-CRP and diabetes[18] and airway diseases such as chronic obstructive pulmonary disease[19] and asthma[20] have been reported. In the present study, disease severity was promptly related with hs-CRP in stable bronchiectasis demonstrating that hs-CRP may be considered as a good biomarker in low-grade systemic inflammation in those patients.

Stable phase of bronchiectasis patients with higher levels of systemic markers of inflammation have been researched.[8] Other authors[21] have suggested that even in the periods of clinical stability, patients with non-CF bronchiectasis might experience increased bronchial inflammation. During an acute exacerbation, especially an infective episode, large quantities of neutrophils migrate into the airway, which can result in the increased levels of proteolytic agents. So, these agents eventually participate in the deterioration of the lung matrix and eventually contribute to the development of bronchiectasis. The same authors[21] observed that the increase in inflammation during exacerbations ultimately decreases with antibiotic treatment so it does not disappear entirely. This may be the due to the higher hs-CRP levels observed in our patients with multiple exacerbation related hospitalizations.

CONCLUSION

To conclude that, there was a good association between serum hs-CRP and HRCT scores especially in patients with stable non-CF bronchiectasis. Increased HRCT scores and decreased rest oxygenation saturation were relatively associated with increased levels of serum hs-CRP, which is suggestive of serum hs-CRP might be a useful biomarker which can directly reflects the degree of systemic inflammation in stable non-CF bronchiectasis. Therefore, further studies in this area of interest are still required in order to elucidate the clinical significance of the role of hs-CRP in the progression of bronchiectasis and treatment response, either in anti-inflammatory pharmacological therapy or in routine pulmonary rehabilitation programs.

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