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Original Research Article

A Prospective Research to Investigate the Link Between Serum C-reactive Protein and Disease Severity in COPD Patients

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Abstract

Aim: Evaluating serum C-reactive protein level in patients with chronic obstructive pulmonary disease and its correlation with disease severity. **Methods:** A prospective study was conducted in the Department of General Medicine, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. for the period of 1 year. 100 COPD patients and 100 asymptomatic individuals were selected as the control group. COPD patients underwent spirometry tests, and the severity of disease was determined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The main inclusion criteria for COPD patients were having symptoms or history of COPD with FEV1/FVC below 70% after using a bronchodilator. **Results:** In this study, 200 subjects were investigated (100 patients with COPD and 100 individuals as controls). In the COPD group, 58 subjects (58%) noted cigarette smoking during the study, 18 subjects (18%) reported cigarette smoking in the past, and 34 subjects (34%) mentioned a history of baking. In the control group, 16 subjects (16%) noted cigarette smoking during the study; 8 subjects (8%) mentioned cigarette smoking in the past, and five subjects (10%) reported a history of baking. In this study, hsCRP was measured in 98 patients with COPD and 94 control subjects. The mean hsCRP was 7519±417 ng/mL in the COPD group and 2874±393 ng/mL in the control group. In the comparative study of the two groups using t-test, a significant difference was observed ($p<0.001$). The COPD group underwent spirometry and blood gas measurements, and then FEV1, FEV1%, FVC, and FEV1/FVC parameters were measured. The severity of the disease was determined by the GOLD criteria, where 32 subjects (32%) were GOLD II, 48 subjects (48%) were GOLD III, and 20 subjects (20%) were GOLD IV. There was no case of GOLD I found among the subjects because patients were hospitalized. Mean FEV1 was 1.25 L/s, mean FVC was 2.126 l, and mean FEV1/FVC was 57%. **Conclusion:** The findings of the present study demonstrated that plasma CRP is not only effective in the evaluation of inflammation in COPD, but also useful as a marker in monitoring inflammation during COPD treatment. CRP is decreased during treatment by inhaled corticosteroids.

Keywords: CRP, COPD, FVC

Introduction

COPD is a chronic inflammatory lung disease characterized by progressive airflow limitation and parenchymal destruction.[1] It often causes remarkable symptom burden, including chronic cough, sputum production, breathlessness, and exercise intolerance.[1–3] The Global Initiative for Chronic Obstructive Lung Disease guideline recommends multiple symptomatic assessments rather than just measuring breathlessness with lung function.[1] Among several questionnaires measuring health-related quality of life, the COPD assessment test (CAT) is widely used in routine practice.[4–6] It is an easy and simple measurement with an eight-item questionnaire, which is designed to quantify the impact of COPD symptoms on the patient health status with scores of 0–40.[4] In clinically stable COPD patients, the CAT is also closely related to the St George's Respiratory Questionnaire.[7,8]

C-reactive protein (CRP) is a representative systemic biomarker reflecting the total systemic burden of inflammation in individuals.[9] Serum CRP is elevated in stable COPD, and it correlates with disease severity and adverse health outcomes of patients with mild-to-moderate COPD.[10] The Copenhagen City Heart Study and Copenhagen General Population Study showed that increased levels of CRP and other systemic

biomarkers were associated with increased risk of COPD exacerbations.[11] CAT score is also associated with patients at high risk of exacerbation and changes significantly during and after exacerbations.[6,12] Moreover, an elevated CAT score at exacerbation reflects exacerbation severity.[6] Regarding the relationship between CAT score and CRP, change in CAT score from baseline to exacerbation onset was positively cor- related to change in serum CRP.[6,13]

Materials and Methods

A prospective study was conducted in the Department of General Medicine, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India for the period of 1 year, after taking the approval of the protocol review committee and institutional ethics committee. 50 COPD patients and 50 asymptomatic individuals were selected as the control group. COPD patients underwent spirometry tests and the severity of disease was determined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

The main inclusion criteria for COPD patients were having symptoms or history of COPD with FEV1/FVC below 70% after using a bronchodilator. Diseases such as hemoptysis, pneumothorax, acute coronary disease, recent MI, pulmonary embolism, vascular aneurysm, recent surgery, acute infection, history of malignancy, or any inflammatory process other than COPD, were the exclusion criteria for COPD patients. The inclusion criteria for the control group were those of age 50 years old or older, with no signs of the exclusion criteria of the COPD group, and no history of COPD, shortness of breath, or coughing.

Procedure

In this study, all individuals in the control and COPD groups were visited, all individuals were examined, and their history taken. The information was entered into a special form. For all subjects, information such as age, sex, history of smoking, baking, medical his- tory of the patient, as well as the vital signs, were recorded. In the COPD group, the patient's tests (in- cluding CBC and biochemistry) were examined, and if patients had any of the exclusion criteria, they were excluded. In the control group, patients were selected based on examination and history, and in case of a history of earlier diseases, they were excluded based on the exclusion criteria. In both groups, the individuals underwent blood sampling, and the serum sample of the patients was centrifuged. For

each individual, 3 samples were separated to measure hsCRP, and one sample was separated as a backup. The samples were stored at -20°C until further use. HsCRP was measured in 47 COPD patients and 41 control patients. Due to the sensitivity of the hsCRP measurement, the hsCRP was measured three times for each sample, and the mean was considered as the averaged results of hsCRP. Serum hs-CRP was measured by immunoturbidometry assay (Roche Diagnostics, Mannheim, Germany) and an auto analyzer (Lysis, Milan, Italy), with a normal value defined as < 5000 ng/L.

Statistical analysis

Statistical analysis was carried out using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were indicated as percent (for categorical) and mean (SD) (for continuous) variables. We used *t*-test to compare the values between groups; with $P<0.05$ set as the level of statistical significance.

Results

In this study, 200 subjects were investigated (100 patients with COPD and 100 individuals as controls). The COPD group consisted of 120 men (60%) and 80 women (40%), whereas the control group was comprised of 62 men (62%) and 38 women (38%). Thus, the COPD and control groups were matched in terms of sex. There was no significant difference between these two groups. The mean age was 66.98±11.3 years in the COPD group and 66.02±9.7 years in the control group. Therefore, the COPD and control groups were matched in terms of age.

In the COPD group, 58 subjects (58%) noted cigarette smoking during the study, 9 subjects (18%) reported cigarette smoking in the past, and 34 subjects (34%) mentioned a history of baking. In the control group, 16 subjects (16%) noted cigarette smoking during the study; 8 subjects (8%) mentioned cigarette smoking in the past, and five subjects (10%) reported a history of baking. In this study, hsCRP was measured in 98 patients with COPD and 94 control subjects. The mean hsCRP was 7519±417 ng/mL in the COPD group and 2874±393 ng/mL in the control group. In the comparative study of the two groups using t-test, a significant difference was observed ($p<0.001$).

The COPD group underwent spirometry and blood gas measurements, and then FEV1, FEV1%, FVC, and FEV1/FVC parameters were measured. The severity of the disease was determined by the GOLD criteria, where 32 subjects (32%) were GOLD II, 48 subjects (48%) were GOLD III, and 20 subjects (20%) were GOLD IV. There was no case of GOLD I found among the subjects because patients were hospitalized. Mean FEV1 was 1.25 L/s, mean FVC was 2.126 l, and mean FEV1/FVC was 57%.

The correlation between serum hsCRP and age, FEV1, PaO_2, and FEV1/FVC was studied in patients with COPD, where the Pearson correlation coefficients between hsCRP and the above-mentioned variables equaled 0.181, 0.083, -0.339, and -0.051, respectively ($P<0.05$ in the correlation between hsCRP and FEV1, and $P>0.2$ in other cases).

Regarding smoking and its relationship with the severity of COPD, 58 patients reported as current smokers, where nine subjects had moderate COPD, 15 subjects had severe COPD, and two subjects had very severe COPD. In this category, there was a significant relationship between the severity of COPD and current smoking ($P=0.038$). Furthermore, 18 subjects reported as past smokers. In this group, there was a significant correlation between the severity of COPD and a history of smoking ($P<0.001$). Moreover, from among patients with COPD, 34 patients noted a history of baking. In this group, there was no significant correlation between the severity of COPD and a history of baking ($P=0.27$). The correlation between hsCRP in patients with COPD was

r=0.031, and the correlation between hsCRP in the control group was r=0.001.

The correlation between the severity of COPD and hsCRP equaled r=0.325 (P=0.041). Therefore, there is a significant correlation between the severity of COPD and hsCRP. There is also a significant correlation between hsCRP and the severity of COPD

Table 1: Demographic characteristics and studied variables among COPD patients and asymptomatic individuals (control group)

Variables	Control	COPD	P-value
Age	66.02±9.7	66.98±4.10	0.59
Gender			
Male	62 (62%)	60 (60%)	
Female	38 (38%)	40 (40%)	
Smoking			
Now smoking	26 (16%)	58 (58%)	
Past smoking	8 (8%)	9 (18%)	
Baking	10 (10%)	34 (34%)	
Lung Function			
FEV1/L	-	1.25	
FVC/L	-	2.126	
FEV1/FVC	-	57%	
hcCRP (mmol/L)	4287±393	7519±417	0.001*

*P<0.05; statistically significant

Table 2: Smoking and its relationship with severity of COPD

Moderate No. (%)		COPD severity Severe No. (%)	Very severe No. (%)	Total	P-value
Now smoking	24 (41.38)	30 (51.72)	4 (6.89)	58	0.042
Past smoking	-	2 (11.11)	16 (88.89)	18	<0.001*
Baking	12 (35.29)	20 (58.82)	2 (5.88)	34	0.243

P<0.05; statistically significant

Discussion

In this study, serum hsCRP level was measured in COPD patients and control subjects, and the correlation between partial pressure of oxygen (PaO_2), FEV1, and age was examined with the above- mentioned blood factor. Serum CRP (SCRP) is a risk factor for cardiovascular and thromboembolic diseases[14], and in patients with COPD, the pulmonary inflammation apparently leads to systemic inflammation because the use of inhaled corticosteroids in these patients has been associated with a decrease in SCRP and other markers of systemic inflammation.[15] It is observed that in these patients, SCRP>3 mg/L is associated with a ten-year increase in mortality .[16]

In this study, the hsCRP level was measured for the control and COPD groups. CRP increases the risk of thrombotic events and cardiovascular mortality. In the lungs, CRP has a protective function against bacteria and apoptotic cells in the form of an intrinsic immune system. At first, CRP is produced by hepatocytes in the liver in response to IL-6, and then enters the lungs through the plasma. The inflammation in COPD activates epithelial cells and increases alveolar macrophages and other inflammatory cells which are responsible for the release of IL-6. This in turn leads to

an acute phase response and an increase in plasma CRP. Moreover, IL-6 regulates two other acute phase reactors, namely fibrinogen and al-anti trypsin, both of which affect the pathogenesis of COPD.[16] In further support of IL-6 in the development of COPD, studies have revealed that IL-6 increases the number of CD8 and CD4 cells, macrophages, B cells, and pulmonary neutrophils, which are matched with changes seen in the pathology of COPD. On the other hand, an increase in IL-6 leads to airspace enlargement in emphysema, peribronchial accumulations, monocellular cells, increased wall thickness of airways, sub- epithelial fibrosis, and increased airway response. In animals, a contact with ozone decreases IL-6 and, consequently, reduces pulmonary injury. Therefore, plasma CRP is associated with IL-6-dependent processes in airways, leading to the progress of COPD and severe clinical problems.[16,17]

In this study, to eliminate the role of infection in increasing CRP, all patients with abnormal CXR (indicating pneumonia) who were febrile or had leukocytosis were excluded. In this study, consistent with the study by Tores *et al*. (2006), in Spain, and Seemungal *et al*. (2007), the mean hsCRP level between control group and COPD group was different by greater than 3.3 mg/L, which was significant ($P<0.001$).[18,19] A significant negative correlation between hsCRP and FEV1% was found in this research study ($r=0.31$, $P=0.4$). A similar correlation was also reported between FEV1% and hsCRP by Fimognari *et al*. (2007) ($r=0.37$, $P=0.01$), which is also consistent with the results from a study by Seemungal *et al*. (2009).[18,20]

Conclusion

The results of the current research indicated that plasma CRP is not only helpful in the assessment of inflammation in COPD, but also valuable as a marker in monitoring inflammation during COPD therapy. CRP is lowered with therapy by inhaled corticosteroids. Moreover, the examination of the probable insufficiency of vitamin B12 and folic acid is recommended in patients with COPD, in addition to the measurement of the blood level of IL-6 in patients with COPD exacerbation. Furthermore, examining nutritional status, BMI, and serum albumin and their link with the outcome of the illness is essential in individuals with COPD.

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