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Original Research Article

Evaluating Serum C-Reactive Protein Level in Patients with Chronic Obstructive Pulmonary Disease and its Correlation with Disease Severity

Barun Kumar Kundu[1], Rajnish Kumar[2], Shashi Kant Kumar[3]

[1]Senior resident, Department of General Medicine, Madhubani Medical College and Hospital, Madhubani, Bihar, India

[2]Senior resident, Department of Skin & VD, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

[3]Assistant Professor, Department of Pathology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

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Corresponding author: Dr Rajnish Kumar
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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, Madhubani Medical College and Hospital, Madhubani, Bihar, India, from October 2019 to September 2020. 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.

Results: In the COPD group, 30 subjects (60%) noted cigarette smoking during the study, 11 subjects (22%) reported cigarette smoking in the past, and 19 subjects (38%) mentioned a history of baking. In the control group, 10subjects (20%) noted cigarette smoking during the study; 4 subjects (8%) mentioned cigarette smoking in the past, and five subjects (10%) reported a history of baking. The mean hsCRP was 7739±427ng/mL in the COPD group and 2994±483 ng/mL in the control group. In the comparative study of the two groups using t-test, a significant difference was observed ($p<0.001$). Regarding smoking and its relationship with the severity of COPD, 30 patients reported as current smokers, where nine subjects had moderate COPD, 16 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 ($P=0.027$). Furthermore, 10 subjects reported as past smokers. In this group, there was a significant correlation between the severity of COPD and a history of smoking ($P<0.001$). The correlation between the severity of COPD and hsCRP equaled $r=0.342$ ($P=0.039$). 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.

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: COPD, CRP, Severity.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) is ~10% in adults older than 40 years[1] According to World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD and more than 3 million people died of COPD in 2005, corresponding to 5% of all deaths globally[2] This number is projected to rise by 30% during the next 10 years and estimates show that COPD will become the third leading cause of death worldwide in 2030[2] Approximately 50% of patients with COPD have at least one exacerbation per year and >20% are readmitted within 30 days, with a total of nearly 800000 hospitalisations and USD50 billion in healthcare costs annually[3,4]

The chronic inflammation in COPD, orchestrated by multiple inflammatory cells and mediators in the airways & the lung tissue is induced by inhalation of noxious gasses & particulate matter. Systemic inflammation & oxidative stress are the most important features of COPD. Although the origin of systemic inflammation present in COPD remains poorly understood & correlations in the regulation of inflammation in the pulmonary & systemic compartments are not well documented yet, it is clearly established that some inflammatory markers are risen in systemic circulation[3,5] of the blood based bio markers, C-Reactive Protein has shown the greatest promise[6] In COPD patients increased CRP levels are associated with poor lung function, reduced exercise capacity & worsened quality of

life as well as being a significant predictor of all cause mortality[7,10] C Reactive protein is a potential biomarker of systemic inflammation that is synthesized predominantly by the hepatocytes in response to tissue damage or inflammation[11] Several previous studies have documented that CRP levels are increased in stable COPD patients[12] However in most studies patients with co-morbidities like Diabetes mellitus & cardio-vascular disease, known to be associated with higher CRP levels were not excluded.[13,14] On the other hand, another study demonstrated that CRP had a weak correlation with COPD severity in elderly stable patients.[15] Many studies have shown a raised CRP in COPD patients[15] but these studies have not excluded diabetics, patients with hypertension or cardiovascular diseases.

Materials and Methods

A prospective study was conducted in the Department of General Medicine, Madhubani Medical College and Hospital, Madhubani, Bihar, India from October 2019 to September 2020, 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 history 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 22.0 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, 100 subjects were investigated (50 patients with COPD and 50 individuals as controls). The COPD group consisted of 34 men (68%) and 16 women (32%), whereas the control group was comprised of 35 men (70%) and 15 women (30%). 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 64.88±7.63 years in the COPD group and 64.77±9.7 years in the control group. Therefore, the COPD and control groups were matched in terms of age. In the COPD group, 30 subjects (60%) noted cigarette smoking during the study, 11 subjects (22%) reported cigarette smoking in the past, and 19 subjects (38%) mentioned a history of baking. In the control group, 10subjects (20%) noted cigarette smoking during the study; 4 subjects (8%) mentioned cigarette smoking in the past, and five subjects (10%) reported a history of baking.

The mean hsCRP was 7739±427ng/mL in the COPD group and 2994±483 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 17 subjects (34%) were GOLD II, 26 subjects (52%) were GOLD III, and 7 subjects (14%) were GOLD IV. There was no case of GOLD I found among the subjects because patients were hospitalized. Mean FEV1 was 1.29 L/s, mean FVC was 2.236 l, and mean FEV1/FVC was 60%.

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 0.173, 0.075, -0.328, and -0.046, 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, 30 patients reported as current smokers, where nine subjects had moderate COPD, 16 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=0.027). Furthermore, 10 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, 19 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=0.33). The correlation between hsCRP in patients with COPD was r=0.039, and the correlation between hsCRP in the control group was r=0.001.

The correlation between the severity of COPD and hsCRP equaled r=0.342 (P=0.039). 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	64.77±9.7	64.88±7.63	0.55
Gender			
Male	35(70%)	34(68%)	
Female	15(30%)	16(32%)	
Smoking			
Now smoking	9 (18%)	30(60%)	
Past smoking	4 (8%)	11 (22%)	
Baking	5 (10%)	19 (38%)	
Lung Function			
FEV1/L	-	1.27	
FVC/L	-	2.136	
FEV1/FVC	-	60%	
hcCRP (mmol/L)	2994±483	7739±427	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	12 (40)	16(53.33)	2 (6.67)	30	0.045
Past smoking	-	1(9.09)	10 (90.91)	11	<0.001*
Baking	6(31.58)	11(57.89)	2 (10.53)	19	0.245

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[16] 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[17] It is observed that in these patients, SCRP>3 mg/L is associated with a ten-year increase in mortality [18]

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[18]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.[18,19]

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)[20,21]. A The correlation between the severity of COPD and hsCRP equaled r=0.342 (P=0.039). 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)[20,22].

Conclusion

CRP is decreased during treatment by inhaled corticosteroids. Moreover, the evaluation of the possible deficiency of vitamin B12 and folic acid is recommended in patients with COPD, in addition to the evaluation of the serum level of IL-6 in patients with COPD exacerbation. Furthermore, evaluating nutritional status, BMI, and serum albumin and their correlation with the outcome of the disease is required in patients with COPD.

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