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Original Research Article

Evaluation of Serum C-Reactive Protein Levels in Stable COPD Patients and Its Correlation with Severity

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ABSTRACT

C-reactive protein (CRP) is a stable and excellent biomarker of systemic inflammation which is easy to measure. COPD is an inflammatory disorder of lung with widespread Systemic manifestations as well as systemic inflammatory response. C-reactive protein levels may be increased in COPD patients. Present study investigates C-reactive protein level in COPD patients and its relation with their ventilatory function. Study included 56 stable COPD patients with mild to moderate severity, in age group 40-70 years and 56 nonsmoking controls in the same age group. Clinical and physiological characteristics were determined and C-reactive protein levels were measured. This study confirms the finding of higher C-reactive protein levels in smoking COPD patients (4.0 vs 4.9 mg-L^{-1}) as compared to nonsmoking COPD patients. It also confirms that level of C-reactive protein in ex-smoking COPD population remains significantly higher than nonsmoking control group (7.8±1.8 vs 4.9±0.5mg/l). Present study shows that C-reactive protein levels correlates well with FEV_1% (c-0.24, p0.029) and GOLD stage of disease (c0.19, p0.040). We recommend that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients. It also provides us strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

Key words: COPD, C-reactive protein (CRP) level.

INTRODUCTION

COPD is a multisystem disorder that is frequently associated with significant extra-pulmonary manifestations. [1] The mechanisms underlying systemic manifestations of COPD are of great interest because they account for a large part of morbidity. Their assessment and management is important for the improvement by future outcome of COPD patients. These systemic manifestations are associated with systemic changes including evidence of increased oxidative stress, activation of circulating inflammatory cells and increased levels of pro-inflammatory cytokines. [2,3]

Various pathological processes in lung and systemic tissues of COPD patients

are associated with increased circulating biomarker levels. C-reactive protein (CRP) is a circulating protein that is largely but not exclusively produced by hepatocytes as a part of acute phase response. C-reactive protein is an excellent and stable biomarker for low grade systemic inflammation in body. [4] It may be used as a biomarker of COPD severity, systemic inflammatory response associated with COPD and its systemic complications. [5]

With this background our study was undertaken to evaluate the serum levels of C-reactive protein in stable COPD patients and its correlation with their ventilatory functions and severity of disease.

Aims and Objectives

To find out association/correlation of serum C-reactive protein level with ventilatory function in stable COPD patients, if any.

MATERIALS AND METHODS

The study was conducted in our department of respiratory medicine. After obtaining clearance from the ethical committee of the institute; study was undertaken on indoor and outdoor patients. Informed consent of all the participants was taken.

Three hundred and fifty patients were enrolled for the study, out of which Fifty six patients met the criteria for diagnosis of COPD and had complete data available for study.

Fifty six patients of age 40-70 years with mild to moderate grade of COPD (FEV_1>50% predicted), with no exacerbations reported in last 3 months, were chosen from the outpatient department and were selected as cases for the study. Patients having recent abdominal, thoracic or ophthalmic surgery, recent coronary events, high blood pressure or any clinical evidence of infection, inflammation or CCF in previous three months were excluded. Fifty six apparently healthy nonsmoking subjects of similar age (mean±SD 58±12) were also included in the study, as control.

After selection of patients, detailed history was taken to obtain information regarding age, education, occupation, socioeconomic status, personal habits, smoking, diabetes mellitus, and hypertension. A thorough clinical examination was done. Routine investigations including complete blood count, erythrocyte sedimentation rate to exclude any infection, sputum for acid fast bacilli to rule out pulmonary Koch's, serum bilirubin and SGPT to exclude liver pathology (as CRP is mostly produced by liver) was done.

Patients were subjected to spirometry. Pre and post bronchodilator study was done in all COPD patients. Best of three consecutive tests were taken into consideration. Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1) and the ratio of FEV1/FVC, peak expiratory flow during middle half of FVC (FEF 25-75 or MMEFR) were measured. Participants were divided into four subgroups- mild, moderate, severe, very severe grade of severity of COPD, as per GOLD criteria. [6]

C-reactive protein was measured in serum from blood sample obtained in the morning (mean time 9.30 am) after 4hrs of fasting. Measurement was done by an Immunochemical method known as Immunoturbidimetry, [7] most accurate method.

Statistical Analysis: Variables were presented as a percentage, mean ± standard deviation or median depending on their distribution. As C-reactive protein values have non-normal distribution, logarithmic transformation was used to perform parametric testing. Univariate ANOVA with 95% confidence intervals (CI) for the

estimation of differences was used to compare groups. Bivariate correlations between variables were evaluated by Pearson's correlation. Statistical analysis was done using STAT PLUS® Statistical Analysis Programme version 2008 developed by ANALYSIS SOFT®.

OBSERVATIONS

After analyzing the patients and matched volunteer controls, observations were made. There were 12(21.4%) patients in the age group of 41-50 years, 20(35.7%) in 51-60 years, 24(42.9%) in the age group of 61-70 years. There were 51(91.1%) males and 5(8.9%) females. Out of 56 cases, 41(73.2%) cases were bidi or cigarette smokers, 5(8.9%) were having other risk factors (occupational and indoor air pollution), whereas 10 (17.9%) had exposure to both.

Thirty (53.5%) patients were previously using inhaled β_2-agonist, four (7.2%) oral methylxanthines, twelve (21.4%) oral methylxanthines plus inhaled β_2-agonist and ten (17.9%)were taking inhaled β_2-agonist plus inhaled steroid.

During the period of stability for last 3 months, spirometry revealed 16(28.6%) of patients having mild COPD and 40(71.4%) as having moderate COPD.

TABLE 1: Clinical and physiological characteristics of COPD patients (cases)

Clinical and physiological parameters	subjects	values
Mean Age (years)	56	58±12
Mean FEV_1% predicted	56	67±17
GOLD stage I(% of patients)	16	28.6%
GOLD stage II(% of patients)	40	71.4%
Exacerbations in last one year	06	2
Smoking, % of patients	41	73.2%

Comparision between cases and controls showed C-reactive protein levels were higher in chronic obstructive pulmonary disease patients than controls (4.9 vs 3.1 mg-L^{-1}). C-reactive protein levels was not equal between ex- smoking and smoking COPD patients, being higher in the later(7.8±1.8 vs 4.9±0.5mg/l).

TABLE 2: Parameters that significantly correlated with log C-reactive protein levels

Variable	correlation	p-value
FEV_1%	-0.24	0.029 (S)
GOLD stage	0.19	0.040 (S)

* p value significant(S) ≤0.05
* p value non significant(NS) ≥0.05

DISCUSSION

There is now sufficient evidence to support the presence of extrapulmonary consequences of COPD that can be detected clinically. They can be also measured by the increased level of systemic markers. C-reactive protein is one of these markers. It is an acute phase protein synthesized predominantly by the hepatocytes in response to tissue damage or inflammation. Gan and co workers, [8] showed that C-reactive protein is elevated in patients who actively smoked, had reduced lung function or even stable COPD. Study by Sin DD et al, [9] demonstrated that in COPD patients-C-reactive protein levels predicted cardiovascular mortality. Lacy P et al [10] 2004, demonstated that cardiovascular mortality and inflammation decreased with treatment with inhaled fluticasone. Pinto Plata et al, [11] have shown that patients with COPD have higher levels of C-reactive protein independent of cardiovascular risk factors. Higher C-reactive protein level in stable COPD patients was noted by Karadag F.et al [12] As per American heart association, there should be no detectable C-reactive protein in blood of normal population.

Our study also confirms the previous finding of higher C-reactive protein levels in smoking COPD patients (4.0 vs 4.9 mg-L^{-1}) as compared to nonsmoking COPD patients, as had been demonstrated by Gan WQ et al [4] The level of C-reactive protein in ex-smoking COPD population remained significantly higher than nonsmoking

control group (7.8±1.8 vs 4.9±0.5mg/l). Similar findings were also observed in study done by Casanova C.et al [13] and SFP Man et al. [4] Pinto Plata et al [11] also found similar results.

The present study also confirms the finding produced by Gan WQ et al [8] supporting the fact that when lung function worsens, C-reactive protein levels increases. This study shows linear negative correlation of serum C-reactive protein levels with FEV_1% (c-0.24, p0.029). This could also explain the direct relationship found between C-reactive protein levels and GOLD stages (c0.19, p0.040).

CONCLUSION

Our study confirms that C-reactive protein levels are higher in COPD patients. This study also confirms the finding of higher C-reactive protein levels in smoking COPD patients as compared to nonsmoking COPD patients. The level of C-reactive protein in ex-smoking COPD population remained significantly higher than nonsmoking control group. This suggests that inflammatory state seems to persist, probably at seemingly lower level, despite smoking cessation. C-reactive protein level is associated with important clinical variables like FEV_1%, GOLD stage which help to predict prognosis and patient outcome. Thus we conclude that measurement of C-reactive protein levels may be a useful tool to predict the prognosis and patient outcome in COPD patients. It also provides us strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

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