To study the serum C-reactive protein level and its correlation with prognostic variables in stable COPD patients

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Abstract

Introduction: C-reactive protein 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 and associated Systemic inflammatory response. C-reactive protein levels are increased in COPD patients. Present study investigated C-reactive protein level in stable COPD patients and its relation with clinically important outcome variable, exercise capacity. **Method:** 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. **Result:** This study confirms the finding of higher C-reactive protein levels in smoker COPD patients (4.9 vs 4.0 mg-L^{-1}) as compared to nonsmoker COPD patients. It also confirms that level of C-reactive protein in ex-smoker COPD population remains significantly higher than nonsmoker control group (4.9±0.5 vs 3.1mg/l). **Conclusion:** C-reactive protein level was strongly associated and correlated with 6 minute walk distance, FEV_1 and GOLD stages, so C-reactive protein level can indirectly reflect prognosis of COPD patient and his exercise capacity. 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 strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

Keywords: COPD, C-reactive Protein Level, Exercise Capacity, 6MWT.

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Introduction

COPD being a multisystem disorder, is frequently associated with significant extra-pulmonary manifestations [1]. The mechanisms underlying the systemic manifestations of COPD should attract great interest, because these account for a large part of morbidity. And its assessment and management is critically important for the improvement in future treatment and outcome of COPD patients. These systemic manifestations have been 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 stages of disease in lung and systemic tissues of COPD patients, could also be associated with raised circulating biomarker levels. C-reactive protein is an excellent and stable biomarker for low grade systemic inflammation [4]. It is also useful as an indirect biomarker of COPD severity, systemic inflammatory response associated with COPD and downstream respiratory and systemic complications [5].

With this background the study was undertaken to evaluate the serum levels of C-reactive protein in stable COPD patients and to observe its correlation with

prognostic factor of COPD i.e. exercise capacity (6MWT), FEV_1 and GOLD stage.

Aims and Objectives

1. To know the mean serum C-reactive protein level in normal healthy individual as well as COPD patients in the same age group.
2. To find out association of serum C-reactive protein level with prognostic variables like exercise tolerance, FEV1 and GOLD disease stage in stable COPD patient.

Material and Methods

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 6 months, were chosen from the outpatient department and were selected as cases for the study. Patients having recent abdomino-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. Simultaneously, fifty six apparently healthy nonsmoking subjects of similar age were also included as control.

After selection of patients, detailed history was taken to obtain information regarding age, education, occupation, socioeconomic status, personal habits, smoking, diabetes mellitus, hypertension etc. 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 billirubin and SGPT to exclude liver pathology (as CRP is mostly produced by liver) was done. Patients were then subjected to 6 minute walk test and spirometry.

In spirometry, best of three consecutive tests were taken into consideration. Patients were advised to stop bronchodilators and anticholinergic drugs for a period of 12 hours before spirometry. 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. Pre and post bronchodilator study was done in all patients and there was no significant reversibility after bronchodilators in COPD patients. Participants were divided into four subgroups- mild, moderate, severe, very severe grade of COPD as per WHO GOLD criteria[6].

C-reactive protein was measured in serum, by immunoturbidimetry[7], in blood sample obtained in the morning (mean time 9.30 am) after 4hrs fasting.

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 were 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®.

Results

After analyzing the the patient population few observations were made .Mean age of patients was 58+_12 years. 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. Mean body mass index (BMI) of these patients was 18+_3 Kg/m^2

Thirty (53.5%) patients were using inhaled β_2-agonist, four(7.2%) oral methyl-xanthines, twelve(21.4%) oral methyl-xanthines plus inhaled β_2-agonist and ten(17.9%)were taking inhaled β_2-agonist plus inhaled steroid. During the period of stability spirometry revealed 16(28.6%)of patients having mild COPD and 40(71.4%) as having moderate COPD, with overall mean FEV_1 67+_17% predicted.

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}). Moreover C-reactive protein levels were not equal between ex-smokers and current smoker COPD patients being higher in the later. In 6 minute walk test (6MWT), Mean distance

travelled by cases was 401+_99 meters. Analysis of different variables to find out correlation with C-reactive protein levels was done. Comparisions of log C-reactive protein levels adjusted for 6 minute walk distance, $FEV_1\%$ and Body mass index did not reach statistical significance for sex, number of exacerbations smoking status and corticosteroids use.

Table-1: **Parameters that significantly Correlated with log C-reactive protein levels**

Variable	Correlation	p-value
6 minute walk distance	-0.28	0.001
$FEV_1\%$	-0.24	0.029
GOLD stage	0.19	0.040

log C-reactive protein levels showed statistically significant correlation with 6 minute walk distance, $FEV_1\%$ and GOLD stage. Then the variables showing significant correlation with log C-reactive protein levels were selected for multivariate analysis.

Table 3: **Result of multivariate analysis**

Predictive parameter	Regression coefficient				p-value
	value	SEM	95% CI	standardised	
6 minute walk distance	-0.004	0.001	-0.002-0.001	-0.206	0.04
$FEV_1\%$	0.008	0.008	-0.010-0.023	0.298	0.40
GOLD stage	-0.019	0.125	-0.263-0.233	-0.031	0.80

Result of multivariate analysis showed that 6 minute walk distance was the best explanatory factor for log C-reactive protein levels and rest others could not significantly correlated.

Table 2: Comparision of association of serum C-reactive protein with other variables in different studies

Study	year	6MWD	FEV_1	GOLD	BMI	No.of exacerbations
Torres et al[8]	2008	Negative association(c=-0.30,p=0.001)	Negative association(c=-0.20,p=0.030)	Positive association(c=0.17,p=0.040)	Positive association(c=0.17,p=0.050)	-
Kirdar S et al[9]	2008	-	-	-	Negative association(p=0.034)	-
Barnes P.J.et al[10]	2006	-	-	-	Positive association(p=0.044)	-
SFP Man et al[4]	2006	-	Negative association(p=<0.001)	-	-	-
CelliB.R.et al[11]	2006	-	-	-	-	No significant association
Koechlin et al[12]	2004	Negative association	-	-	-	-
Garrod R et al[13]	2007	Negative association(r=0.50,p=<0.01)	-	-	-	-
Doron Arnson et al[14]	2006	-	Negative association(p=<0.001)	-	-	-
Present study	2015	Negative association(c=-0.28,p=0.001)	Independent Negative association(c=-0.24,p=0.029)	Independent positive association(c=0.19,p=0.040)	Independent positive association(c=0.18,p=0.050	No significant association

Discussion

This study investigated the influence of prognostic factors on C-reactive protein levels in a well defined population of stable COPD patients. The main finding of this study is that C-reactive protein levels is mostly associated and correlating with 6 minute walk distance. The study also found that C-reactive protein levels also correlated independently with two other important prognostic variables: FEV_1 and GOLD stage.

There is now sufficient evidence to support the presence of extra-pulmonary consequences of COPD that can be detected clinically. They can be also measured by the increased level of systemic bio-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 [15] 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[16], demonstrated that in COPD patients-C-reactive protein levels predicted cardiovascular mortality. Lacy P et al[17] 2004, demonstated that cardiovascular mortality and inflammation decreased with treatment with inhaled fluticasone. Pinto Plata et al[18], 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 also noted by Karadag F.et al [9].

Our study also confirms the previous finding of higher C-reactive protein levels in smoking COPD patients (4.9 vs 4.0 mg-L^{-1}) as compared to nonsmoking COPD patients, as also 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 (4.0 vs 3.1 mg-L^{-1}). Similar findings were also observed in study done by Casanova C.et al[8] and SFP Man et al.[4]. Then Pinto plata et al[18] also found similar results.

In present study using pearsons bivariate linear correlation coefficient correlation of serum C-reactive protein levels was found with FEV_1%, 6 minute walk distance, GOLD stage but result of multivariate analysis showed that only 6 minute walk distance significantly correlated with C-reactive protein levels. Similar results were found in some previous studies.

It was also observed that C-reactive protein levels inversely correlated with 6 minute walk distance. Broekhuizen et al 2006[19] found that C-reactive protein increases with poor exercise capacity. This indicates measuring C-reactive protein levels in stable conditions could indirectly reflect the exercise capacity of these patients, which is an important prognostic factor of the disease.

This study confirms the previous finding of higher C-reactive protein levels in smoking COPD patients as compared with nonsmoking COPD patients, as demonstrated by Gan WQ 2005[15]. The level of C-reactive protein in ex-smoking COPD population remained significantly higher than nonsmoking control group. This suggest that once initiated the inflammatory state seems to persist, albeit at a seemingly lower level. It provides us strong argument to develop therapies aimed at decreasing inflammation independent of smoking cessation.

Conclusion

Our study confirms that C-reactive protein levels are higher in COPD patients. This biomarker levels are associated with important clinical variables like FEV_1%, GOLD stage ,and 6 minute walk distance, which help to predict prognosis and patient outcome. Of these 6 minute walk distance is most strongly associated with C-reactive protein levels. So C-reactive protein levels indirectly reflects exercise capacity of stable COPD patients. 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.

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