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Original article

Level of C-Reactive Protein in Stable Chronic Obstructive Pulmonary Disease

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ABSTRACT

The usefulness of CRP as a marker of systemic inflammation in stable COPD was assessed from the present study. Estimation of CRP level was estimated in 50 stable COPD patients and the results compared to that of 50 healthy individual and its relationship with clinical features of COPD was evaluated. CRP level was significantly higher in stable COPD patients (5.15±1.35mg/l) compared to healthy controls (1.23±0.57mg/L) and it correlated well with the disease severity. Circulating CRP can be used as a prognostic biomarker of low grade systemic inflammation in stable COPD patients as its half –life is 18-24 hours and easy to measure.

KEYWORDS: Chronic Obstructive Pulmonary Disease, C-reactive protein

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs due to varying combinations of the disease of the airways and emphysema [1]. It is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in the individual patient. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particle or gases [2]. It is recognised as fourth leading cause of death and according to the Global Burden of Disease (GBD) study 2000, COPD was responsible for an estimated 2.75 million deaths worldwide [3]. The prevalence of COPD in India was estimated as 4.1% according to a study conducted among 35,295 adult subjects of over 35 years of age [4]. Many factors contribute to the risk of developing COPD, including exposure to toxic fumes and gases, environmental air pollution, occupational exposure to dust particles and smoke, poor nutrition, childhood respiratory and hereditary [5].

Clinical feature of COPD include chronic cough with or without expectoration followed by difficulty in breathing which is persistent and gradually progressive which result from pathological changes in the airway and lung parenchyma. Changes include chronic inflammation and structural modifications resulting from repeated injury and repair. In addition to the presence of chronic local inflammation in both the airways and lung parenchyma, there is increasing evidence of systemic inflammation in patients with COPD which may contribute to the pathogenesis of atherosclerosis and cardiovascular disease [6].

Systemic effects of COPD are attributable to oxidative stress and altered circulating levels of inflammatory mediators and acute phase proteins. Levels of inflammatory proteins such as C – reactive protein (CRP), tumor necrosis factor (TNF) and interleukin (IL) -6 are increased in systemic circulation in such patients. Levels of inflammatory proteins due to COPD reflect the total systemic burden of inflammation in several disorders, including cardiovascular disease,

osteoporosis and even depression. The main clinical value of CRP is its ability to reveal early inflammation when other clinical parameters are vague [7].

It is an acute phase protein used as a sensitive marker of inflammation produced in the liver in response to acute inflammation in the body. It is raised in COPD and is a significant predictor of future risk of cardiovascular event and death in mild to moderate COPD and provides additional prognostic information beyond that of smoking, FEV1 and other traditional risk factors in COPD and may enable more accurate detection of patients at a high risk of mortality [8]. The extra pulmonary manifestations of COPD must be considered in evaluating its severity. Therefore this study was conducted to evaluate the serum levels of CRP as a biomarker of systemic inflammation in stable COPD and their values were compared with that of normal individuals.

MATERIALS AND METHODS

The study was a case control study conducted in the Department of Biochemistry in collaboration with the Department of Respiratory Medicine, Regional Institute of Medical Sciences Hospital, India from the year September 2010 to August 2012. Fifty patients who attended the Outpatient department of Respiratory Medicine and fulfilled the case definition of stable COPD were taken as the study group. Stable COPD was defined as a patient with COPD who has no exacerbation within the past six weeks, does not have cardiac involvement and any known systemic inflammatory disease. A provisional diagnosis of COPD was made after taking detailed history of the patient. A patient with dyspnea that is persistent, worsen over time, increases on exertion; chronic cough which may be intermittent and with or without sputum production; history of chronic smoking or exposure to risk factors like occupational dust and chemical or smoke from biomass and heating fuel are presumed as having COPD.

The diagnosis of COPD was confirmed by spirometry findings:

a) FEV1/ FVC < 70%

b) FEV1 < 80% of predicted

A person who had presence of co-morbid medical conditions, COPD on oral / systemic steroids in the past six weeks and those who did not give consent were excluded from the study. Chest X-ray and electrocardiogram were done in all patients to rule out cardiac involvement and other respiratory diseases. Another 50 age and sex matched healthy individual above 45 years of age free from any disease were taken as controls.

Ethical approval was obtained from the RIMS ethical Committee and written informed consent was taken from all the participants.

Detailed history regarding the duration of disease, age of onset of disease, history of smoking and duration of smoking and pack – year, associated symptoms like cough, sputum production etc. were recorded. History of exacerbation defined by previous hospitalization due to COPD was noted.

Pack – year is defined as number of cigarette smoked by a person over years ie. number of pack smoked per day multiplied by number of year smoked; assuming one pack of cigarette contains twenty sticks of cigarette [5].

Current smoker is one who had smoked more than 100 cigarettes in his life time and is currently smoking daily. Former smoker is one who had smoked more than 100 cigarettes in his life time, but not smoked for the last one year. Never- smokers are those who never smoke or smoke less than 100 cigarettes in their life time [9]. Dyspnea was graded according to Modified Medical Research Council (MMRC) Dyspnea Scale [10].

Spirometry was performed using Helios Spirometer model no RMS 701 (Recorder and Medicare System Pvt Ltd, India) to confirm COPD and severity of disease was graded according to Global Initiative for Obstructive Lung Disease (GOLD) [2]. Spirometer was calibrated for each patient according to the height, weight, age and gender. It was done in standing position and nose was clipped to prevent air escaping from the nose. Patient inhaled air through the mouthpiece with maximal effort then held the breath less than one second then blew out as hard as fast as possible to empty the lung. The procedure was repeated for atleast three times and best effort was taken and recorded.

Three millilitres of blood was drawn from the anticubital veinin a plain vail and CRP was estimated in the Department of Biochemistry, RIMS, Imphal. The level of CRP was estimated by using high sensitivity C- reactive protein enzyme immunoassay test kit (BIOMERICA). The minimum detectable concentration of this method was 0.1mg/L CRP and upper limit was 10mg/LCRP.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 17.

RESULTS

Out of the 50 cases and controls, 35(70%) were males and 15(30%) were females in both the groups. The mean age of the patient was 67.2$\pm$5.9 and that of controls was 66.28$\pm$7.7 years. When CRP level of COPD patients was compared to that of controls irrespective of demographic and clinical parameters, COPD patients had significantly higher level of CRP compared to the controls [table 1]. It was also observed that mean CRP level was significantly higher in COPD patients than in the control in different age group and it was found to be higher in higher age group. Males had higher CRP level than female patients but the difference was found to be insignificant (5.24$\pm$1.32 vs 4.96$\pm$1.44; p=0.5). Mean CRP levels of both gender was significantly higher in COPD patients than the controls (p<0.001).

Table 1: Age-wise distribution of Mean CRP level in cases and controls

Age	COPD Cases		Controls		p-value
	Number	CRP level mg/ L (Mean ±SD)	Number	CRP level mg/ L (Mean ±SD)	
45-49	0	0	2	0.5±0	
50-59	4	2.8±0.73	6	0.58±0.11	P=0.0091
60-69	23	4.7±1.1	22	0.94±0.23	P<0.0001
70-79	23	5.9±1.0	20	1.8±0.36	P<0.0001

All COPD cases had history of smoking, 41(82%) were current smoker and 9(18%) were ex-smokers. All COPD cases had history of smoking, 41(82%) were current smoker and 9(18%) were ex-smoker. Out of 50 control subject 37(74%) were current smoker, 11(22%) were ex- smoker and 2(4%) never smoked. There was no significant difference between the mean CRP level of current and ex smoker in both the study groups [Table 2].

Table 2: Mean CRP level and smoking status

SMOKING status	COPD Cases		Controls		p-value
	Number (%)	CRP level in mg/L (Mean±SD)	Number (%)	CRP level in mg/L (Mean±SD)	
Current smoker	41(82)	5±1.36	37(74)	1.15±0.54	<0.0001
Ex-smoker	9(18)	5.8±1.1	11(22)	1.60±0.50	<0.0001
Never smoker	0	0	2(4)	0.55±0.07	
Pack-year (Mean±SD)	50(100)	26.16±6.62	48(92)	16.2±4.5	<0.0001

Table 3.Clinical features among COPD patients based on GOLD and MMRC and their mean CRP levels.

Clinical features		**Number of cases (%)**	CRP level in mg/L (Mean ± SD)	p-value
Chronic cough		50(100%)		
Sputum		45(90%)		
GOLD Staging	Stage 1	0	0	0.010
	Stage 2	38(76%)	4.88±1.38	
	Stage 3	12(24%)	6.01±0.84	
	Stage 4	0	0	
MMRC	Stage 1	19(38%)	4.38±1.38	0.0023
	Stage 2	11(22%)	5.27±1.39	
	Stage 3	20(40%)	5.82±0.90	
	Stage 4	0	0	

As shown in Table 3, all the COPD patients had chronic cough, 45(90%) had sputum production. On assessment of the severity of the disease using GOLD staging, 38 patients (76 %) have moderate (stage 2) and 12 patients (24%) have severe degree (stage 3). The mean level of CRP was found to be 4.88±1.38 mg/l in patient with stage 2 GOLD staging and it was found to increase upto 6.01±0.84 in stage 3.Degree of dyspnoea was graded using MMRC dyspnoea scale, 19 patients (38%) had grade 1 dyspnoea, 11 patients (22%) have grade 2 dyspnoea and 20 patients (40%) have grade 3 dyspnoea. As MMRC staging increases the mean level of CPR was found to be increased significantly. In stage 1 MMRC staging 19 patients had their CPR level 4.38±1.38 mg/l and it was found to increased upto 5.82±0.90 mg/l in patients of stage 3 MMRC staging. The mean CRP level was found to increase significantly in patient with history of dyspnoea (5.78 ±1.07mg/l) compared to patients without history of dyspnoea (4.35±1.26mg/l).

DISCUSSION

COPD is the major cause of morbidity and mortality throughout the world. In addition to the presence of chronic inflammation in the airways and lung parenchyma, there is increasing evidence of systemic inflammation in COPD patients which strongly influences the quality of life and increases mortality, leading to weight loss, muscle wasting and osteopenia, tissue depletion and psychological problem. When CRP level of COPD patients was compared to that of controls irrespective of demographic and clinical parameters, COPD patients had significantly higher level of CRP compared to the controls [Table 1]. It was also observed that mean CRP level was significantly higher in COPD patients than in the control in different age group and it was found to be higher in higher age group. CRP is an acute-phase protein synthesised by the hepatocytes in response to tissue damage or inflammation reflecting total systemic burden of inflammation of individuals [4].

Levels of CRP, interleukin-6 and tumour necrosis factor are increased in systemic circulation in such patients. The main clinical value of CRP is its ability to reveal early inflammation when other clinical parameters are vague. Majority of the patient were above 60 years of age and CRP was significantly higher in COPD patients compared to the controls. There was significant difference in the level of CRP level among males and females which correlates with the findings of Man SPF and co-workers. The mean CRP level was 5.0±1.36mg/l in COPD patients and 1.15 ±0.54 mg/dl in control among current smoker while it was 5.8±1.1mg/l in COPD patients and 1.60±0.050mg/l in control among ex –smoker. Broekhuizen et al [11] has similar results in his study where current smoker had mean CRP level of 5.1±3.2 mg/l and ex-smoker had 4.3±3.3 mg/l. Gan WQ et al also showed in their study that CRP was elevated in patients who actively smoked and stable COPD cases. Many studies had shown that CRP level in stable COPD patients correlated with FEV1, FVC, IC/TLC etc.

When severity of disease was assessed using GOLD staging it was found that patients with severe degree have higher mean CRP level (6.01±0.84mg/l than those with moderate degree COPD (4.88±1.3mg/l). In a study conducted by Torres et al [12] it was found that CRP level correlated independently with important prognostic clinical variables of COPD such as FEV1, FVC, IC/TLC, GOLD stage and BODE index. In contrast, Mitra SF et al [13] found no significant correlation between the level of CRP and FEV1 in his study. MMRC dyspnea scale [10] was used for grading dyspnoea in this study. 38% (n=19) of COPD patients have grade 1, 22% (n=11) have grade 2 and 40% (n=20) have grade 3 dyspnea and their mean CRP levels were 4.38±1.38mg/L, 5.27±1.39mg/L and 5.82±0.90mg/L respectively. The difference between the mean CRP levels in different grades of dyspnoea observed in this study was statistically significant which was similar to the findings of Garrot R et al. A study by JP De Torres et al revealed that as lung function worsens CRP level also increases. This explain the direct relationship found between CRP levels and GOLD stages or the BODE index.

There were several limitations to the present study. First serum CRP level was measured at only one time-point. Therefore, the impact of changes in CRP level over time on mortality of COPD patients is unknown. Additionally, it is uncertain how the blood levels of these molecules are linked to the pathology of the lung disease in COPD. Notably CRP is not lung specific; therefore, their blood levels may not correlate with what is happening in the lungs. Future studies will be needed in these specific populations in order to determine the potential utility of the fibronectin to CRP ratio in predicting cardiac events in these patients. Moreover, since only patients with COPD were studied in the present study, comparisons of the current findings with those in the general population are not possible.

CONCLUSION

It is seen from the above study that CRP level was higher in patients with stable COPD compared to the controls and also the level of CRP correlates with the severity of the disease. Thus it can be used as an inflammatory marker to provide the prognostic information of the disease.

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