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# Serum C-Reactive Protein Level in COPD Patients and Normal Population

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## ABSTRACT

**Background:** Serum C-Reactive Protein (CRP) is increased in patients with chronic obstructive pulmonary disease (COPD). It is used as a predictive factor for extra-pulmonary complications determining the prognosis of disease. It has not yet been defined whether this increase is due to the disease itself or is accompanied by ischemic heart disease and cigarette smoking. Thus, we decided to measure the serum CRP level in COPD patients without ischemic heart disease and also in healthy subjects by enzyme-linked immunosorbent assay (ELISA) and then we evaluated its relation with cigarette smoking, severity of dyspnea, exacerbation episodes, severity of disease and use of inhaled steroids.

**Materials and Methods:** A comparative-descriptive study was performed on 45 stable COPD patients in 2006. All under study patients were males.

The exclusion criteria included ischemic heart disease and other causes of CRP increase. The control group consisted of 45 healthy men. The samples were selected consecutively. The serum CRP was measured by ELISA (high sensitive). Data were analyzed by SPSS software version 13.

**Results:** Mann-Whitney test showed significant difference between serum CRP levels of COPD patients without ischemic heart disease (52.49 ng/ml) and healthy subjects (28.51 ng/ml) ( $p=0.01$ ).

There was a significant difference between the serum CRP level and the severity of dyspnea in COPD patients ( $p=0.04$ ). No significant difference was detected between CRP level and the severity of disease, exacerbation episodes and use of inhaled steroids. Moreover, there was no significant difference between serum CRP and cigarette smoking in COPD patients and healthy subjects.

**Conclusion:** The results showed that COPD itself can increase the serum CRP without ischemic heart disease and cigarette smoking. Since CRP is known as a systemic inflammatory marker and a major factor causing extrapulmonary complications, we hope this marker be applied for follow-up of patients, evaluation of treatment methods and their efficacy. (*Tanaffos* 2007; 6(2): 51-55)

**Key words:** C-Reactive Protein, Chronic Obstructive Pulmonary Disease, Normal population

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and increasing mortality in developing and developed countries (1). Global initiative for chronic obstructive lung disease (GOLD) has estimated that this disease is probable to be the third cause of death in the world by the year 2020 (2). Although COPD primarily involves the lungs, the chronic inflammatory process causes systemic manifestations. Recently, it has been suggested that systemic inflammation may indicate a missing link between airways dysfunction and extrapulmonary complications of the disease but it can not determine the source of inflammation (3).

One of the inflammatory markers which is increasingly evaluated in COPD patients is CRP (4). This factor is increased in COPD patients and relates to the pulmonary function. Also, it is known as a predictive factor for the course of COPD (5). Cardiac infarction, unstable angina, sudden death and stroke are also accompanied by increased (6,7). Some studies have shown that the most common cause of mortality in mild and moderate forms of COPD is cardiovascular disease (8).

CRP increase in COPD patients may be either due to the disease itself accompanying the systemic inflammation or related factors such as ischemic heart disease and cigarette smoking (7,9). Thus, we decided to measure serum CRP level in COPD patients without known ischemic heart disease and compare it with healthy humans. We also evaluated the correlation of serum CRP level with severity of disease, use of inhaled steroids and severity of dyspnea in COPD patients and also its relation with cigarette smoking in both COPD patients and healthy subjects.

## MATERIALS AND METHODS

A comparative-descriptive study was performed in 2006. First, patients with COPD were selected

among the patients referred to pulmonary clinic of Shaheed Sadoughi hospital, Yazd. This group of patients had a history of cough, sputum, persistent dyspnea, cigarette smoking and other COPD risk factors. They had  $FEV_1/FVC < 70\%$  and  $FEV_1 < 80\%$  predicted in their spirometry and asthma was ruled out in them by assessing their clinical history and response to bronchodilators (less than 12% increase in  $FEV_1$  after inhaling salbutamol 400 $\mu$ g) (10,11). The selected patients had no history of exacerbation during the past two months. Ischemic heart disease was ruled out in them by clinical history, physical examination, echocardiogram (ECG), echocardiography, exercise test and angiography in suspected cases. Thereafter, a group of healthy subjects who had no history of ischemic heart disease with normal pulmonary function test and matched COPD patients in terms of age, sex and history of cigarette smoking were selected among those referred to blood transfusion center in Yazd. It is noteworthy that in both groups, subjects with a history of congestive heart failure, malignancy, liver cirrhosis, end stage renal failure, rheumatoid arthritis, tuberculosis and systemic infection were excluded from the study. A written consent was obtained from both groups. A questionnaire was filled out containing demographic characteristics, history of cigarette smoking, spirometric results, severity of disease based on GOLD's criteria, severity of dyspnea based on Modified Medical Research Council (MMRC) scale, exacerbation episodes of disease during the past years, history of inhaled steroid use in COPD patients and demographic characteristics and history of cigarette smoking in healthy subjects. After resting for 10 min, 3 cc of blood sample was taken from each person, poured into a clot tube and then coagulated. Serum sample was separated by centrifugation and stored at  $-70^{\circ}\text{C}$  in 0.5 cc vials. After collecting of samples, ELISA

test (HS CRP kit, DRG Company) was performed. This kit showed CRP level as a quantitative measure and its sensitivity was 10ng/ml. Data were analyzed by descriptive (percentage mean and standard deviation) and comprehensive statistics (Kruskal-Wallis test, Mann-Whitney test) and SPSS software ver. 13.

## RESULTS

In this study, 45 COPD patients without ischemic heart disease and 45 healthy subjects were assessed. All cases were males. The two groups were matched in terms of age (age range 40-85 yrs) and cigarette smoking there were 29(64.45%) smokers in each group).

Regarding severity of disease according to GOLD Criteria, none of the COPD patients were in stage I, and 46.65%, 28.95% and 24.45% were in stage II, III and IV, respectively. Assessment of the severity of dyspnea according to MMRC scale showed that no patient was in stage of and IV and 20%, 42.22% and 37.78% were in stage I, II and III, respectively. The number of exacerbations in 66.65% of patients was  $\leq 2$  times in a year and in 33.35% of the remaining was more than 2 times a year. Sixty percent of patients were using inhaled corticosteroids. Mann-Whitney test showed that the mean CRP level in COPD patients without ischemic heart disease was significantly higher than healthy subjects (52.49 ng/ml vs 28.51 ng/ml,  $p=0.01$ ).

Kruskal- Wallis test showed that the mean serum CRP level in COPD patients was significantly correlated with severity of dyspnea, which was 22.78 g/ml, 28.88 ng/ml and 36.90 ng/ml in stage I, II and III, respectively (Table 1). These statistical tests showed that the mean CRP level in COPD patients was not significantly correlated with severity of disease, number of exacerbations and use of inhaled corticosteroids. Based on Mann- Whitney test, the mean CRP level had no significant relationship with

cigarette smoking (neither in COPD patients healthy subjects).

Table 1. The mean of CRP level in COPD patients according to severity of dyspnea.

Severity of dyspnea	No	The mean of CRP level (ng/ml)
Stage I	9	22.78
Satge II	19	28.88
Satge III	17	36.90

Kruskal-Wallis test H= 5.12 P=0.04

## DISCUSSION

The present study showed that there was a significant difference in mean serum CRP level between COPD patients and healthy subjects as CRP serum concentration was higher in patients with COPD. Yende et al. reported a higher level of serum CRP in cases with an obstructive pattern in their spirometry (3.5 mg/L) in comparison to normal population (2.5 mg/L) ( $p<0.0001$ ) (4).

In a study conducted by Broekhuizen et al. stable COPD patients had increased levels of inflammatory markers like CRP ( $p=0.03$ ) (12).

Pinto-Plata et al. showed that there was a significant higher level of CRP in COPD patients ( $50.03\pm 1.51$  mg/L) rather than smoking ( $2.02\pm 1.04$  mg/L) and non smoking control groups ( $2.24\pm 1.04$  mg/L) ( $P<0.001$ ) (13).

In this study, there was no significant difference between smoking and non-smoking COPD patients and healthy subjects regarding serum CRP level which was consistent with Pinto-Plata et al's study (13). In our opinion, although cigarette smoking has a role in initiation of inflammatory process in COPD patients, it is not the leading cause of increased inflammatory markers. It should be noticed that not all cases develop inflammatory reaction following cigarette smoking and only some of them will show

this reaction which can be due to genetic differences (13). Thus, we can predict the possibility of developing COPD in the future by measuring inflammatory markers in smokers. Regarding the severity of disease based on GOLD criteria, the mean serum CRP level was increased in severe cases but this correlation was not statistically significant. Pinto-Plata et al. showed that there was no significant difference between the severity of disease and serum CRP level (13) but de Torres and co-workers indicated that serum CRP level was significantly increased by aggravation of disease (14). Therefore, consequently, although we expect the inflammatory process to be worse and the inflammatory markers to be increased by increasing the severity of disease, more studies are required in this regard. Based on results, there was a significant difference between the mean CRP level of patients and severity of dyspnea as with increased severity of disease according to MMRC scale), the mean CRP level increased as well as. In a study by Schneider (15), there was also a significant difference between the severity of dyspnea and the level of CRP ( $p=0.004$ ). Since the severity of dyspnea increased by progression of COPD, we assume that there is a direct relationship between the severity of dyspnea and increased serum CRP level.

The present study did not show a significant difference between the number of exacerbations and increased CRP level. Pinto-Plata et al. confirmed this finding in their study (13). In a study conducted by Tina et al. CRP levels were significantly higher in patients with exacerbations than stable patients ( $p<0.001$ ) but no difference was detected between the number of exacerbations and CRP level (16).

In our study, there were no significant difference in the mean CRP level between patients using inhaled corticosteroids and those who did not use it.

Pinto-Plata et al. showed that patients who used inhaled corticosteroids had lower CRP level than those who did not use it (13). However, the patients were in the same stage in terms of severity of disease.

de Torres et al. reported no relationship between CRP level and steroid use (14). However, we expect the serum CRP level to be decreased by initiation of inhaled steroids (17) but since we usually prescribe inhaled corticosteroids for COPD patients at severe stages ( $FEV_1<50\%$ ) and CRP level is higher at the same time, so the effects of inhaled steroids on lowering serum CRP level are not clear. Therefore, we need to compare the level of this factor before and after the use of inhaled steroids.

COPD patients in our study did not have a known clinical ischemic heart disease. These patients had a higher level of CRP in comparison to the control group. Therefore, we can conclude that the increased CRP level in COPD patients is not due to the concurrent ischemic heart disease alone. Pinto-Plata and colleagues showed the same results (13).

CRP is an inflammatory marker and inflammation has a role in pathogenesis of atherosclerosis and cardiovascular disease. On the other hand, cardiovascular disease is one of the most common cause of mortality in all stages of COPD and also the most common causes of death in mild and moderate stages of disease (8, 18).

As a result, COPD patients without a known cardiovascular disease are at the risk of future events and CRP may help predicting them. As a whole, COPD itself can increase the level of CRP without presence of a relationship with ischemic heart disease and cigarette smoking. Since CRP is a systemic inflammatory marker and systemic inflammation is one of the major factors in development of extrapulmonary complications, we hope to use this

marker for the follow up of patients and assessing the effects of therapeutic methods. Our limitations were low sample size and assessment of only male patients.

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