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Correlation of CRP and Serum Fibrinogen Levels with Disease Severity, Clinical Factors and Pulmonary Function Tests in COPD Patients

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ABSTRACT

Background: *Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease and C-reactive protein (CRP) and fibrinogen are considered as main systemic inflammatory biomarkers. This study aimed to evaluate the alterations of CRP and serum fibrinogen levels in COPD patients and their correlation with the severity of disease, arterial O_2 saturation and opium or cigarette consumption.*

Materials and Methods: *This was a descriptive case-control study conducted on 31 COPD patients and 29 healthy controls selected by using easy sampling method in Afzalipour Hospital. Serum levels of CRP and fibrinogen were measured by ELISA method and analyzed using SPSS software version 15.*

Results: *The mean serum level of CRP in the understudy patients (13.15±13.72 mg/L) was significantly higher than that of the controls (3.53±1.12 mg/L)(P=0.000). However, no significant difference was found in the mean serum level of fibrinogen between cases (3.81±0.93 mg/dl) and controls (3.72±0.9 mg/dl)(p=0.82). Also, no significant correlation was detected between the serum level of CRP or fibrinogen and severity of the disease (P=0.92 and P=0.58, respectively). A statistically significant relationship was found between the serum levels of CRP and fibrinogen and arterial O_2 saturation (P=0.02). There was no significant difference in the serum levels of CRP and fibrinogen between the opium users (p=0.19) and other patients (p=0.15).*

Conclusion: *According to our study results, COPD, per se, can increase the inflammatory biomarkers including CRP. Raised serum level of CRP is indicative of systemic inflammation which results in extra-pulmonary manifestations like cardiovascular diseases, cerebrovascular accidents, osteoporosis, and cachexia. Therefore, with routine measurement of this marker, we can evaluate the severity of systemic inflammation in these patients and choose the best treatment accordingly.* ***(Tanaffos 2010; 9(1): 28-33)***

Key words: *Fibrinogen, Chronic obstructive pulmonary disease, C-reactive protein, Pulmonary function test*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease mainly caused by cigarette smoking and includes 3 major diseases of chronic bronchitis, emphysema, and small airways disease (1).

COPD is characterized by airflow limitation which is not completely reversible. Airways disease is usually progressive and is associated with

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pulmonary inflammatory response to chronic exposure to inhaled toxic gases and particles (1).

COPD is undoubtedly an important disease. According to the WHO report, 2,660,000 deaths have occurred worldwide due to COPD in 1999 (1).

COPD is the forth leading cause of death in the United States. According to the "Global Initiative for Chronic Obstructive Lung Disease" (GOLD) estimates, COPD will be the third leading cause of death by the year 2020 (2).

Systemic manifestations in COPD patients are not caused by the alterations in pulmonary function alone; a systemic inflammatory disease is also involved (3-5).

Systemic inflammation is a risk factor for most of the complications that occur in these patients including atherosclerosis, cachexia, loss of appetite and osteoporosis (6) and is associated with increased rate of cardiovascular diseases, cerebrovascular accidents, morbidity and mortality (7).

Circulatory cytokines released due to the inflammation of the lungs are considered as a possible cause (4,8).

Interleukin 6 (IL-6) may be responsible for the increased serum level of fibrinogen and hypercoagulability in these patients (4) and tumor necrosis factor α (TNFα) may contribute to weight loss and skeletal muscular dysfunction (4).

COPD is a prevalent disease in our country. Cigarette smoking, bread baking in rustic ovens, working in mining industries especially coal mining, and mainly opium consumption are among the most common causes of COPD in Iran. Therefore, this study was conducted to evaluate the serum levels of CRP and fibrinogen as the biomarkers of systemic inflammation, to investigate their association with different causative factors especially opium consumption, and to offer a more efficient treatment for these patients.

MATERIALS AND METHODS

This was a descriptive case-control study conducted on 31 COPD patients and 29 healthy controls chosen by using the easy sampling method. Healthy controls were examined by a pulmonologist for any abnormality. They were also evaluated in terms of exclusion criteria including history of current or previous cigarette smoking, opium consumption and high risk occupations affecting lung function. A written consent was obtained from subjects. After 10 minutes of relaxation, 5 cc of blood was drawn from a peripheral vein from the inside of the elbow using a 5 cc syringe, 2 cc of which was added to the 3.2% sodium citrate tubes and stored for the measurement of fibrinogen and the remaining 3 cc was stored for the measurement of CRP. Collected blood samples were transferred to the laboratory in a cold box (laboratory standard method). Understudy patients (case group) were selected from patients presenting to the pulmonary clinic of Afzalipour Hospital. Patients with a history of cough, sputum production, long-term dyspnea, and COPD risk factors such as cigarette smoking, opium consumption, occupational exposure to toxic substances and bread baking in rustic ovens were examined by a pulmonologist and those with a confirmed diagnosis of COPD based on signs and symptoms and physical examinations underwent spirometry (MIR Co. Spirometer). The spirometer measured various parameters among which FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and ratio of FEV1/FVC were noted. The test was performed 3 times and the most correct result was selected (1, 2, 9). Patients with FEV1/FVC ratio of < 0.7 who were using salbutamol inhaler were asked to undergo a second spirometry test 15 minutes later. If the FEV1 increase was less than 12% or 200 ml, the patient would be considered as a COPD patient and severity of disease would be classified according to the GOLD criteria as follows:
FEV1/FVC <0.7 and FEV1≥ 80%: mild

FEV1/FVC<0.7 and 50% ≤ FEV1 < 80%: moderate
FEV1/FVC<0.7 and 30%≤ FEV1< 50%: severe
FEV1/FVC<0.7 and FEV1<30%: very severe

A written consent was obtained from these patients and a questionnaire containing the demographic characteristics of patients, history of smoking, history of opium consumption, occupation, and history of bread baking in a rustic oven was filled out for them.

The inclusion criteria for the study were FEV1/FVC<0.7 and no response to bronchodilator.

The exclusion criteria were as follows:

1- Acute exacerbation of disease in the past 4 weeks
2- Fever higher than 38˚C with oral measurement
3- Presence of underlying diseases which would result in further inflammation and increased CRP such as various infections, cancers, rheumatic diseases, acute and chronic liver diseases, acute and chronic renal failure, and congestive heart failure
4- Taking oral corticosteroids

For patients who met the inclusion criteria, pulse oximetry was performed using a pulse oximeter (Nemoxy, model 412).

Serum concentration of fibrinogen (mg/dl) was measured in the laboratory using a coagulameter (Labi Tac, made in Germany). Serum level of CRP (mg/L) was measured using nephlometry (Minineph, made in UK). Blood samples of both cases and controls were analyzed in the same laboratory using the same kit by the same technician who was blinded to the study population. Data were collected and analyzed using SPSS software, one way ANOVA, Kruskal-Wallis test, Mann-Whitney test, independent sample t-test, and linear regression model. P value<0.05 was considered significant and statistical power was considered as 80%.

RESULTS

In this study, 31 COPD patients and 29 healthy controls were evaluated. The mean age of COPD patients was 62.58 ±11.39 yrs (range 40-84 yrs). There were 28 males (95.3%) and 3 females (9.7%).

Severity of disease according to the GOLD criteria was mild in 3 cases (9.7%), moderate in 10 cases (32.2%), severe in 7 cases (22.6%) and very severe in 11 cases (35.5%).

Twenty-six cases (83.9%) were using opium during the study period while 5 cases were not (16.1%). Twenty-seven cases (87.1%) were current smokers and 4 cases (12.9%) were nonsmokers.

In terms of occupation, there was 1 carpet-weaver (3.2%), 17 farmers (54.8%), 5 coal miners (16.1%), 4 employees (12.9%) and 4 businessmen (12.9%).

The 29 healthy controls were all males with the mean age of 58.21±8.84 yrs (range 46-75). None of them had a high risk occupation affecting lung function.

In COPD patients, the mean concentration of CRP was 13.72±13.15 mg/L and the mean concentration of fibrinogen was 3.81±0.93 mg/dl.

In controls, the mean concentration of CRP was 3.53±1.12 mg/L and the mean concentration of fibrinogen was 3.72±0.9 mg/dl.

The mean FEV1/FVC ratio was 57.26±9.26 and the mean percentage of arterial oxygen saturation was 86.96%± 6.42%.

No significant correlation was found between the serum level of fibrinogen and value of FEV1 (p=0.58). Also, there was no significant correlation between the serum level of CRP and FEV1 value (p=0.92). However, a significant correlation was detected between the serum level of CRP and SaO2 (p=0.02). A significant correlation was also detected between the serum level of fibrinogen and SaO_2 (p=0.02) (Table 1).

The mean serum level of CRP in COPD patients (13.72±13.15 mg/L) was significantly higher than that of healthy controls (3.53±1.12 mg/L)(p=0.00)

However, no significant difference was found in the serum level of fibrinogen between patients (3.81±0.93 mg/dl) and controls (3.72±0.9) (p=0.82) (Table 2).

Table 1. The levels of CRP and fibrinogen and the percentage of arterial oxygen saturation in COPD patients based on FEV1 value.

	Mild FEV1≥80%	Moderate 50%≤FEV1<%80	Severe 30%≤FEV1<%50	Very severe FEV1<30%	P-value† ANOVA
Level of fibrinogen (mg/dl) (Mean±SD)	3.56±1.59	3.77±0.9	4.01±0.95	3.80±0.97	0.58
Level of CRP (mg/L) (Mean±SD)	3.73±0.45	21.7±18.7	7.6±7.8	22.4±43.1	0.92
Arterial oxygen saturation (%) (Mean±SD)	92±2	88±4.6	90.4±4.3	83.46±7.09	0.02*

* Significant($p<0.05$)

† Analysis of variance

Table 2. Comparison of the mean level of fibrinogen and CRP between COPD patients and controls

	COPD patients	Controls	P-value Mann-whitney test
Mean serum level of fibrinogen (mg/dl)	3.81±0.93	3.72±0.9	0.82
Mean serum level of CRP (mg/L)	13.15±13.72	3.53±1.12	0.000

Although the serum level of CRP was higher in those not using opium compared to opium addicts (20.07±14.51 versus 11.82±13.44, respectively), the difference was not statistically significant (Mann Whitney test, p=0.19). Also, the difference in the serum levels of fibrinogen between opium addicts and others (3.92±0.94 versus 3.26±0.73, respectively) was not statistically significant (independent sample t-test, p=0.15).

DISCUSSION

According to our study results, the mean serum level of CRP was significantly higher in COPD patients compared to controls (13.15±13.72 versus 3.53±1.12) which was in accord with the study results of de Torres. In his study, level of CRP in patients was also higher than that of controls (4.17 versus 1.8 mg/L) (10).

In a study conducted by Broekhuizen and colleagues in the Netherlands, the serum level of CRP was higher than the normal limit in COPD patients (3).

In another study conducted by Karadag and coworkers in Turkey, the serum level of CRP was higher in COPD patients compared to controls (11).

CRP is a pentraxin produced mainly but not exclusively by hepatocytes as an acute inflammatory response. There is a consensus that inflammatory markers especially CRP can activate the complement system via the classical pathway and stimulate inflammatory cytokines like IL-8 and IL-6 resulting in the development of a chronic inflammatory process in the patient's body.

In this study no significant difference was found in the fibrinogen serum level of COPD patients and controls (3.81±0.93 mg/dl versus 3.72±0.9 mg/dl, respectively).

However, in a study conducted by Groenewegan and his colleagues in Masstricht University in the Netherlands, the serum levels of inflammatory biomarkers including CRP, fibrinogen, and TNFα were higher in COPD patients compared to controls(12).

In another study performed by Valipour A and coworkers on COPD patients, serum levels of inflammatory biomarkers including CRP and

fibrinogen were higher in these patients compared to controls (13).

In a study conducted by Highashimoto and coworkers and also in another study by Wedzicha et al. the serum levels of CRP and fibrinogen were higher in COPD patients compared to controls (14, 15).

In our study, no significant difference was found in the mean serum level of fibrinogen between cases and controls. Therefore, further comparative studies with larger sample sizes are required in this regard.

COPD is known as a risk factor for thrombotic accidents especially deep thrombophlebitis and thromboembolism. Various studies have demonstrated that thromboembolic events in these patients are not caused by decreased mobility alone. Increased serum levels of inflammatory factors mainly IL-6 and fibrinogen also play a role in this regard. IL-6 and fibrinogen are both considered as precoagulation biomarkers and thrombotic accidents are a reflection of vascular endothelial inflammation and increased serum level of precoagulation biomarkers like fibrinogen.

In our study, no significant correlation was found between the level of CRP and FEV1 (indicative of disease severity according to GOLD criteria). However, de Torres et al. Groenewegan et al. and Valipour et al. in their studies found a significant correlation between the increased serum level of CRP and fibrinogen and decreased FEV1 and disease severity (10, 12, 13).

In this study, we also evaluated the effect of opium and cigarette consumption on the serum level of CRP and fibrinogen and we found that the serum level of CRP in those using opium alone, in smokers, and in those using both opium and cigarette was higher than healthy controls. However, no significant difference was found between these 3 groups. According to our study results, opium consumption similar to cigarette smoking increases the serum level of CRP in these patients and results in a chronic systemic inflammatory process.

In our study, we found a significant correlation between the serum levels of CRP and fibrinogen and arterial oxygen saturation. This finding was in accord with that of de Torres et al. (10) who also found a significant negative correlation between the serum levels of CRP and fibrinogen, and arterial oxygen saturation and PaO_2.

These data suggest that the serum level of CRP as an inflammatory biomarker, increases in COPD patients causing a systemic chronic inflammatory process and increasing the chance of cardiovascular and cerebrovascular accidents, cachexia, and osteoporosis. These complications result in increased mortality and morbidity and decreased survival rate. Therefore, it is recommended to measure the serum level of CRP in COPD patients during their routine clinical visits. Patients with higher levels of CRP should be considered for a more aggressive treatment. They are also advised to quit smoking and opium consumption and undergo rehabilitation therapy. Pharmacologic therapy and life style change are also recommended for these patients in order to decrease the related complications and increase their survival rate.

Study Limitations

The majority of our understudy population were males. It would have been better if there was equal number of males and females.

Also, our sample size was small and therefore we could not reach the level of significance for some understudy variables. Further investigations on a larger sample size are required in this regard.

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