Study of Serum C-Reactive Protein Level in Patients with COPD

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Abstract

Aim of the Work: The aim of this work was to study the usefulness of serum CRP as a systemic inflammatory marker for COPD patients and to evaluate ischemic heart diseases (IHD) and smoking as potential causes of raised CRP levels in COPD.

Subjects and Methods: Forty male patients with COPD were admitted to chest department, Benha University Hospital were included in this study and 40 healthy male of the same age and sex as a control group (20 smokers and 20 non-smokers) with no history of ischemic heart diseases and with normal ventilatory function tests. The patients and controls were subjected for full clinical evaluation including a full clinical and family history, History of any other co-morbidities that may raise the C-reactive protein as ischemic heart diseases, hypertension, diabetes mellitus, tuberculosis, malignancy, hepatic cirrhosis, end-stage renal disease, rheumatoid arthritis and any systemic infection or inflammation that could be associated with increased CRP values. General & local examination, routine laboratory tests, plain chest X-ray (P.A. and lateral view), Body mass index, Pulmonary function tests (spirometry) before and after bronchodilatation, Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar and venous blood samples for C-reactive protein measurement.

Results: The level of CRP was higher in COPD cases compared to normal controls (smokers and non smokers) and the difference between them was statistically significant (p<0.05). Also the level of CRP was proportionally related to the stage of the disease as there was a significant increase in CRP level with increasing the severity of COPD. Very severe COPD cases have higher level of CRP than severe and moderate cases. CRP was also raised in severe cases than moderate cases and the difference between them was highly statistically significant (p<0.01).

Conclusions: Serum CRP levels are raised in COPD patients without clinically relevant IHD and independent of cigarette smoking.

Key Words: COPD – Smokers – Non smokers – Serum c-reactive protein – Ventilatory function tests – Smoking index – Body mass index (BMI).

Introduction

COPD is a preventable and treatable disease state characterized by airflow limitation which is progressive, not fully reversible, associated with airway inflammation, hyperresponsiveness, and systemic manifestations including skeletal muscle dysfunction, cachexia, cardiovascular and osteo-skeletal alteration. The airflow obstruction is generally due to chronic bronchitis or emphysema [1]. CRP is a member of diverse class of defense molecules called acute phase proteins. The levels of acute phase proteins rise rapidly during infection and after injury [2]. This factor is increased in patients with chronic obstructive pulmonary disease (COPD). It has not yet been defined whether this increase is due to the disease itself or is accompanied by ischemic heart diseases and cigarette smoking. It is used as a predictive factor for extrapulmonary complications determining the prognosis of the disease [3]. It can also predict the incidence of ischemic heart disease complicating COPD patients [4].

Aim of the work:

The aim of this work is to study the usefulness of serum CRP as a systemic inflammatory marker for COPD patients and to evaluate ischemic heart diseases (IHD) and smoking as potential causes of raised CRP levels in COPD.

Subjects and Methods

This study was performed on 80 subjects, 40 male patients with COPD and 40 healthy male of the same age and sex as a control group (20 smokers and 20 non-smokers) with no history of ischemic heart diseases and with normal ventilatory function tests. COPD patients were admitted to chest department, Benha University Hospital in the peroid between March 2009 and March 2010. All subjects were submitted to the following:
- History taking (including smoking history) and clinical examination.
- Body mass index (BMI).
- Radiological examination (plain CXR postero-anterior and lateral).
- Ventilatory function tests (spirometry) before and after bronchodilatation by using Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL. All results were calculated as percent of predicted except for FEV1/FVC. COPD patients were classified according to their post-bronchodilator FEV1 into mild (FEV1 ≥80% predicted), moderate (50%≤FEV1<80% predicted), severe (30%≤FEV1<50% predicted), and very severe (FEV1<30% predicted or FEV1<50% plus chronic respiratory failure) [5].
- Venous blood samples for C-reactive protein measurement.

Components from human origin were tested and found to be negative for the presence of HBsAg, HCV and HIV. However, samples were handled cautiously as potentially infectious. Fresh serum (stable 7 days at 2-8 °C or 3 months at -20 °C). The CRP-latex agglutination test for the qualitative and semi-quantitative detection of the CRP in human serum was performed.

- Reference values: Up to 6mg/L.
- Performance characteristics:
  - Analytical sensitivity: 6mg/L.
  - Diagnostic sensitivity: 95.6%.
  - Diagnostic specificity: 96.2%. [6]
- Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar.

**Selection criteria:**
- COPD patients were in a stable state (i.e. not in acute exacerbations).
- Post-bronchodilator FEV1/FVC <70% and reversibility is <12% (confirming the diagnosis of COPD).

**Exclusion criteria:**
- By history & examination any disease that may elevate CRP level as follows [7]:
  - Cardiovascular co-morbidities (hypertension, ischemic heart diseases and cerebral vascular diseases) Diabetes mellitus- Inflammatory bowel diseases-arthritis-hepatic cirrhosis-end-stage renal disease-any systemic infection or inflammation that could be associated with increased CRP values.
  - Patients who had tuberculosis, bronchiectasis, malignancy or connective tissue disorders.
  - By spirometry: Improvement of FEV1 >12% or 200ml after bronchodilator.

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, analysis of variance [ANOVA] test and chi-square test by SPSSV [8].

**Results**

The results of this study are shown in the following Tables & Figures.

<table>
<thead>
<tr>
<th>Table (1): Demographic data of studied subjects as regards age, weight, height &amp; body mass index.</th>
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<tr>
<td>No.</td>
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<tr>
<td>Age/year</td>
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<td>Wt/Kg</td>
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<p>| Table (2): Levels of serum CRP (mg/l) in patients and controls. |</p>
<table>
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<th>CRP (mg/l)</th>
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<tbody>
<tr>
<td>Patients</td>
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<tr>
<td>Mean±SD</td>
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<tr>
<td>R: 6–96</td>
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<p>| Table (3): Correlation between serum CRP level (mg/l) and pre-bronchodilator FEV1 (% pred.) of COPD cases. |</p>
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<th>r</th>
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<tr>
<td>Pre FEV 1%</td>
<td>-0.61</td>
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Table (4): Correlation between serum CRP level (mg/l) and smoking index among COPD patients.

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<thead>
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<th></th>
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<th>p</th>
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<tr>
<td>Smoking Index</td>
<td>0.48</td>
<td>&lt;0.05</td>
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</table>

Table (5): Comparison in control groups as regarding smoking index and serum CRP level (mg/l).

<table>
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<tr>
<th>Control smokers</th>
<th>Control non-Smokers</th>
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<tr>
<td>Number</td>
<td>20</td>
</tr>
<tr>
<td>CRP –ve (&lt;6)</td>
<td>–ve (&lt;6)</td>
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<tr>
<td>Smoking Index</td>
<td>391.5±287.95</td>
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<td>R:50–1000</td>
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Table (6): Correlation between serum CRP level (mg/l) and BMI of COPD patients.

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<th>BMI</th>
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<tr>
<td></td>
<td>−0.12</td>
<td>&lt;0.05</td>
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Fig. (1): Comparison of CRP levels (mg/l) according to the stage of the disease.

Discussion

COPD is considered as multi component disease, including weight loss, nutritional abnormalities, skeletal muscle dysfunction, risk for myocardial infarction, angina, osteoporosis, bone fractures, depression and sleep disorders [9].

Several systemic inflammatory mediators such as tumour necrosis factor α (TNF-α), interleukins (ILs), acute phase proteins (C-reactive protein, fibrinogen, lipopolysaccharide binding protein (LBP) and leucocytes are increased in COPD [10]. The present study was done To measure the level of CRP in COPD patients and determine its relationship to factors known to predict the outcome in COPD.

The demographic data of the studied subjects included in this study are illustrated in Table (1). The mean age of COPD patients was 58.04 ± 9.59 years, the mean weight was 77.53 ± 14.44Kg, the mean height was 171.04±7.86cm and the mean BMI was 26.63±5.27. There was significant difference between control non smokers and COPD cases as regards age and significant difference between control smokers and control non smokers group as regard BMI. In the current study, the level of CRP was higher in COPD cases compared to normal controls (smokers and non smokers) and the difference between them was statistically significant (p<0.05) (Table 2). The increase in CRP level in COPD patients in comparison to control smokers means that CRP levels are raised in COPD patients independent of cigarette smoking denoting that the increase in CRP is secondary to systemic inflammatory processes associated with COPD as the level of CRP was normal in the control group even if they are smokers. This result is in agreement with Broekhuizen et al. [2] who measured the level of systemic anti-inflammatory mediators (tumor necrosis factor α, interleukins, CRP, fibrinogen and lipopolysaccharide binding protein) in 102 patients with COPD and found that they were characterized by systemic inflammatory process indicated by raised CRP level. Also this result is in agreement with Pinto-plata et al. [11], Halvani et al. [3] and Yanbaeva et al. [12].

Halvani et al. [3] performed a comparative-descriptive study on 45 stable COPD patients in 2006. All understudy 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. Serum CRP was measured by ELISA (high sensitive).

The Results 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). Moreover, there was non significant correlation between serum CRP and cigarette smoking in COPD patients and healthy subjects. Yanbaeva et al. [12] performed a case-control study on 355 COPD patients and 195 healthy smokers. Plasma levels of CRP, IL-6 and fibrinogen were measured in the total study group.

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They found that COPD patients had higher baseline median levels of circulating inflammatory markers. This difference was still significant after adjustment for age, sex, smoking status, BMI and pack-years smoked.

C-reactive protein (CRP) level had provided a reliable indicator of bacterial infection and some authors had reported CRP levels to be significantly elevated in patients with exacerbations of COPD and purulent sputum [13]. This could be explained by the nature of COPD as a complex chronic inflammatory disease of the lungs involving several types of inflammatory cells and variety of inflammatory mediators. Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic repercussions [14]. One of the inflammatory markers which are increasingly evaluated in COPD patients is CRP [15].

In our study, the level of CRP was related to the stage of the disease as there was a significant increase in CRP level with increasing the severity of COPD: very severe COPD cases have higher level of CRP than severe and moderate cases, CRP was also raised in severe cases than moderate cases and the difference between them was highly statistically significant (p<0.01) (Fig. 1). These results are in agreement with Karadag et al. [16], HE et al. [17] and Corsonello et al. [18].

Karadag et al. [16] made a study on thirty-five male patients with stable COPD and 30 age and sex-matched subjects with normal pulmonary functions. Serum CRP, Serum TNF-α and IL-6 concentrations were measured. They found that sixty percent of the patients had severe or very severe COPD and 40% moderate COPD patients. Serum CRP was significantly higher in stable COPD patients than control subjects (p<0.001), while TNF-α and IL-6 concentrations were not statistically different. HE et al. [17] performed an observational study on forty-four patients with stable COPD, 10 smoking controls and 10 non-smoking controls, induced sputum and peripheral blood samples were obtained simultaneously for measurement of inflammatory cell numbers and the concentrations of IL-6 and CRP.

They found that CRP levels in sputum were significantly higher in stage II, III and IV COPD patients than in smoking and non-smoking controls (p<0.01) and as the disease stage progressed, airway inflammatory cells and IL-6 levels increased. Circulatory concentrations of IL-6 and CRP in stages III and IV COPD patients were significantly higher than in smoking and non-smoking controls (p<0.05 and p<0.01, respectively). Additionally, there were positive correlations between sputum and blood IL-6 and CRP levels (r=0.566, p<0.01 and r=0.443, p<0.01, respectively). Corsonello et al. [18] made an observational study on 223 consecutive outpatients aged 65 years or more with stable COPD. Patients were grouped according to normal/ increased ESR/CRP values. They found that CRP was inversely correlated with the forced expiratory volume in the first second (FEV1%) and concluded that CRP, but not ESR, shows correlation with COPD severity. This could be explained by the observation that CRP is one of the useful predictors for irreversible airway obstruction due to some kind of systemic inflammation and that CRP elevation in COPD followed a pattern of association with disease severity and morbidity [19].

In the current work there was highly significant negative correlation between CRP level and FEV1% predicted in which CRP level is increased with decrease of FEV1% in COPD patients (Table 3).

Our result is in agreement with Mannio et al. [20] who examined the prevalence of increased CRP in COPD patients in the national health nutrition examination survey III. It was found that 41% of moderate COPD patients (FEV1 >50-80% predicted) had CRP level >3mg/l and 6% had level of >10mg/l, where as 52% of patients with severe COPD (FEV1 <50% predicted) had CRP level >3mg/l and 23% had level >10mg/l.

This result is also in agreement with Shaabana et al. [21] who conducted a cross-sectional analysis based on 531 subjects (mean age at baseline: 37±7 years, 50% women and 42% non-smokers). Lung function was expressed as a percentage of predicted FEV1 and CRP was measured. They concluded that FEV1 as a % of predicted values was negatively associated with serum CRP concentration (p<0.02) and in longitudinal analysis; changes in CRP levels during follow-up were associated with annual FEV1 decline. This could be explained by the fact that subjects with lower FEV1 may have higher exposure to tobacco smoke or to environmental insults that lead to a subtle decline in lung function and, in parallel, induce a low-grade inflammatory response [22]. The result of this study showed significant positive correlation between smoking index and serum CRP level (p<0.05) (Table 4).

The level of circulating CRP among control group, including smokers and non smokers, was less than 6mg/l (Table 5). This result is in agreement with Gan et al. [10] who noticed the importance of CRP level in COPD patients and demonstrated that...
CRP is elevated in patients who actively smoked and had reduced lung function. Also in agreement with this study Gan et al. [23] carried cross sectional survey on 7685 participant aged more than 40 years, to determine the independent contributors of active cigarette smoking and reduced FEV 1 as well as their potential interaction on systemic inflammation. The participants were stratified into 4 equal groups based on FEV 1%; each group is further categorized as active smoker or non-smoker according to serum nicotine level. Serum level of CRP was compared across predicted FEV1%. They found that there is an additive effect of active smoking and reduced FEV 1 on CRP level. Tanni et al. [24] performed a cross-sectional analysis comparing 53 COPD ex-smokers, 24 COPD current smokers, 24 current smokers controls and 34 never-smoker controls. Assessments included medical history, body composition, spirometry, and plasma concentration of tumor necrosis factor-alpha (TNF-α), interleukins (IL)-6, IL-8, and C-reactive protein (CRP).

They found that IL-6 and CRP were significantly higher in COPD patients when compared to smoker and never-smoker controls and the multiple regression analysis confirmed the association of these mediators with disease, but not with smoking status (p<0.001). This could be explained by the fact that cigarette smoking has a role in initiation of inflammatory process in COPD patients but it is not the leading cause of increased inflammatory markers and it should be noticed that not all cases develop inflammatory reaction following cigarette smoking and only some of them will show. This reaction can be due to genetic differences [11]. In this study, there was significant negative correlation between CRP level in blood and BMI in which CRP level is increased with decrease of BMI in COPD patients (Table 6). This results is in agreement with Schols et al. [25] who observed high CRP level in a special subset of 16 COPD patients with high resting energy expenditure and low fat free mass (FFM). It agreed also with Sarioglu et al. [26] who investigated the relationship between BODE index, quality of life, CRP, TNF-α, and IL-8. In their study 88 males, 15 females (103 stable COPD) were evaluated by pulmonary function tests, arterial blood gas analysis, body mass index, dyspnea scale and serum levels of CRP, TNF-α, IL-8. There was a significant relationship between BODE index and COPD stage (p<0.01); duration (p<0.013); number of exacerbations (p<0.01) and annual hospitalization rates (p<0.01). A negatively significant relationship was observed between BODE and PO2 (p<0.01) while there was a positively significant relationship with PCO2 (p<0.01). CRP was also negatively correlated with BODE (p=0.019) as BODE index has a strong correlation with various COPD follow-up and systemic inflammation. Hallin et al. [27] studied forty nine patients with moderate to severe COPD. Spirometry was preformed, physical capacity was determined by a progressive symptom limited cycle ergometer test, 12-minutes walk distance and hand grip strength test. Nutritional status was investigated by anthropometric measurements, (weight, height, arm and leg circumferences and skin fold thickness) and bioelectrical impedance assessment was performed. Blood samples were analyzed for C-reactive protein (CRP) and fibrinogen.

They found that working capacity was positively related to forced expiratory volume in 1 s (FEV 1) (p<0.001), body mass index and fat free mass index (p=0.01) and negatively related to CRP (p=0.02).

In contrary, this result disagreed with De Torres et al. [28] who showed that BMI correlates directly with CRP. Also in disagreement with Eagan et al. [29] who found that COPD patients with low FFMI (Fat free mass index) had lower not higher plasma levels of CRP and TNF-R1, whereas higher fat mass was associated with higher CRP and TNF-R1.

This may reflect the fact that adipocytes are the source of a substantial portion of base line IL-6 production [30] which principally induces the production of CRP [31].

In conclusion our results show that CRP levels are raised in COPD patients without clinically relevant IHD and independent of cigarette smoking. The increase in CRP levels was associated with a steeper FEV 1 decline, also Low BMI is associated with the degree of severity of COPD and systemic inflammation reflected by elevated CRP level.

References


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