C-Reactive Protein Levels in Patients with Chronic Obstructive Pulmonary Disease: Role of Infection

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Key Words

Chronic obstructive pulmonary disease · C-reactive protein · Acute exacerbation · Pneumonia · Inflammatory markers

Abstract

Objective: To investigate the value of C-reactive protein (CRP) as a marker of chronic obstructive pulmonary disease (COPD) exacerbations or specifically bacterial exacerbations and to evaluate a correlation between raised CRP levels and other markers of inflammation in patients with an acute exacerbation (AECOPD). **Subjects and Methods:** The medical records of patients with AECOPD were retrospectively analyzed. They were categorized according to the nature of sputum as mucoid or purulent and to the findings on chest radiographs as with pneumonia (PCOPD) or without pneumonia. Stable COPD (SCOPD) patients and a group of asymptomatic nonsmokers were also included in the study. **Results:** All COPD patients (SCOPD: 30; AECOPD: 51; PCOPD: 32) and control subjects (30) were male. The mean CRP levels and WBC counts of the groups were PCOPD: 108.1 ± 61.8 mg/l and $13.7 \pm 6.8 \times 10^9$ /l; AECOPD: 36.8 ± 43.9 mg/l and $11.4 \pm 4.8 \times 10^9$ /l; SCOPD: 3.9 ± 1.4 mg/l and $7.9 \pm 1.9 \times 10^9$ /l; control: 2.1 ± 0.9 mg/l and $7.7 \pm 1.1 \times 10^9$ /l. The mean CRP level of AECOPD was statistically different from those of PCOPD and SCOPD ($p = 0.0001$, $p = 0.002$, respectively). The sensitivity and specificity of CRP to determine an acute exacerbation were 72.5 and 100%, respectively. Among the patients with AECOPD, 25 had purulent sputum and a mean CRP level of 46.4 ± 48.6 mg/l, which is significantly higher

than the CRP level (28.0 ± 44.5 mg/l) of the 18 patients with mucoid expectoration ($p = 0.015$). Among the mucoid-expectorating subgroup, the patients with leukocytosis had significantly higher CRP levels than the patients without leukocytosis ($p = 0.034$). **Conclusion:** A high serum CRP value may indicate an infectious exacerbation in COPD patients and it correlates with sputum purulence and increased serum WBC counts.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease state characterized by airflow limitation that is not fully reversible. In the chronic course of the disease, episodes of acute exacerbations often occur. The most widely used criteria in defining an acute exacerbation of COPD (AECOPD) are those of Anthonisen et al. [1]. A diagnosis of AECOPD is considered when there is worsening of the previous stable state with some, or all, clinical symptoms such as increased dyspnea, increased sputum volume and increased sputum purulence. Any one of the following features such as wheezing, cough, chest tightness, tachypnea, heart rate of 20% above baseline, lethargy or pyrexia may also be present with one of these symptoms. Although some of these symptoms may reflect an increase in airflow obstruction, they may also be related to tracheobronchial tree infections. Airway infections are responsible for the majority of exacerbations

in COPD [2]. Approximately 50% of the exacerbations are caused by bacterial pathogens; however, currently it is not possible to differentiate bacterial from nonbacterial causes of acute exacerbations [3, 4]. It is believed that the change of sputum color from mucoid to purulent during exacerbations is due to neutrophil recruitment in the airways, so sputum purulence seems to be a reliable marker of bacterial infections [5].

C-reactive protein (CRP) is a marker of inflammation. Following an acute-phase stimulus, its values may increase from $<50 \mu\text{g/l}$ to $>500 \text{ mg/l}$, that is, 10,000-fold, which suggests it has a significant biological function [6]. Recently, several studies have shown that serum CRP levels are increased in patients with COPD [7, 8], stable COPD (SCOPD) [9] and AECOPD [10], thereby suggesting that the CRP level is a marker of AECOPD but not necessarily of bacterial infection. However, in a recent study it was suggested that CRP may be used as a marker of significant bacterial infection [11]. The value of CRP as a prognostic biomarker in AECOPD patients was investigated further in 2 other studies [12, 13]; one suggesting that a high serum CRP concentration 14 days after an index exacerbation might be used as a predictor of recurrent exacerbations within 50 days [12], while the other did not prove valuable in predicting short-term or long-term exacerbation outcome [13]. However, the plasma levels of CRP as well as copeptin and procalcitonin were elevated during acute exacerbations and the CRP level was particularly elevated in Anthonisen type 1 exacerbations [13].

All the above-mentioned studies show that the CRP levels are increased in both stable and exacerbated COPD patients; however, there remain problems about the interpretation of the increased levels of this protein. In a recent guideline [14] it was stated that an elevated level of CRP in the patient's serum ($>50 \text{ mg/l}$) could increase the chance that the patient involved does have pneumonia. However, a cutoff value for diagnosing an AECOPD or bacterial infection as a cause of acute exacerbation has not been determined yet. Whether simultaneous assessment of other inflammatory markers in addition to CRP would aid in antibiotic prescription decision is another query. The current study, therefore, addressed the following questions. (a) Can CRP be used as a marker of COPD exacerbations or specifically bacterial exacerbations? (b) Is there a correlation between raised CRP levels and other markers of inflammation, such as sputum purulence or leukocytosis? (c) Is there a correlation between CRP levels and the degree of respiratory dysfunction measured during exacerbations as it has been previously shown in SCOPD patients?

Subjects and Methods

Study Subjects

The study was conducted at Suleyman Demirel University Research and Practice Hospital, Isparta, Turkey, a tertiary-care teaching hospital. The medical records of all COPD patients ($n = 180$) admitted to the hospital between January 2005 and January 2006 were retrospectively evaluated. Patients were considered to have had AECOPD if they had experienced any of the 3 symptoms that constitute Anthonisen's criteria [1]. Patients with AECOPD were categorized according to the nature of expectoration as having a mucoid (opaque/milky) or purulent (yellow-green coloration) sputum. All patients with AECOPD were also categorized according to radiologic findings. Chest radiographs were evaluated by 2 investigators (A.B. and O.K.) and patients who had new infiltrates on chest X-rays were considered to have pneumonia (PCOPD). Routine baseline ECGs of all patients were investigated for ruling out an acute coronary syndrome. Patients were excluded from the study if: they had no CRP measurement on the admission day, or they had received antibiotic treatment within a week before admission; or they used systemic steroids (in a prednisone-equivalent dosage of $>20 \text{ mg/day}$ for >2 weeks); or they had bronchiectasis (radiologically proven or history of phlegm expectoration $>30 \text{ ml/day}$), tuberculosis or other inflammatory diseases such as malignancy, arthritis, inflammatory bowel diseases or connective tissue disorders.

SCOPD patients without a history of exacerbation for the previous 2 months were recruited prospectively from our outpatient settings. A group of asymptomatic nonsmokers who were all age- and sex-matched with the patients were also included in the study as controls. The SCOPD patients and controls gave written informed consent.

Measurements

The demographic features, the pulmonary function test results and the values of arterial blood gas analyses measured within 24 h of admission were obtained from the records of the patients with AECOPD, while they were performed in the outpatient department in the SCOPD and the control groups. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and $\text{FEV}_1/\text{FVC}\%$ were measured using a spirometer (Spirovit SP-10, Schiller, Baar, Switzerland) according to the standards of the American Thoracic Society [15]. For arterial blood gas analyses, blood was drawn from the radial artery while the patients were breathing room air. Arterial oxygen and carbon dioxide tensions were analyzed with a blood gas analyzer (Roche OMNI® C, Roche Diagnostics, Germany). Venous blood samples for leukocyte count and CRP were taken and analyzed on the day of admission. The CRP levels were measured by nephelometry (Dade Behring, Marburg, Germany).

Statistical Analyses

All statistical analyses were performed using the SPSS statistical package (version 11 for Windows, SPSS; Chicago, Ill., USA). The association between 2 quantitative variables was evaluated with Pearson's correlation coefficient. The results were expressed as the means and standard deviation for quantitative variables and as frequencies for categorical findings. To compare the means of 2 independent groups, Student's *t* test was used, while nonparametric data were analyzed with the Mann-Whitney U test. The

Table 1. Age, smoking history, PFT, ABG analyses, CRP levels and leukocyte counts of the total study population

	Healthy controls (n = 30)	COPD		
		SCOPD (n = 30)	AECOPD (n = 51)	PCOPD (n = 32)
Age, years	66.7 ± 4.8	66.6 ± 6.9	68.7 ± 8.4	69.2 ± 9.4
Smoking history				
Pack-years	–	53.4 ± 31.9	65.3 ± 35.4	59.8 ± 34.7
Never	30 (100)	1 (3.3)	2 (3.9)	3 (9.4)
Former	–	29 (96.7)	35 (68.6)	22 (68.7)
Current	–	–	14 (27.5)	7 (21.9)
FEV ₁ , l	3.25 ± 0.44	1.22 ± 0.50	0.91 ± 0.32	0.95 ± 0.32
FEV ₁ , % predicted	90.3 ± 11	44.7 ± 12.7	32.7 ± 12.9	31.7 ± 9.6
PaO ₂ , mm Hg	87.2 ± 6.5	62.6 ± 16.9	54.7 ± 13.7	54.1 ± 13.3
PaCO ₂ , mm Hg	38.9 ± 1.4	40.7 ± 7.5	45.8 ± 12.6	44.7 ± 12.0
CRP, mg/l	2.1 ± 0.9	3.9 ± 1.4	36.8 ± 43.9	108.1 ± 61.3
Leukocyte count, 10 ⁹ /l				
Mean ± SD	7.7 ± 1.1	7.9 ± 1.9	11.4 ± 4.9	13.7 ± 6.8
Range	6.0–9.8	4.2–10.9	4.2–31.5	3.8–33.6

Figures are means ± SD or numbers of subjects with percentages in parentheses. PFT = Pulmonary function tests; ABG = arterial blood gas; PaO₂ = partial pressure of arterial oxygen; PaCO₂ = partial pressure of arterial carbon dioxide. FEV₁: 1 patient within the AECOPD and 3 patients within the PCOPD group did not have the measurement of PFT. CRP: p = not significant, control versus SCOPD; p = 0.002, SCOPD versus AECOPD; p = 0.0001, AECOPD versus PCOPD.

Kruskal-Wallis test was applied while nonparametric data of several groups were compared. The level of statistical significance was taken as $p < 0.05$.

Results

Of the 180 patients with COPD, 113 were included in the evaluation (SCOPD: 30, AECOPD: 51, PCOPD: 32); and also the 30 control subjects. The remaining 97 patients were excluded due to absence of CRP measurement on the admission day (41), recent antibiotic prescription (15), receiving systemic steroids (11) and coexistent diseases such as bronchiectasis (13), malignancy (8) and other inflammatory diseases (9).

The demographic features, pulmonary function tests, mean CRP levels and WBC counts of the groups are shown in table 1. All subjects were male and the majority of them were elderly with an age >65 years. There was no statistical difference among the groups according to mean age. There were 6 patients who never smoked in the COPD groups who had carried occupational risk factors for the disease.

The mean CRP levels were higher in all groups with COPD when compared with healthy controls (table 1), with PCOPD exhibiting the highest level (108.1 ± 61.3 mg/l). The difference between patients with SCOPD and AECOPD was statistically significant ($p = 0.002$). None of the controls and SCOPD patients had CRP levels >10 mg/l, while all patients with PCOPD had elevated CRP values (>10 mg/l). The normal range of CRP is 0–10 mg/l. Using 10 mg/l as a cutoff point in determining the presence of an acute exacerbation, CRP measurement had a sensitivity and specificity of 72.5 and 100%, respectively (fig. 1).

The CRP levels were positively correlated with leukocyte count both in the AECOPD group ($r = 0.575$, $p = 0.0001$) and in the entire study population ($r = 0.536$, $p = 0.0001$). There was no significant difference between either the control group and the SCOPD group ($p = 0.627$) or the AECOPD and PCOPD groups ($p = 0.111$) in terms of mean WBC counts, the only significant difference was between the AECOPD and SCOPD groups ($p = 0.005$) (fig. 2).

Regarding the quality of sputum, 8 patients reported no sputum expectoration, 18 had mucoid sputum and 25 reported increased sputum purulence in the group with an AECOPD. There was no significant difference in the

Fig. 1. Distribution of CRP levels in COPD groups.

Fig. 2. Mean WBC counts in COPD patients and in controls.

Table 2. The relation between sputum purulence, WBC counts and serum CRP levels in AECOPD patients

	Mean CRP level, mg/l		P
	normal WBC count	leukocytosis	
Mucoid sputum	10.6 ± 11.7 (10)	49.7 ± 60.6 (8)	0.034
Purulent sputum	38.7 ± 35.1 (9)	50.7 ± 55.4 (16)	NS

Figures are means ± SD. Values in parentheses are numbers of patients. Eight patients without sputum expectoration were not included in the presented data. NS = Not significant.

mean CRP levels between the patients without sputum expectoration (27.3 ± 16.6 mg/l) and the patients with mucoid sputum (28.0 ± 44.5 mg/l) in the AECOPD group. Within the AECOPD group, the mean CRP levels were significantly higher within the subgroup with purulent expectoration (46.4 ± 48.6 mg/l) than the mucoid-expectorating subgroup ($p = 0.015$). The distribution of

the CRP values in the COPD groups as shown in figure 1 indicates that 10/26 (61.5%) of the AECOPD patients with mucoid sputum had CRP levels >10 mg/l, and 4/25 (16%) with purulent sputum had CRP values within normal limits. The sensitivity and specificity of measuring a high CRP level in detecting a bacterial infection was as 84 and 38.4% in the AECOPD group, respectively.

When both sputum purulence and the presence of leukocytosis were assessed in relation with CRP levels, the patients with mucoid sputum and without leukocytosis had the lowest mean CRP levels and the differences between this group and the other subgroups were statistically significant ($p = 0.013$). The mean CRP levels of likewise stratified patients are shown in table 2 and figure 3.

Lastly, the CRP levels negatively correlated with partial pressure of arterial oxygen, FEV₁ and FEV₁% in the overall study population ($r = 0.317$, $p = 0.0001$; $r = 0.203$, $p = 0.0001$; $r = 0.410$, $p = 0.0001$, respectively). However, a similar analysis showed no correlation between the above-mentioned parameters when the population was restricted to the AECOPD group.

Fig. 3. Mean CRP levels in AECOPD patients grouped according to sputum purulence and the presence of leukocytosis. leu(-) = Normal leukocyte count; leu(+) = leukocytosis.

Discussion

The mean CRP levels in this study were higher in the SCOPD than the control group, similar to the several other studies [7–9, 16]; however, the difference was not statistically significant. A recent meta-analysis by Gan et al. [16] emphasized that patients with COPD had higher levels of CRP than control subjects in all the studies evaluated, indicating the presence of a systemic inflammation in patients with SCOPD. Overall, the standardized mean difference in the CRP level between COPD and control subjects was reported as 0.53 units [16]. Several studies [8, 9, 17, 18] measuring CRP levels in SCOPD patients showed that high CRP levels correlate with poorer performance in the 6-min walk test, impaired energy metabolism and

respiratory distress, and in addition, they relate to increased mortality. However, no association between respiratory dysfunction and CRP levels in the AECOPD patients was observed in our study, most probably due to poor lung function in the presence of bacterial infection, which is the most important stimulus for CRP synthesis.

Compared to the SCOPD patients the CRP levels were increased in AECOPD, similar to several previous studies [10–13, 19]. The value of CRP measurement had been investigated with regard to the determination of an exacerbation as well as bacterial infection [10, 11, 19]. Dev et al. [10] showed that CRP may be a marker for COPD exacerbation but not necessarily a marker of bacterial infection. Recently, Hurst et al. [19] have shown that among 36 plasma biomarkers for confirming COPD exacerbation and predicting exacerbation severity CRP was the most selective biomarker, but it was neither sufficiently sensitive nor specific by itself, and the authors concluded that CRP was useful in confirming the diagnosis of exacerbation, in the presence of a major exacerbation symptom. Another study by Weis and Almdal [11] showed that CRP levels may be a marker of significant bacterial infection and thus, they may be used in deciding whether or not to start antibiotic treatment. A similar observation was made in our study.

Tracheobronchial infections have generally been considered as the leading cause of exacerbations of COPD and bacteria are the most common etiologic agents. However, since the lower respiratory tract is frequently colonized by bacteria in COPD patients even in the clinically stable state, routine bacteriologic culture of sputum is often unreliable in demonstrating infection as the cause of an exacerbation. Stockley et al. [5], in a prospective study, showed that green purulent sputum was 94% sensitive and 77% specific for high concentrations of bacteria. Similar observations of purulent sputum as a marker of bacterial infection were made in this study, in which the sensitivity of CRP measurement in determining bacterial infections in the AECOPD and PCOPD groups was 84 and 100%, respectively. A novel finding of this study was revealed in a subgroup analysis in which the patients with mucoid sputum and concomitant leukocytosis had higher CRP levels compared to the patients without leukocytosis. It is well known that even patients with pneumonia may have mucoid sputum, especially when the etiologic agent is an atypical pathogen. Additionally, several previous studies have shown that atypical bacterial agents may have a role in AECOPD, revealing evidence of acute infection with *Chlamydia pneumoniae* in 4–34% of patients [20–23]. Therefore, the presence of mucoid sputum may

not rule out a bacterial infection and the need of antibiotic therapy in AECOPD patients. Unfortunately, the studies measuring CRP levels in AECOPD patients to date did not consider simultaneous determination of other inflammatory markers. Therefore, we suggest further studies to be performed in order to investigate the efficacy of antibiotic therapy in AECOPD patients with mucoid sputum, if they have a concomitant rise in leukocyte count and CRP level.

The highest mean level of CRP was measured in the PCOPD group in the current study. Ritland and Melbye [24] observed markedly elevated values of CRP in pneumonia patients, but in most patients with acute asthma, acute exacerbation of COPD and acute bronchitis the values were within the normal ranges. Similarly, Smith and Lipworth [25] also showed that the CRP levels were considerably higher in patients with community-acquired pneumonia (217 ± 16 mg/l) compared with those who had purulent bronchitis without pneumonia (18 ± 3 mg/l). A gradual increase in the mean serum CRP levels was detected in the current study in respective groups with SCOPD, mucoid-expectorating AECOPD, purulent

expectorating AECOPD and PCOPD. This may support the hypothesis suggesting that local inflammatory response of the host parallels the increase in bacterial load and there must be a minimum bacterial load in the airways for symptoms of an acute exacerbation to appear [26].

Conclusion

The findings of this study show that an increased serum CRP value (>10 mg/l) indicates an exacerbation in COPD patients. However, some patients with AECOPD, mostly those with mucoid sputum and normal WBC counts, had CRP levels <10 mg/l. In AECOPD patients with mucoid sputum, an elevated CRP level with concomitant leukocytosis may be an indication of a bacterial infection. Therefore, future studies investigating the efficacy of antibiotic treatment in AECOPD groups stratified according to the presence of various inflammatory markers including CRP are needed.

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