The Importance of Serum Procalcitonin Levels in Patients with Chronic Obstructive Pulmonary Disease Exacerbations

**Aim:** Chronic obstructive pulmonary disease (COPD) is a preventable and treatable, but progressive disease and hospital admissions of patients with COPD are frequently due to acute exacerbations. Acute phase reactants are capable of demonstrating the inflammation; however, they cannot be employed to make a difference between bacterial and nonbacterial causes of the inflammation. Recently, measurement of procalcitonin (PCT) levels appears to be useful in order to minimize this problem. The aim of this study was to examine whether the treatment arrangements based on serum PCT levels in patients presenting with COPD acute exacerbations will be appropriate or not.

**Materials and Methods:** Nineteen patients with acute exacerbation of COPD and 16 patients with stable COPD as the control group were enrolled in this study. Erythrocyte sedimentation rates (ESR) and complete blood count (CBC) were obtained. Routine biochemical analysis and chest radiographs were examined in all patients. All complaints of the patients were recorded and parameters (hemogram, ESR, serum procalcitonin, hospital stay) were compared.

**Results:** Mean serum PCT levels in COPD patients with exacerbations was 1.8 ng/ml and in stable COPD patients was 0.2 ng/ml. A significant correlation was established between serum procalcitonin (PCT) levels and duration of hospital stay, ESR and sputum purulence (P = 0.002, P = 0.007 respectively). There was no significant correlation between serum PCT levels, white blood cell count and complaints of patients.

**Conclusions:** We concluded that serum PCT measurements would be effective in guiding the treatment in patients with acute exacerbations of COPD.

**Key Words:** Procalcitonin, COPD, acute exacerbation, acute phase reactants
Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable as well as treatable disease that might also have extra-pulmonary manifestations. Airflow obstruction is not completely reversible and generally follows a progressive course. It is characterized by an abnormal inflammatory response of the lungs against harmful particles or gases (1).

COPD is a chronic inflammatory disease. It may cause hospital admissions in those who do not receive regular treatment or even in those who do as a result of intervening pulmonary infections.

Many physiological changes occur in the host in order to restore the impaired homeostasis during bacterial and viral infections. These physiological changes are generally known as the acute phase response and involve metabolic, endocrinologic, neurologic and immunologic events. Macrophages activated by the stimulation of the infectious agent or its products initiate this acute phase response via the cytokines (tumor necrosis factor-TNF, interleukin-IL-1, IL-6) they release.

White blood cell (WBC) (leukocyte) count, absolute neutrophil count, rod count and ratio, erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels are the most frequently used markers of acute phase responses in clinical practice.

In patients with COPD, the clinical manifestations of systemic infections due to infectious and non-infectious causes are similar. The differential diagnosis of these two conditions is very important in order to administer the correct treatment regimen and avoid unnecessary antibiotic use, thus reducing the morbidity, mortality and care-related costs. The decision to use antibiotics and selection of the type of antibiotic may be difficult in a significant number of cases, primarily due to the challenges encountered in confirming the diagnosis of bacterial infections. Classical diagnostic instruments including CRP and leukocyte count do not have sufficient specificity in differentiating between bacterial infections, non-infectious systemic inflammations or viral infections. Therefore, more specific and reliable markers that might be helpful in deciding the treatment are needed in these patients.

Recently, serum procalcitonin (PCT) has been used as an infection marker (2-5). Since the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase. There is even a specific cut-off value for PCT for the establishment of a bacterial infection (6,7).

The aim of this study was to investigate whether the measurement of PCT can be used in the differentiation of bacterial and non-bacterial infection causes of COPD exacerbation, thus helping in planning the treatment.

Materials and Methods

Nineteen COPD patients presenting with symptoms of cough, sputum production, increased shortness of breath, high fever or chest pain on the affected side were considered to be experiencing acute exacerbations and were included as the study group. Sixteen age- and sex-matched patients with stable COPD were included as the control group. Approval of the hospital local ethics committee was obtained and the investigators covered the cost of the PCT kit.

COPD patients who received antibiotics before coming to the outpatient clinic were excluded from the study. Blood samples were collected from all patients in order to perform complete blood count and routine biochemistry, as well as to analyze acute phase reactants and serum PCT. Direct inspection and culturing of the sputum specimens that were obtained from patients with sputum production were performed. Complaints of the patients were recorded, posterior-anterior (PA) chest X-rays were obtained and infiltrations, if any, were recorded. Duration of hospital stay, sputum production and other complaints such as pain on one side of the chest and high fever were also recorded. Broad-spectrum antibiotics were started in all patients displaying a possible bacterial etiology for the exacerbations.

We concluded that serum PCT levels over 0.5 ng/ml were valuable for bacterial infections.

The blood collected for serum PCT measurement was centrifuged and kept at -80 °C until the time of the measurement. PCT measurement was performed by the Brahms Diagnostica device using the immunoluminometric method with the inclusion of the device’s own kit.
Statistical Analysis

Parametric data were analyzed by the Spearman’s correlation test and Pearson’s correlation test, and non-parametric data were analyzed by Mann-Whitney U test, Fisher’s exact test and chi-square test.

Results

The mean age of the study group was 63 ± 5.2 years, and included 4 females and 15 males. The mean age of the control group with stable COPD was 56.3 ± 11.5 years, and included 5 females and 11 males. Demographic characteristics of the patient and control groups are shown in Table 1.

Ten out of 19 patients in the study group had fever ≥38.0 °C, while the remaining 9 patients had normal body temperature. Seven patients had purulent sputum and 12 had a non-productive cough. In 5 of those with purulent sputum, bacterial growth was shown in sputum culture. The results were as follows: Gram-negative bacillus in 1 patient, S. pneumoniae in 2 patients and H. influenzae in 2 patients. In 12 out of 19 patients, serum PCT was high, which supported bacterial infection. Seven of 12 patients with high serum PCT levels had purulent sputum. Eleven patients had one-sided chest pain. The mean duration of hospital stay was 7 ± 3.2 days. Upon assessment of the patients’ PA chest X-rays, 8 were found to have infiltrations.

As expected, in the group presenting with COPD exacerbation, high levels of WBC, serum PCT and ESR were determined (Table 2).

We found significant correlations between serum PCT levels and ESR, hospital stay, and purulence of sputum (P = 0.002, P = 0.001, P = 0.007 respectively) (Table 3).

Table 1. Demographic characteristics of the groups.

<table>
<thead>
<tr>
<th></th>
<th>COPD Exacerbation (n = 19)</th>
<th>Stable COPD Group (n = 16)</th>
</tr>
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<tbody>
<tr>
<td>Age (year)</td>
<td>63 ± 5.2</td>
<td>56.3 ± 11.5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/4</td>
<td>11/5</td>
</tr>
<tr>
<td>Smoking history (n / pack-year)</td>
<td>16 / 38 ± 6</td>
<td>12 / 42 ± 11</td>
</tr>
<tr>
<td>Ex-smoker (n / year)</td>
<td>3/4</td>
<td>4/5</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>82 ± 3.7</td>
<td>84 ± 4.6</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>52 ± 10.4</td>
<td>58 ± 8.8</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>61 ± 7.3</td>
<td>64 ± 6.1</td>
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FVC: Forced vital capacity. FEV1: Forced expiratory volume in 1 second.

Table 2. Infection parameters in the study and control groups.

<table>
<thead>
<tr>
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<th>COPD Exacerbation (n = 19)</th>
<th>Stable COPD Group (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cell (mm³)</td>
<td>12400 ± 4600</td>
<td>6200 ± 2800</td>
<td>0.002</td>
</tr>
<tr>
<td>PCT (ng/ml)</td>
<td>1.8 ± 0.8</td>
<td>0.2 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>38 ± 17</td>
<td>8.1 ± 3.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of hospital stay (day)</td>
<td>7 ± 3.2</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.05 statistically significant.
There was no statistically significant correlation between the body temperature and infiltrations on chest X-rays ($P = 0.370$), nor between chest pain and infiltration ($P = 1.00$). The correlation between PCT value and WBC count was also not significant ($P = 0.991$).

**Discussion**

Calcitonin, being the precursor of PCT, is secreted from thyroid medullary cells and is related with calcium metabolism (6). PCT is a protein having a molecular weight of 13 kD and it consists of 116 amino acid residues (7). The exact regions of its secretion are not yet clear. Some literature suggests that PCT is secreted from neuroendocrine cells of the liver, small intestine and thyroid cells (6,8). In healthy humans, its normal serum level is 0.1 ng/ml (6). In a previous study, administration of bacterial endotoxin to healthy individuals resulted in an increase in PCT levels starting two hours after administration, with a peak value reached in 12 hours (9). Consequently, the serum level remains constant for another 12 hours and decreases back to normal level in 20-24 hours. PCT gives rapid response to bacterial infections (4). Following the administration of bacterial endotoxin, PCT levels increase faster and return to normal range more rapidly compared to the levels of CRP. Like PCT, the levels of acute phase reactants such as IL-6 and TNF-alpha also increase rapidly in case of infections (7). However, to assess the serum levels of these reactants is difficult since regression to normal levels is also rapid. The means of elimination from serum are not well defined; however, proteolysis by binding blood proteins is a suggested mechanism (6,8). PCT is a considerably stable molecule in laboratory conditions and preserves its stability in repeated melting and freezing conditions (8-10).

The sensitivity and specificity of PCT in bacterial infections were found to be 92.6% and 97.5%, respectively (11,12). In delayed bacterial infections (3-30 days), the sensitivity and specificity reached 100%. Serum PCT level above 0.5 ng/ml indicates bacterial infections, whereas levels above 2 ng/ml show sepsis (9). When the threshold level of PCT indicative of bacterial infection was accepted as 0.5 ng/ml, the positive and negative predictive values were found to be 100% and 87%, respectively (11,12).

In this study, we have demonstrated that serum PCT levels have high sensitivity and specificity in displaying the inflammatory response in patients admitted with COPD exacerbation. In the stable COPD patients that constituted the control group, serum PCT levels were found to be within normal limits.

Moreover, previous studies have shown that serum PCT levels were increased generally in infections of bacterial origin and this increase was more marked especially in patients with septicemia (13-15). In the literature, studies performed in patients with pneumonia revealed that serum PCT levels have high sensitivity and specificity in showing the inflammatory response caused by pneumonia (16-19). It has also been suggested in

<table>
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<th>Parameters</th>
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<tr>
<td>PCT</td>
<td>0.690</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR</td>
<td>0.582</td>
<td>0.007</td>
</tr>
<tr>
<td>Purulent sputum</td>
<td>0.440</td>
<td>0.03</td>
</tr>
<tr>
<td>Infiltration</td>
<td>0.672</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>0.695</td>
<td>0.006</td>
</tr>
<tr>
<td>Purulent sputum</td>
<td>0.420</td>
<td>0.03</td>
</tr>
<tr>
<td>Infiltration</td>
<td>0.122</td>
<td>0.37</td>
</tr>
<tr>
<td>ESR</td>
<td>0.122</td>
<td>0.37</td>
</tr>
<tr>
<td>Body temperature</td>
<td>0.001</td>
<td>0.991</td>
</tr>
<tr>
<td>Infiltration</td>
<td>0.001</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*P* < 0.05 statistically significant.
some studies that serum PCT levels might have a relatively higher sensitivity and specificity in differentiating pneumonias of bacterial origin from those of viral origin (20-23).

It has always been difficult to decide whether to start antibiotics in patients admitted to outpatient clinics with COPD exacerbations. Complaints of the patients (increased coughing, increased sputum purulence, increased shortness of breath, high fever), radiological examinations, and laboratory measurements help clinicians in this respect. PCT measurements, on the other hand, may enable clinicians to distinguish bacterial infections from non-bacterial ones and may make the antibiotic decision easier with an increased confidence. In general, this patient group does not have an isolated lung problem and frequently has additional diseases such as cardiac failure or coronary artery disease, and the antibiotics to be administered have a narrow therapeutic index. Studies have shown that the diagnostic efficacy of leukocyte count is not high; it has either moderate or low efficacy (15). In this study, we also were unable to find any significant relationship between PCT and WBC count. This suggests that WBC count is not a significant factor in identifying a bacterial infection.

We found that PCT has a moderately significant correlation with both ESR and purulent sputum. When both of these parameters are used in combination with the PCT value in identifying bacterial infection, the level of significance is increased considerably. However, a poorly significant relationship was found with the infiltration observed in PA chest X-ray, suggesting that infiltration does not necessarily always have a bacterial etiology.

A significant correlation was found between the PCT level and the duration of hospital stay, suggesting that stable disease phase is achieved later in COPD exacerbations of bacterial etiology. In 12 of 19 COPD patients with acute exacerbations, the serum PCT levels were higher than 0.5, and 7 patients had purulent sputum. This suggests that COPD exacerbations with a high PCT value may be a result of a bacterial infection even if a bacterial growth is absent, and antibiotic use is mandatory in these patients. Chang et al. (24) showed that patients admitted with COPD exacerbation and positive sputum cultures for bacterial pathogen had significantly higher PCT values. A similar result was found in another study of the same investigator performed in August 2006 (25).

In another study, it was shown that PCT may be used as a diagnostic tool in lower respiratory tract infections and tuberculosis. In that study, PCT was measured high in cases of COPD exacerbations caused by bacterial infections (26). PCT measurements may also be used to reveal the disease severity (27,28).

In conclusion, the results of this study suggest that PCT may be used to guide the antibiotic therapy in COPD exacerbations when the radiographic and clinical parameters are not diagnostic.

References


