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ORIGINAL ARTICLE

IL-6 And IL-8 Levels İn Patients With Acute Exacerbation Of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is characterized by an abnormal inflammatory response of airways due to inhalation of harmful gases and particles. Frequent exacerbations are associated with increased pulmonary and systemic inflammation. Interleukin-6 (IL-6) and interleukin-8 (IL-8) are systemic inflammation markers.

Aim: The relationship of serum IL-6 and IL-8 levels in patients of exacerbated COPD with pulmonary function tests (PFT), forced expiratory volume in one second (FEV_1), FEV_1/ forced vital capacity (FVC) values, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were studied.

Methods and Materials: Twenty-seven patients with exacerbated COPD and 20 healthy controls were included in the study. In addition to acute exacerbation therapy, antibiotics were used in all patients.

Results: The mean duration of antibiotic usage was 14.1±7.3 days and the mean FEV_1 value was 34.11±10.43. Pretreatment and post treatment IL-6 and IL-8 levels were measured by the ELISA method. Pretreatment IL-6 and IL-8 levels were found to be significantly higher in acute excacerbation cases, when compared to levels in the healthy control group and post treatment levels. But no correlation was found between IL-6, IL-8 levels and CRP, ESR values and FEV_1, FEV_1/ FVC values.

Conclusion: We conclude that cases of exacerbated COPD with greater degrees of obstruction of the airways have higher levels of cytokines in serum. The serum levels of these cytokines can therefore be utilised as the clinical and prognostic parameters for evaluation of the disease status and the therapy executed for the same.

Key Words: IL-6, IL-8, Chronic obstructive pulmonary disease

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Introduction

Some patients of COPD are prone to frequent exacerbations, which are important determinants of health status [3]. Cytokines are extracellular signal proteins (less than 80 kDa) formed by various types of cells in the body. IL-6 is secreted by monocytes, macrophages, T cells, B cells, fibroblasts, epithelial cells of the airway and endothelial cells. IL-8, also known as CXCL8, is a CXC chemokine that is a potent chemoattractant for neutrophils. In general, monocytes, tissue and alveolar macrophages, pulmonary epithelium, cells of the smooth muscles of the airway, eosinophils, fibroblasts, and endothelial cells are its important sources [5], [6]. The levels of

many cytokines are known to be raised in serum in COPD [7], but their contribution to disease severity is still unknown. In this study, the relationship between the levels of IL-6 and IL-8 in the serum of patients with exacerbation of COPD, and PFT; FEV1, FEV1/FVC values CRP, and ESR were studied.

Methods and Materials

Twenty-seven COPD patients with exacerbation of disease, reporting to the Pulmonary Diseases Clinic of the Firat Medical Center, Firat University, (Elazıg, Turkey) were enrolled. The patients had no other pulmonary disease conditions like asthma, bronchiectasis, pneumonia, tuberculosis, or lung cancer. In addition to acute exacerbation therapy, antibiotics were used in all patients. The diagnosis of COPD was made, based on the American Thoracic Society and European Respiratory Society's criteria, with exacerbation identified according to the definition by Anthonisen et al. which is based on an increase in symptoms of dyspnea, sputum volume and sputum purulence with or without symptoms of upper respiratory infection and then subdivided depending on the number of symptoms [8],[9]. The control group included 20 non-smoking, healthy volunteers with laboratory findings within normal limits and no complaints. Spirometric tests were performed in all subjects in the pre and post-treatment period according to international guidelines using a Fukuda Denshi Spirosift 500 [10],[11]. The reversibility of airway obstruction was assessed according to GOLD [12]. Indices of airflow obstruction, FEV_1 and FEV_1/FVC were measured. FEV_1 and FVC were expressed as percentages of predicted values (FEV_1 % and FVC %), according to the prediction equations of the European Respiratory Society [13].

Therapy was initiated in patients with combinations of inhalational β_2 agonist, inhalational ipratropium bromide and inhalational steroid treatment. In addition to this, antibiotic (macrolide or beta lactam group) treatment was instituted in all COPD patients who had all the three cardinal symptoms (dyspnoea, increasing of sputum volume and sputum purulence). Approval of the ethics committee was taken for the study. Prior written informed consent was obtained from each patient after giving a brief explanation about the study.

Determination Of Cytokine Levels

Pre and post treatment venous blood samples (5 ml) were obtained from all patients. The blood samples were centrifuged at 5000 rpm for 10 min; sera collected, were stored at -80 ^{0}C until assayed. Similarly, blood samples were obtained from the control group; serum was separated and stored at -80 ^{0}C. IL-6 and IL-8 levels in all serum samples were measured simultaneously by the ELISA method. A commercial kit was used for this purpose, and the study was performed according the kit procedure (Medgenix, Biosource International, Camarillo, USA). Pre treatment and post treatment CRP levels (nephelometric technique, Dade Behring BN II) and ESR (Westerngren method) were also measured.

Statistical Analysis

Statistical analyses were made by the SPSS 11.0 version for Windows. Wilcoxon's Signed Ranks Test was used for evaluations within groups and Mann Whitney-U Tests were used for comparisons between groups. Correlations between parameters were evaluated with Spearman correlation analysis. P values <0.05 were accepted as statistically significant.

Results

The demographic characteristics of subjects enrolled into the study are shown in [Table/Fig 1]. The mean duration of antibiotic use was 14.1±7.3 day and the mean FEV_1 value was 34.11±10.43 (%). Pretreatment and post treatment serum IL-6 and IL-8 levels were measured by the ELISA method. Mean serum cytokines, CRP, ESR levels and FEV_1, FEV_1/FVC values of patients and of healthy control groups both pre-treatment and post-treatment, are presented in [Table/Fig 2]. Pretreatment IL-6 and IL-8 levels in acute exacerbation cases were found to be significantly higher as compared to that of the healthy control group as well as post treatment. But no correlation was found between IL-6, IL-8 levels and CRP, ESR, FEV_1, FEV_1/ FVC values.

(Table/Fig 1) Demographic data of patients with COPD.

	Patients (n:27)
Age (years)	59.0 ± 13.41
Gender (M/F)	19/8
Increasing of sputum volume (n)	27
Sputum purulence (n)	27
Dyspnea (n)	27
Mean duration of antibiotic use (day)	14.1±7.3

(Table/Fig 2)Mean serum cytokine and CRP, ESR levels and FEV_1, FEV_1/FVC values of patients in the pre and post treatment and of healthy control group.

	Pre-treatment (n:27)	Post-treatment (n:27)	Control (n:20)
IL-6 (pg/ml)	229.02±128.99*	151.83± 94.44	21.15± 10.99
IL-8 (pg/ml)	305.52±255.72*	179.11 ± 80.66	27.12 ± 5.18
FEV_1(%)	34.11±10.43	49.46 ± 17.23	101.38 ± 5.12
FEV_1/FVC(%)	73.82±22.06	82.3 ± 10.16	102.23 ± 4.88
ESR (mm/h)	19.66±21.21	13.43±6.21	10.71±2,12
CRP(mg/L)	19.40±42.98	12.79±4.32	3.52±1.26

*vs. control and post treatment ($p<0.05$)

Discussion

In this study, the relationship between the levels of pro inflammatory cytokines and therapy in patients with exacerbated COPD were studied. In this study, the pre treatment levels of IL-6 and IL-8 were found to be higher (statistically significant) in patients of COPD pre and post treatment when compared to the control group ($p<0.05$).

Exacerbations of COPD lead to increase in the number of patients reporting to the hospital and the frequency of admissions. It also adversely affects the quality of life of the patients and restricts their daily activities[14]. Such patients demonstrate elevated airway cytokine levels, suggesting the presence of increased inflammation that may increase their susceptibility to exacerbation. Inflammatory response during COPD exacerbation is variable, but increases in interleukin-6 (IL-6) levels during the exacerbation are related to the presence of a common cold. The reduction of COPD exacerbations can have an important impact on the considerable morbidity and mortality associated with COPD [3].

Patell IS et al. reported that within the COPD group, the IL-6 and IL-8 response was lower in the cells of patients taking inhaled corticosteroids and the study had demonstrated significant differences between primary airway epithelial cytokine production in patients with chronic obstructive pulmonary disease and smokers with normal pulmonary function, both constitutively and in response to an inflammatory stimulus[15].

In the study by Bhowmik and colleagues, it was found that there was a relationship between the exacerbation frequency and the level of sputum cytokines. The levels of IL-6 and IL-8 were found to be increased in the sputum of patients who had been stable at the baseline and who experienced frequent exacerbations as compared to those who experienced infrequent exacerbations. During exacerbation, increases were found in the level of IL-6 in induced sputum, and the levels of IL-6 were higher when exacerbations were associated with symptoms of common cold [16]. Increased levels of IL-6, IL-1 beta, tumour necrosis factor-alfa and IL-8 in sputum have been measured [6].

Schmidt Ioanas M. reported that the sputum levels of cytokines were significantly increased as compared to serum levels[17]. In the study by Kochetkova EA, changes in the cytokine status in COPD patients was established and an increase in pro-inflammatory cytokines and change in anti-inflammatory cytokines was observed. There was hyper production of serum pro- inflammatory cytokines (IL-1 beta, IL-6, IL-8, TNF-alpha) dependent on FEV_1 [18].

Exacerbation of COPD is associated with greater nasal, sputum, and serum inflammation than that seen in a stable state. During exacerbation, inflammatory

markers were found to be highly correlated within nasal wash and serum, but not sputum[19].

The results of this study are in concordance with similar studies performed earlier. IL-6 and IL-8 levels were found to be significantly higher during COPD exacerbation as compared to the healthy control group and post treatment levels. But no significant correlation was found between IL-6, IL-8 levels and CRP, ESR, FEV1 and FEV_1/ FVC values.

Conclusion

Cases of exacerbated COPD with greater degrees of obstruction of the airways have higher levels of cytokines in serum. This can be interpreted to mean that these cytokines are related to the clinical and prognostic parameters and can be useful for evaluation of the therapy instituted for the disease.

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