STABİL DÖNEM KOAH'LI HASTALARDA SERUM NEOPTERİN VE IL–8 DÜZEYLERİ İLE HAVA YOLU OBSTRÜKSİYONU ARASINDAKİ İLİŞKİ

THE RELATIONSHIP BETWEEN SERUM NEOPTERIN AND IL–8 LEVELS AND AIRWAY OBSTRUCTION IN PATIENTS WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ÖZ

***Giriş**: Prospektif randomize olgu kontrollü çalışmamızda, stabil dönemdeki KOAH olgularında serum neopterin ve IL–8 düzeylerini saptamak ve bunların hastalık ağırlığını belirlemede kullanılıp kullanılamayacağını araştırmayı amaçladık.*

***Gereç ve Yöntem:** çalışmaya göğüs hastalıkları polikliniğimize başvuran 30 stabil dönem KOAH hastası ve aynı yaş ve cinsiyetten 30 sağlıklı kontrol alındı. Her iki grubun serum neopterin ve IL-8 düzeyleri analiz edildi.*

***Bulgular:** Serum ortalama neopterin düzeyleri KOAH grubunda; 22.08±5.27 nmol/l, kontrol grubunda 5.36±2.42 nmol/l (p=0.000). Serum ortalama IL–8 düzeyleri KOAH grubunda 31.63±16.49, kontrol grubunda 11.59±3.15 pg/ml saptandı (p = 0.000). KOAH grubunda serum ortalama IL–8 ile FEV1 % beklenen arasında istatistiksel olarak anlamlı negatif orta kuvvette korelasyon bulundu (pearson korelasyon testi, r= -0.389, p= 0.036). KOAH grubunda arteriyel PO2 ile serum ortalama IL–8 düzeyi arasında istatistiksel olarak anlamlı negatif orta kuvvette korelasyon saptandı (pearson korelasyon testi, r= -0.456, p=*

ABSTRACT

***Aim:** This study designed as a prospectively case-controlled clinical trial aims to detect serum neopterin and IL–8 levels in patients with stable Chronic Obstructive Pulmonary Disease (COPD) and to examine whether these levels can be used as a marker in the evaluation of the severity of COPD.*

***Material and Methods:** The study sample included 30 patients with stable COPD attending the outpatient clinic of chest diseases and 30 age- and gender-matched healthy controls. Both groups' serum neopterin and IL-8 levels were analyzed.*

***Results:** The mean serum neopterin levels were found to be 22.08 ± 5.27 nmol/l and 5.36 ± 2.42 nmol/l in the COPD and control groups, respectively (p= 0.000). The mean serum IL–8 levels were found to be 31.63±16.49 and 11.59±3.15 pg/ml in the COPD and control groups, respectively (p= 0.000). We found the statistically significant, negative and medium level correlation between the mean serum IL–8 and FEV1% predicted in the COPD group (Pearson's correlation test, r= -0,389, p= 0,036). A statistical significant, negative and medium level correlation was also*

0.011). Arteriyel PO2 ile serum ortalama neopterin düzeyi arasında, arteriyel PCO2 ile serum ortalama IL–8 düzeyi arasında ve arteriyel PCO2 ile serum ortalama neopterin düzeyi arasında korelasyon saptanmadı. KOAH grubunda hastalığın süresi, sigara kullanım süresi (paket-yıl) ile serum ortalama neopterin ve IL–8 düzeyleri arasında korelasyon saptanmadı. KOAH'ta hastalığın süresi ile sigara kullanım süresi (paket-yıl) arasında pozitif yönde ve istatistiksel olarak anlamlı orta kuvvette korelasyon saptandı (pearson korelasyon testi, r= 0.492, p= 0.006).

***Sonuç:** Stabil KOAH'lı olgularda serum IL-8 düzeylerinin yüksek olması, arter kan gazları ve solunum fonksiyon testleri ile korelasyon göstermesi hastalık ağırlığı ve inflamasyonun derecesini belirlemede kullanılabileceğini göstermiştir. Birçok inflamatuvar hastalıkta olduğu gibi KOAH' ta da neopterinin yüksek saptanması sistemik inflamatuvar cevabın aktivasyonunun bir göstergesi olmasına karşın hastalığın ağırlığını belirlemede bir kriter olarak kullanılıp kullanılamayacağını belirlemek için daha fazla katılımlı çalışmalara ihtiyaç olduğu kanısındayız.*

detected between the mean serum IL–8 level and arterial PO2 in the COPD group (Pearson's correlation test, r= -0.456, p= 0.011). No correlation was found between arterial PO2 and the mean serum neopterin level; between arterial PCO2 and the mean serum IL–8 level and between arterial PCO2 and the mean serum neopterin level. No correlation was found in the COPD group between the period of the disease, pack-year history of smoking and the mean serum neopterin and IL–8 levels. We also found the statistically significant, positive and medium level correlation between the period of COPD and pack-year history of smoking (Pearson's correlation test, r= 0.492, p= 0.006).

***Conclusion:** Serum IL-8 levels were high in patients with stable COPD. Therefore, the correlation between IL-8 levels, blood gases, and pulmonary function tests reveal that IL-8 can be used as a marker of disease and inflammation severity. As in many inflammatory diseases, detection of high neopterin levels in COPD patients is an indicator of the activation of a systemic inflammatory response; however, we believe that studies with larger sample sizes are required to determine whether neopterin level can be used as a marker in the evaluation of the severity of COPD.*

INTRODUCTION

Inflammation is a physiological response to tissue damage caused by infectious, physical, chemical, and other agents. During the processes of both acute and chronic inflammation, various mediators are released in the inflammation area and some of these mediators trigger systemic response to inflammation. Chronic obstructive pulmonary disease (COPD) is characterized by obstruction of the airway which is not fully reversible. Chronic inflammation has a key role in the pathogenesis of COPD. Symptoms, functional abnormalities, and complications of COPD can be explained on the basis of this underlying inflammation and the resulting pathology (1,2).

Neopterin is a low molecular weight pteridine compound produced by guanosine triphosphate and it shows the activation of cellular immunity. It is produced by human monocytes/macrophages which are activated by the stimulation of IFN-γ (interferon gamma) released by activated T lymphocytes (3-5). Neopterin levels are elevated in various acute and chronic inflammatory cases such as malign, autoimmune and infectious diseases (1,6-12). Studies reported that there is a positive correlation between clinical progression and serum neopterin levels (2,13).

This study aims to detect serum neopterin and IL–8 levels in patients with stable Chronic Obstructive Pulmonary Disease (COPD) and to examine whether the serum levels of inflammatory cytokines can be used as a marker in the evaluation of the severity and progression of COPD.

MATERIAL AND METHODS

The study sample included 30 patients with stable COPD attending the outpatient clinic of chest diseases and 30 healthy controls. Details of the experimental and control groups are given below.

Group 1 (COPD): Patients whose FEV1/ FVC ratios measured through pulmonary function testing (PFT) were < 70% were considered to have COPD. The severity of the disease was determined based on post-bronchodilator FEV1. Increase in dyspnea and increased volume and purulence of sputum were considered as the predictors as COPD acute exacerbation and patients with exacerbation were excluded from the study. The patients in this group were categorized into three groups: stable patients with moderate COPD; stable patients with severe COPD and stable patients with very severe COPD. Obstruction levels were classified based on the FEV1 levels as follows: Moderate (50% < FEV1 < 80%), severe (30% < FEV1 < 50%) and very severe (FEV1 ≤ 30%) (GOLD 2004). Patients with mild COPD were not included in the study (FEV1 > %80). Local ethics committee approval was obtained for the study (2005/1110).

Inclusion criteria

1. Patients with moderate, severe or very severe COPD based on the FEV1 levels whose post-bronchodilator FEV1/ FVC < % 70 (predicted).
2. Smokers who reported not having smoked for at least 1 year.
3. Patients had proven not to have any malignant, autoimmune or infectious disease (tuberculosis, etc.) affecting their immune system by clinical and physical examination and laboratory tests.
4. Patients with normal liver and kidney function.
5. Patients who do not have any other disease such as chronic kidney failure (CKF), Diabetes Mellitus (DM) and Coronary artery disease.

Exclusion criteria: 1. Patients with mild COPD based on the FEV1 levels whose post-bronchodilator FEV1/ FVC < % 70 (predicted).

2. Those who still smoke or have not been smoking for less than 1 year.

3. Patients with COPD acute exacerbation.

4. Patients who received antibiotic treatment for acute exacerbation at least a month ago.

5. Those with CKF, DM, coronary artery disease or any malign, autoimmune or infectious disease.

6. Those who received drugs that affect the immune system (use of immune suppressive medications in the last 1 month or systemic corticosteroid therapy with a daily dose of more than 20 mg).

Group 2 (control group):

Healthy controls of the same age and gender with the COPD group members who have never smoked or have not been smoking for at least a year were included in the study. All participants were subject to detailed physical examination. We paid attention that complete blood count and blood biochemistry revealed no evidence of infection or any other disease and the patients did not receive any medication. PFT and arterial blood gas (ABG) analysis were performed in all patients in the group.

Serum Sampling: In order to determine the neopterin and IL–8 levels, venous blood samples were drawn from all patients and controls into biochemistry tubes on arrival at the hospital before they received any treatment. The blood samples were centrifuged at 1500 rpm for 10 min and the serums were stored at -80 °C until the analysis. During all these processes, the samples were kept away from light.

Neopterin Measurement: The neopterin levels were examined using a Neopterin ELISA (IBL Immuno-Biological-Laboratories, Hamburg) kit. The kit's standard range was < 10 nmol/lt.

IL–8 Measurement: We employed the ELISA method using the Human IL–8/NAP–1 (BioSource International, Inc. 542 Flynn Road Camarillo, California 93013 USA) kit. The minimum detectable dose of this kit was < 0.7 pg/ml.

ABG Analysis: Allen's test was performed in all groups and the patients' ulnar arteries were found to be normal. A 2 cc blood sample was drawn from radial arteries of the participants while they were breathing room air in a sitting position. The samples were examined using Bayer Chiron device which measures with heat selective electrodes. The pH, PaO2, PaCO2, HCO3, and SO2% levels were recorded.

Pulmonary Function Testing: PFT was performed through simple spirometry using a Schiller- spirovit SP–10 spirometer.

Statistical Analysis: The data were analyzed using SPSS statistical software. We used Independent sample T-test for inter-group comparison of independent samples and the Pearson's and Spearman's correlation tests for intra-group correlation of independent samples. $p< 0.05$ was considered to be statistically significant.

RESULTS

The study sample included a total of 60 participants, i.e. 30 male patients with stable COPD and 30 healthy controls. Both groups' serum neopterin and IL-8 levels were analyzed.

The mean age of the COPD group was 66.63± 6.95 years old and that of the control group consisting of 30 healthy males was 66.73±4.84 years old. Table 1 shows the following parameters: mean age, sedimentation rates, CRP, total white blood cell counts, average PFT values and ABG analysis.

According to the FEV1 values of 30 patients in the COPD group, 11 patients had moderate COPD (36.7%), 15 patients had severe COPD (50%) and 4 patients had very severe COPD (13.3%).

The mean serum neopterin levels were found to be 22.08 ± 5.27 nmol/l and 5.36 ± 2.42 nmol/l in the COPD and control groups, respectively (Table 1). The mean serum IL–8 levels were found to be 31.63±16.49 and 11.59±3.15 pg/ml in the COPD and control groups, respectively (Table 1).

The mean serum neopterin levels of the COPD group were found to be higher at a statistically significant level than that of the control group (Independent-Samples T test, p= 0.000). The mean serum IL–8 levels of the COPD group were found to be higher at a statistically significant level than that of the control group (Independent-Samples T test, p= 0.000) (figure 1).

Table 1. Parameters of study participants

	Group 1 (COPD):	Group 2 (Control):
Age (year)	66.63±6.95	66.73±4.84
PO2 (mm/Hg)	62.6±16.99	87.27±6.55
PCO2 (mm/Hg)	40.70± 7.5	38.92±1.44
O2 sat (%)	87.79±9.77	96.19±1.22
FEV1(%predicted)	62.07±10.57	90.33±10.99
FEV1 (liter)	1.22±0.50	3.25±0.44
FEV1/FVC (%predicted)	56.43±9.86	84.67±6.36
CRP (mg/ml)	3.97±1.45	2.13±0.90
Leucocyte/ mm3	7966±1924	7766±1149
ESR (mm/h)	7.4±4.3	7.37±3.30
Neopterin (nmol/l)	22.08± 5.27	5.36±2.42
IL–8 (pg/ml)	31.63±16.49	11.59±3.15

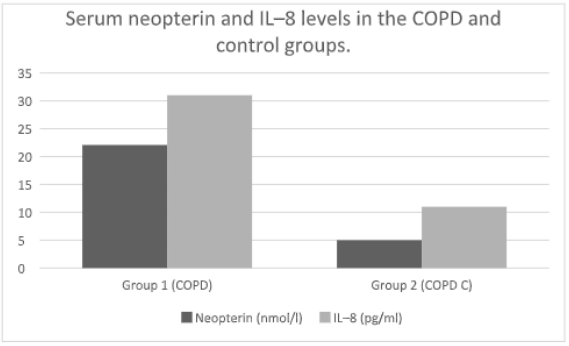

Figure 1. Serum neopterin and IL–8 levels in the COPD and control groups.

No correlation was found between serum neopterin levels and the severity of the disease in the COPD group. We the found statistically significant, negative and medium level correlation between the mean serum IL–8 and FEV1% predicted in the COPD group (Pearson's correlation test, r= -0.389, p= 0.036). A statistically significant, negative and medium level correlation was also detected between the mean serum IL–8 level and arterial PO2 in the COPD group (Pearson's correlation test, r= -0.456, p= 0.011). No correlation was found between arterial PO2 and the mean serum neopterin level; between arterial PCO2 and the mean serum IL–8 level and between arterial PCO2 and the mean serum neopterin level. No correlation was found in the COPD group between the period of the disease, pack-year history of smoking and the mean serum neopterin and IL–8 levels. We also found the statistically significant, positive and medium level correlation between the period of COPD and pack-year history of smoking (Pearson's correlation test, r= 0.492, p= 0.006).

DISCUSSION

In this study, we found that serum neopterin and IL–8 levels, which are the inflammatory biomarkers, were higher at a statistically significant level in the patients with COPD compared to the healthy controls. Besides, we found a positive and significant correlation between serum neopterin and IL–8 levels. A statistically significant negative correlation was detected between IL–8, FEV1 and PaO2 in the COPD group.

COPD is a systemic inflammatory disease which is associated with comorbidities. Various cytokines released from inflammatory cells (TNF-α, IL–8, IL–6, GM –CSF, etc.) are transported into the systemic circulation or contribute to the activation of inflammatory cells through the pulmonary circulation. These cytokines are known to increase serum levels even more during a COPD exacerbation (14,15).

Only a few studies in the literature examined serum neopterin levels in patients with COPD. One of these studies was conducted by Takabatake et al. (3). They reported that serum neopterin levels significantly higher in patients with stable COPD compared to the controls. Takabatake et al. (1) found the serum neopterin levels in patients with stable COPD to be 7.23 ± 4.24 nmol/lt. In our study, serum neopterin levels were found to be 22.08±5.27 nmol/lt in patients with stable COPD, which was significantly higher compared to the serum neopterin levels of the control group. On the other hand, Bühling et al. (16) reported that serum neopterin levels were low in patients with stable COPD, just like in the healthy controls. However, their study included only 8 patients. Therefore, we think that their findings were ascossiated with because of their study consisted of the small sample size. Warwick et al. found that the neopterin and IL-8 levels were increased in induced sputum during acute exacerbation (15).

The macrophage activation marker neopterin is excreted by activated macrophages/ monocytes. The main stimulus for neopterin production is the pro-inflammatory IFN-γ released after T-lymphocyte activation (3, 7, 5,8). High serum neopterin levels support that inflammation still continues and the systemic cellular immune response is active even

during the stable period, although their physiological importance in the patients with stable COPD is not known. In this way, the importance and necessity of anti-inflammatory treatment for COPD have been emphasized once again. As known, increase in some cytokines (such as TNFα and IL–1) in plasma or serum in the patients with COPD strongly supports that local inflammatory response is linked to the systemic circulation through these mediators (17).

Previous clinical and experimental studies proved the relationship between neopterin production and cellular immune activation and revealed that there is a strong correlation between neopterin levels and the severity and progression of infectious and inflammatory diseases (2,8,9,18). However, no correlation was found in this study between the serum neopterin levels of patients with COPD and the clinical parameters studied (predicted FEV1, PaO2, PaCO2 %). Similarly, Takabatake et al. (3) did not found any significant correlation between the serum neopterin levels of the patients with stable COPD and clinical parameters. Our finding of no correlation between the serum neopterin levels of patients with COPD and the clinical parameters which determine the severity of disease was attributed to a small number of patients included in the study. Due to the exclusion of patients with mild COPD and the lack of other subgroups, we were not able to determine whether there is a correlation between the neopterin levels among the subgroups. Hence, we were not able to find out whether there is any correlation with the stage of the disease.

High serum or urine neopterin concentrations is a reliable indicator of systemic inflammatory response syndrome that occurs following an infection of viral, bacterial, protozoal or fungal origin (8). COPD is a disease that progresses with exacerbations. Acute exacerbations are frequent complications of COPD with or without pneumonia which affect the prognosis of disease negatively. There are studies suggesting lipopolysaccharide from pneumococci and Haemophilusinfluenzae may induce the release of interferons, triggering neopterin synthesis from the alveolar macrophages (19). Some studies also suggest that the use of neopterin levels is helpful to determine the severity and progression of diseases in patients with pneumonia (20 21). A recent study which examined the diagnostic and prognostic value of non-invasive methods in such patients reported increased serum neopterin levels in both patient groups (22). However, in this study, it is not possible to reach such a conclusion since acute exacerbation was used as an exclusion criterion.

IL–8 which is a chemoattractant and an activator cytokine for neutrophils can be used to determine the severity of airway inflammation. Various studies reported increased IL–8 levels in induced sputum, bronchoalveolar lavage fluid and serum (18,23-25-27). Some studies used a nasal smear examination and revealed that IL-8 levels increased in patients with COPD (28). Besides, serum IL-8 levels were also shown to be used to predict mortality (29). In this study, we found that serum IL–8 levels were significantly higher in patients with COPD compared to the control group. Besides, we detected a statistically significant negative correlation between IL–8, FEV1 and PaO2 in the COPD group. FEV1 and the degree of hypoxia are the parameters used as a measure of disease severity in COPD. The negative correlation we found between the serum IL–8 levels and these clinical parameters supports that IL–8 can be used as a measure of inflammation, and thus disease severity. It can also be used as a measure of the severity of airway inflammation (30-32).

In conclusion; high serum IL-8 levels in patients with stable COPD and the correlation between IL-8, blood gases, and pulmonary function tests reveal that IL-8 can be used as a marker of disease and inflammation severity.

As in many inflammatory diseases, detection of high neopterin levels in COPD patients is an indicator of the activation of a systemic inflammatory response; however, we believe that studies with larger sample sizes are required to determine whether neopterin level can be used as a marker in the evaluation of the severity and prognosis of COPD.

Limitations of the Study:

1. This study was conducted with small sample size and no comparison was made between the subgroups.
2. We believe that further studies should be conducted with larger sample sizes and should include acute exacerbations and analysis of subgroups in accordance with the new GOLD guidelines.

Disclosure

"The authors have no conflicts of interest to declare".

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