Are Thyroid Functions Changing in Patients with Exacerbated COPD?

KOAH Atakta Tiroid Fonksiyonları Değişir mi?

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ABSTRACT

Objective: Non-thyroidal illness syndrome (NTIS) can be induced by chronic obstructive airway disease (COPD) exacerbation. The aim of this study was to evaluate the thyroid function impairments and the presence of thyroid antibodies in exacerbated COPD patients and to demonstrate the probable relationship with other clinical and biochemical parameters, such as the parameters of arterial blood gases, urea, creatinine, prothrombine time (PT), activated partial prothrombine time (APTT), and international normalized ratio (INR), etc.

Methods: We evaluated 21 patients within the exacerbation period of COPD who had undergone non-invasive mechanical ventilation and had measurements of serum fT3, fT4, and TSH levels and other laboratory tests (glucose, urea, creatinine, hematocrits, hemoglobin, PT, APTT) made on their first to third day of stay in the hospital. Ten of 21 patients had measurements of anti-Tg (antithyroglobulin) antibody and anti-TPO (antithyroperoxidase). The healthy control group consisted of 17 age-matched non-smoking voluntary men admitted to the internal medicine outpatient clinic for general check-up purposes without any complaints or diagnoses. Analyses were made with SPSS 17.0.

Results: We found that 33.33% of the patients with COPD exacerbation had fT3 levels below the normal values, and 14.28% of the patients had TSH levels below the normal values. The average fT3 and TSH levels were lower in the patients with COPD exacerbation compared to the healthy volunteers, and fT4 levels were higher in patients compared to the healthy group (patient group mean±SD (median): fT3 2.52±0.48 (2.69), fT4 0.99±0.16 (1.01), TSH 0.95±0.7 (0.80), p=0.001, p=0.001, p=0.009, respectively). Prothrombin time was negatively correlated with fT3 (rs= -0.520, p=0.03).

Conclusion: Negative correlation of pH with platelet counts and fT3 with prothrombin time were the novel findings of this study. This study is the first one to determine the relationship with thyroid hormones and coagulation in COPD patients. The other finding of the study was lower fT3 levels than healthy controls, which has been supported by other studies. *(JAREM 2014; 1: 18-24)*

Key Words: Thyroid, COPD, COPD exacerbation

ÖZET

Amaç: Tiroid dışı hastalık sendromu kronik obstriktif akciğer hastalığı (KOAH) atağında tetiklenebilir. Çalışmamızda KOAH atağında olan hastalarda tiroid fonksiyon bozukluklarını ve tiroid antikorlarının varlığını ve diğer klinik ve arter kan gazı, üre, kreatinin, international normalized ratio (INR) vb. parametrelerle ilişkilerini değerlendirmeyi amaçladık.

Yöntemler: KOAH atağının 1-3. günlerinde non-invaziv mekanik ventilasyon uygulanan 21 olgu (17 erkek/4 kadın) çalışmaya alındı. Olguların tümünün free T3, fT4, TSH düzeyleri, glikoz, üre, kreatin, hematokrit, hemoglobin, protrombin zamanı (PT), aktive parsiyel tromboplastin zamanı (APTT) parametreleri, 10 olgunun tiroid antikorları değerlendirildi. Dahiliye polikliniğine sağlık kontrolü amaçlı başvuran 17 sağlıklı, sigara içmeyenlerden kontrol grubu oluşturuldu ve benzer parametreleri değerlendirildi. Analizler SPSS 17,0 istatistik programında yapılmıştır.

Bulgular: KOAH'lı olguların yaş ortalaması 5,95±10,63, vücut kitle indeksi 23,19±5,8 kg/m^2 (n=21), sağlıklı olguların yaş ortalaması 54,35±7,33 kg/m^2, vücut kitle indeksi 26,94±5,3 (n=17). Ortalama fT3, TSH düzeyi KOAH'lı olgularda sağlıklı kontrol grubuna göre daha düşüktü, fT4 ise daha yüksekti (hasta grup ort±SD (median); fT3 2,52±0,48 (2,69), fT4 0,99±0,16 (1,01), TSH 0,95±0,7 (0,80). Free T3, KOAH ataktaki olguların %33,33'ünde düşüktü, TSH ise %14,28 olguda normal değerlerin altındaydı (sırasıyla, p=0,001, p=0,001, p=0,009). Protrombin zamanı fT3 ile negatif olarak koreleydi (rs= -0,520, p=0,03).

Sonuç: Protrombin zamanı ile free T3 düzeyleri arasındaki negatif korelasyon bu çalışmada saptanan yeni bir bulgudur. Sağlıklı olgulara göre KOAH atakta saptanan daha düşük fT3 düzeyleri diğer çalışmalarla da desteklenmektedir. *(JAREM 2014; 1: 18-24)*

Anahtar Sözcükler: Tiroid, KOAH, KOAH atak

INTRODUCTION

Non-thyroidal illness syndrome (NTIS) is used to describe the typical changes in thyroid-related hormone concentrations that can arise in the serum following any acute or chronic illness that is not caused by an intrinsic abnormality in thyroid function (1). Non-thyroidal illness syndrome or euthyroid sick syndrome is observed in approximately 44% of patients in the intensive care unit (2). Low circulating levels of thyroid hormones, low or normal Thyroid-Stimulating hormone (TSH), diminished TSH pulsality, and implied presence of central hypothyroidism characterize this syndrome. NTIS can be induced by fasting; sepsis; trauma; burns; surgery; cardiovascular, renal, and liver disease; and chronic obstructive airway disease (COPD). T4 can be converted into active tri-iodothyronine (T3) by iodothyronine deiodinases, which have a tissue-specific distribution. There are three deiodinases (D1, D2, D3). Changes in deiodinase expression have been postulated to play important roles in the altered circulating levels of thyroid hor-

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mones in fasting and nonthyroidal illness syndrome (NTIS) (1, 3). There is a strong correlation between the TT3/TT4 ratio and PaO_2 in COPD patients. TT3 and TT3/TT4 were lower in severe COPD. Hypoxemia seems to be a determinant of the peripheral metabolism of thyroid hormones (4-6). However, the mechanism and exact prevalence of thyroid function impairments in COPD patients have not been extensively studied. The exacerbation period of COPD patients is a critically ill condition that causes hypoxic and metabolic changes.

The aim of this study was to evaluate the thyroid function impairments and the presence of thyroid antibodies in exacerbated COPD patients and to demonstrate the probable relationship with other clinical and biochemical parameters, such as arterial blood gases, urea, creatinine, prothrombine time (PT), activated partial prothrombine time (APTT), and international normalized ratio (INR), etc.

METHODS

We evaluated 21 patients (17 male/4 female) within the exacerbation period of COPD admitted between January 2012 and March 2012 to our clinics who had undergone non-invasive mechanic ventilation and had measurements of serum free T3 (fT3), free T4 (fT4), TSH levels, and other laboratory tests made on their first to third day of stay in the hospital. Patients had transferred to our clinic after observed emergency service. Ten of 21 patients had measurements of the anti-Tg (antithyroglobulin) antibody and anti-TPO (antithyroperoxidase). Written informed consent was obtained from all individuals, and the study was conducted in compliance with the approval of the institutional ethical committee. All included patients were evaluated using the GOLD guideline and were diagnosed with a very severe stage (stage 4-FEV^1 30%< or 50%< plus chronic respiratory failure; mean Forced Expiratory Volume 1 (FEV^1) was 39.38±9.97%). On the day of discharge from the hospital, a pulmonary function test had been administered to determine the clinical stage of COPD. We obtained the patients' pulmonary function test results from hospital records. COPD exacerbation was identified according to Anthonisen's Winnipeg criterion, which defines an acute exacerbation as a sustained, worsening dyspnea, cough, or sputum production, leading to an increased use of maintenance medications or the addition of supplemental drugs, usually for at least 2 consecutive days (7, 8). All of the patients were receiving inhaled steroid, beta agonist, and parenteral theophylline, as well as long-term oxygen and non-invasive mechanical ventilation treatment according to their disease status (BILEVEL, BiPAP, Respironics Inc., USA).

The healthy control group consisted of 17 age-matched non-smoking voluntary men admitted to the internal medicine outpatient clinic for general check-up purposes without any complaints or diagnoses. Patients with known endocrine disorders, diabetes, renal or hepatic failure, or connective tissue disorders or using other medications outside of COPD treatment were excluded from the study. The exclusion criteria mentioned above were also implied to the healthy controls, validating with lab studies where applicable. These selective criteria and time intervals of the study restricted the size of the subject group.

The patients that were admitted to the study had been evaluated for arterial blood gas levels (PaO_2, $PaCO_2$, and saturated O_2) and for clinical chemistry tests, such as glucose, urea, creatinine, hematocrit, hemoglobin, PT (prothrombine time), APTT (partial prothrombine time), PT-INR (international normalized ratio), fT3, fT4, and TSH. Additionally, we obtained the results of the anti-Tg (antithyroglobulin) antibody and anti-TPO (antithyroperosidase) antibody measurements in 10 patients. On the day of discharge from the hospital, a pulmonary function test had been administered to determine the clinical stage according to GOLD.

The normal ranges of serum concentrations of thyroid hormone for our laboratory were as follows: fT3, 2.5-3.9 pg/mL; fT4, 0.58-1.64 ng/dL; and TSH, 0.34-5.6 mIU/mL.

The minimum detectable concentration of thyroid antibodies was reported as 20 IU/mL for Tg-Ab (thyroglobulin antibodies) and 1 IU/mL for TPO-Ab (thyroid peroxidise antibodies). The reference ranges are ≤40 IU/mL for Tg-Ab (thyroglobulin antibodies) and ≤50 IU/mL for anti-TPO. Glucose (glucose oxidase), urea (ureas), creatinine, prothrombine time, and activated partial thromboplastin time were measured by, respectively, enzymatic, Jaffe, and coagulametric methods in our laboratory. Tg-Ab and TPO-Ab were measured by electrochemiluminescence immunoassays in a Coulter-Access device. In addition to the laboratory tests, the following data were obtained and analyzed; age, body mass index (BMI), the duration of smoking, frequency of hospitalization, duration of the disease, and particular period since smoking cessation.

Statistical analysis

The values were presented as mean±SD, median interquartile range (IQR), frequency, and percentage. Normal distribution was assessed using the Shapiro-Wilk test by drawing histograms. Comparison of COPD patients and healthy controls was examined using Mann-Whitney U test. Correlations amongst the variables of COPD patients were determined using the Spearman correlation test. The tests were two-way, and statistical significance values were set at $p<0.05$. Analyses were performed using SPSS 17.0 statistical software.

Data are presented as mean±SD, median IQR, frequency, and percentage. A normality control was made by using the Shapiro-Wilk test and histogram graphics. The comparison of COPD to control group was evaluated by Mann-Whitney U test. Correlations between the variances of COPD were made by Spearman correlation. Tests were two-tailed, and $p<0.05$ was accepted as significant. Analyses were made with SPSS 17.0.

RESULTS

The average age of the patients with COPD was 57.95±10.63 years, with an average BMI of 23.19±5.8 kg/m^2 (n=21), whereas the average age of the control group was 54.35±7.33 kg/m^2, with an average BMI of 28.94±5.3 (n=17). The average BMI of the control group was higher than the patient group (p=0.001) (Table 1). The control group contained only non-smokers, while all of the patients with COPD exacerbation were ex-smokers. The average period since they quit smoking was 5.56±8.2 years, and the average duration of smoking was 48.74±43.99 packet-years. The average period of time since the first symptoms of COPD occurred was 17.52±18.53 years (Table 2). The average blood gas values and the average coagulation parameters of the patients

are shown in Table 2, and the comparison of their thyroid test results and biochemical parameters with the normal values are presented in Table 1. We found that 33.33% (n=7) of the patients with COPD exacerbation had fT3 levels below the normal values, and 14.28% (n=3) of the patients had TSH levels below the normal values. The average fT3 and TSH levels were lower in the patients with COPD exacerbation compared to the healthy volunteers, and fT4 levels were higher in patients compared to the healthy group (patient group mean±SD (median): fT3 2.52±0.48 (2.69) pg/mL, fT4 0.99±0.16 (1.01) ng/dL, TSH 0.95±0.7 (0.80) mIU/mL, p=0.001, p=0.001, p=0.009, respectively) (Figure 1-3).

The difference between the anti-thyroglobulin antibody (Tg-Ab) levels of the patients with COPD and the healthy volunteers was statistically meaningful. Tg-Ab levels were higher in the patient group (Tg-Ab; mean±SD (median): 11.5±4.9 (11.98) IU/mL, TPO-Ab: 18.9±8.9 (16.6) IU/mL, p=0.001, p=0.001, respectively). The results were Tg-Ab: 1.35±1.84 (0.9) IU/mL and TPO-Ab: 1.24±3.32 (0.4) IU/mL for the control group. Tg-Ab levels were negatively

Table 1. The Comparison of Healthy Controls and COPD patients with exacerbation

	Healthy Controls		COPD Patients		
Variables	**Mean±SD**	**Median (IQR)**	**Mean**	**Median (IQR)**	**p***
Age, y	57.95±10.63	60 (50-65.5)	54.35±7.33	55 (48.5-58.5)	0.12
BMI kg/m^2	23.19±5.8	22.3 (21-24.4)	28.94±5.3	28.4 (25.3-30.2)	0.001
O2, saturation	86.2±10.9	88 (79-94.5)	97.58±1.00	97 (97-98.5)	<0.0001
fT3, ng/L	2.52±0.48	2.69 (2.03-2.84)	3.13±0.43	3.15 (3.08-3.4)	0.001
fT4, ng/L	0.99±0.16	1.01 (0.87-1.13)	0.80±0.09	0.79 (0.73-0.9)	0.001
TSH, µIU/mL	0.95±0.70	0.80 (0.35-1.45)	1.76±0.84	1.46 (1.17-2.54)	0.009
TPO-Ab, IU/mL	18.9±8.9	16.6 (11.2-28.5)	1.24±3.32	0.4 (0.35-0.5)	0.001
Tg-Ab, IU/mL	11.5±4.9	10.49 (8.92-13.6)	1.35±1.84	0.9 (0.9-0.9)	0.001
Hematocrit %	42.9±4.64	42.7 (40-46)	44.55±2.91	46 (42-46.6)	0.196
Hemoglobin,gr/dL	14.17±1.56	14.2 (13.3-15.2)	15.21±1.26	15.7 (14-16)	0.034
Glucose, mg/dL	123±39	114 (94-148)	104.64±20.43	104 (89.5-113)	0.011
Urea, mg/dL	40.5±16.7	40.7 (31-47)	16.82±3.45	16 (14.5-18.5)	<0.0001
Creatinine, mg/dL	0.9±0.28	0.9 (0.67-1.15)	0.94±0.18	0.92 (0.82-1)	0.394

*Mann Whitney U Test
BMI (body mass index)
fT3,ng/L (free triiodothyronin)
fT4, ng/L (free thyroxine)
TSH, µIU/mL (thyroid stimulating hormone)
TPO-Ab, IU/mL (antithyroglobulin)
Tg-Ab, IU/mL (thyroglobulin antibodies)
COPD: chronic obstructive airway disease; IQR: interquartile range; SD: sample standard deviation

Table 2. The important clinical features of COPD patients

The features of COPD Patients	**Mean±SD**	**Median (IQR)**
The duration of smoking, y	48.7±43.9	40 (20-60)
The particular period since smoking cessation, y	5.56±8.2	0.5 (0-10)
Recurrent hospitalization, y	2±1.7	2 (0-3)
pO2, mmHg	64.1±25.2	56 (46-76)
pCO2, mmHg	53.9±16.5	50.3 (40.6-65.8)
pH	7.38±0.48	7.38 (7.35-7.40)
HCO3,mEq	30.5±7.3	31.4 (24.3-36.6)
Duration of disease	17.5±18.5	14 (7-20)
Prothrombin Time (PT), seconds	12.44±0.89	12.5 (11.9-13)
INR	1±0.07	1 (0.96-1.06)
APTT (Parsiel Thromboplastin Time), seconds	27.96±3.77	27.5 (25-29.8)

COPD: chronic obstructive airway disease; PT: prothrombin time; INR: international normalized ratio; APTT: activated partial prothrombine time

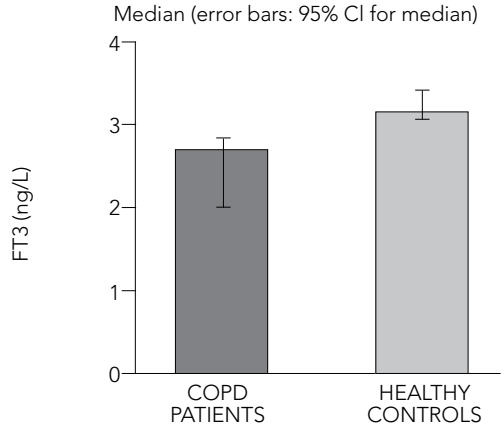

Figure 1. The comparison of fT3 levels of COPD patients with healthy controls
COPD: chronic obstructive airway disease

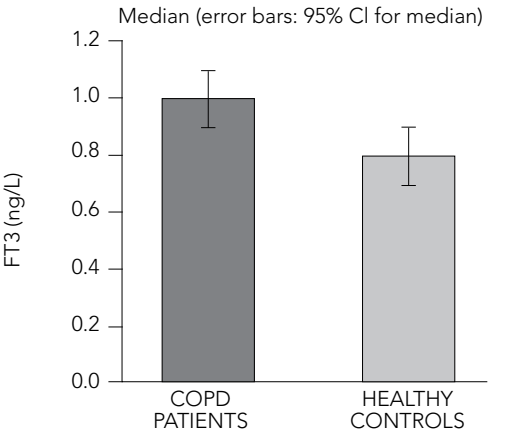

Figure 2. The comparison of fT4 levels of COPD patients and healthy controls
COPD: chronic obstructive airway disease

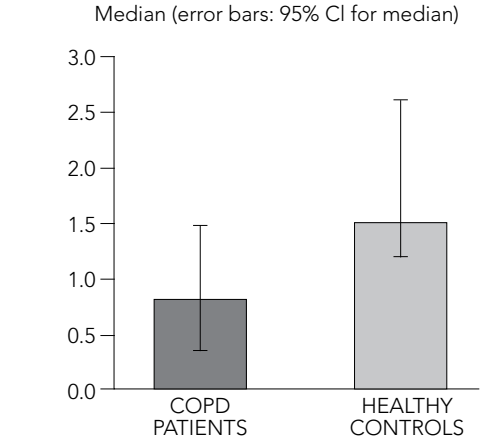

Figure 3. The comparison of TSH levels of COPD patients with healthy controls
COPD: chronic obstructive airway disease

correlated with urea and creatinine levels (r_s=-0.690, p=0.02 and r_s=-0.690, p=0.02, respectively). Creatinine levels were also negatively correlated with fT3 levels (r_s=-0.55, p=0.02 and rs=-0.55, p=0.02, respectively). TSH levels were negatively correlated with fT3 levels and WBC count (r_s=-0.55, p=0.02 and rs=-0.55, p=0.02, respectively). Prothrombin time was negatively correlated with fT3 (r_s=-0.520, p=0.03) (Figure 4). There was no similar correlation in healthy subjects. APTT and INR were not correlated with fT3 levels. pH balance was negatively correlated with platelet count (r_s=-0.36, p=0.01), while arterial pH levels were positively correlated with Tg-Ab levels (r_s=0.718, p=0.019).

DISCUSSION

Nonthyroidal illness syndrome is an adaptive process that promotes survival during life-threating illnesses by reducing metabolic rate and energy cost (9). The changes in serum thyroid hormone levels in critically ill patients occur extensively in critical care units. In COPD, the exacerbation of obstructive symptoms is more distinct, and deterioration in the patient's clinical condition is seen. Patients with COPD exacerbation are exposed to numerous medications as well as non-invasive mechanical ventilation. The important function of thyroid hormone is known to be a regulator of metabolism. Alterations in the peripheral metabolism of thyroid hormones, TSH regulation, and the binding of thyroid hormone cause widespread changes in serum thyroid levels in critically ill patients (10). Thyroid hormone may play a role in the hypermetabolism observed in COPD patients (6).

In our study, fT3 levels and TSH levels in 33.3% and 14.28% of patients were respectively lower than the reference ranges. There are several studies that show alteration of thyroid hormone levels in COPD patients. In those studies, different thyroid hormone levels were observed; in some studies, increased T4 levels were seen, while others reported increased T3 levels, and others found that T3, T4, and TSH levels were changed (5, 11, 12). Karadağ et al. (5) study demonstrated that T3 levels were lower, but they did not evaluate the relations among other biochemical analysis out of arterial blood gases.

Only the study by Dimopoulou et al. (4) reported that there was no difference in thyroid hormone levels in COPD patients compared to a healthy control group. That study also reported a cor-

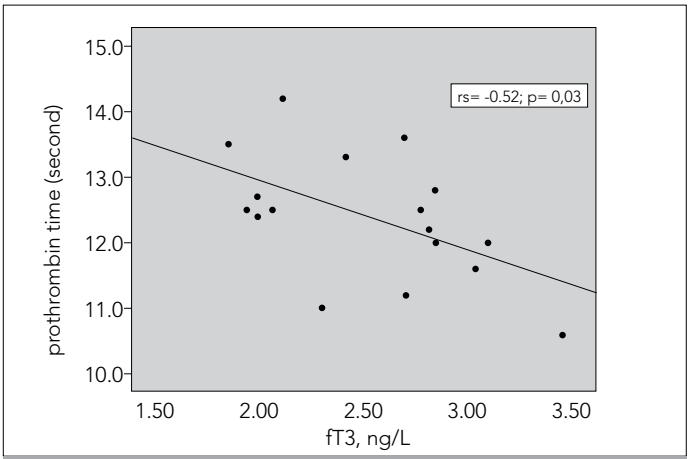

Figure 4. The relation of prothrombin time and fT3 level

relation between the T3/T4 ratio and respiratory tract obstructions (4). Okutan et al. (11) showed that T3 levels are positively correlated with PCO_2. We did not find a correlation with T3 levels and PCO2.

In this study, it was found that COPD patients had lower levels of T3 and higher levels of T4 compared to the control group. These findings are similar to the study done by Mancini et al. (13) who found that COPD patients had lower levels of T3 compared to the control group. The alteration in thyroid hormone levels is thought to be because of decreased turnover of T4 and T3 as an adaptive mechanism in chronic diseases (13). Similarly, TSH levels in COPD patients undergoing acute exacerbation were lower than in the control group. The study by Karadağ et al. (5) also showed that COPD exacerbation patients have decreased TSH levels. Recently, Akbaş et al. (14) found that patients with severe respiratory insufficiency have decreased levels of TSH (14). In our study, patients were under NIMV. Bacakoglu et al. (15) reported the need for invasive mechanical ventilation and hospital mortality in respiratory failure patients with low levels of fT3 and higher levels of fT4.

This study has several limitations, such as lack of a laboratory test pre- and post-NIMV. In a study by Bello et al. (10) serum TSH levels usually remained within the normal range in NTIS, but they increased modestly during recovery. Also, fT4 concentration may be slightly high in the early phase of NTIS under mechanical ventilation. We did not clear NIMV therapy effects on changes in thyroid function.

Fasting leads to a diminution in steady-state T3 levels. Malnutrition is a component of many acute and chronic illnesses (1). Hypermetabolic states and insufficient dietary intake will result in a negative energy balance and may contribute to weight loss in COPD patients. The role of thyroid hormones in COPD patients with cachexia has not been extensively studied (6). A direct action on leptin in hypophysiotropic TRH neurons has been proposed (16, 17). Endotoxins induce D2 (Type 2 iodothyronine deiodinase) and leads thyroid hormones (18). Infections can cause both thyroid hormone changes and exacerbation in COPD patients. There may be several mechanisms of thyroid hormone changes in COPD patients. Future studies should be focused on these points.

A low T3 level represents a biochemical prognostic marker in pulmonary patients with respiratory failure (19). In our study, we did not find a correlation between the recurrence of hospitalization and duration of disease in COPD patients with exacerbation.

In this study, it was found that COPD patients had higher levels of thyroglobulin and thyroid peroxidase antibodies compared to the control group. However, they were in the accepted normal range. Also, our subject group was limited in number. The negative association of smoking with the presence of thyroid antibodies and the associated increased risk for occurrence of thyroid hormones with discontinuation of smoking was reported (20, 21). There has recently been a focus on the relationship between smoking and the autoimmune system (22). Furthermore, COPD has been proposed as an autoimmune disease, like rheumatoid arthritis, because smoking is a risk factor and exacerbations occur both in RA and COPD. Additionally, these diseases have inflammatory features (23). However, the discontinuation period of smoking in our patients was a mean of 5.56±8.2 years. We did not find a correlation between thyroid antibodies and duration of smoking or discontinuation period. We found a positive correlation between thyroid antibodies and arterial PH. There has not been any published literature that showed this relationship. This might point to the influence of metabolic changes as a reason. Thyroid antibodies were negatively correlated with urea and creatinine. Tagher et al. (24) demonstrated that thyroid autoimmunity (increased concentration of anti-thyroid antibodies) and subclinical primary hypothyroidism are highly prevalent in chronic kidney disease. Likewise, fT3 levels were negatively correlated with creatinine levels. Decreased fT3 levels in patients with preterminal and terminal renal failure were shown by Witzke et al. (25). In a study by Carmina Z et al. (26) the fT3 level was significantly low at the peak of inflammation.

In this study, we found that fT3 levels were negatively correlated with prothrombin time. Various abnormalities of coagulation and fibrinolysis with thyroid dysfunction are the consequences of direct effects of thyroid hormones on the synthesis of various hemostatic parameters, according to recent literature. Thyroid autoimmunity may also modify the processes of secondary hemostasis (27). In general, patients with hypothyroidism appear to have an increased risk of bleeding, whereas those with hyperthyroidism are more likely to be prone to thrombosis (27, 28). However, the influence of subclinical hypothyroidism on hemostasis is controversial; both hypercoagulable and hypocoagulable states have been reported. In a study by Erem, some differences in hemostatic parameters and lipid profile between subclinical thyroid patients and healthy controls were reported (29). We did not find any study that reported the relationship between prothrombin time and thyroid hormones in COPD patients. There was a case report that observed prolonged prothrombin time (PT) because of high hematocrit in a COPD patient without coagulation disorder (30). In this study, we observed that pH and platelet counts were negatively correlated. This finding may indicate a hypercoagulable state observed in COPD patients with acidosis. The Biljak et al. study showed that COPD had a significantly increased platelet count. In the Maclay et al. (31, 32) study, platelet activation is increased in patients with COPD during an acute exacerbation. It is well established that COPD is a chronic inflammatory condition with significant extrapulmonary manifestations (7). Systemic inflammation is the first cause of the hypercoagulable state observed in COPD. Furthermore, hypoxia is supposed to activate platelets and induce metabolic changes on platelet membranes and dynamically modulate endothelial function. The ensuing endothelial dysfunction might promote microvascular lesions (33, 34). Sabit et al. (35) observed that hypoxic challenge in patients with COPD resulted in coagulation activation in conjuction with an increase in systemic inflammation.

CONCLUSION

A negative correlation of pH with platelet counts and fT3 with prothrombin time was the novel finding of this study. We did not find any report that designed the same study concept and result. Future prospective studies should be comparatively focused on the relationship among inflammation, coagulation, and metabolic features and daily thyroid hormones changes in different

stages of COPD patients, depending on acid-base balance. The other finding of the study was lower fT3 levels than healthy controls, which has been supported by other studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yedikule Thoracic Diseases and Surgery Center (2/7/2011, Document no: 0013-020711-090911-0013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Hakem Değerlendirmesi: Dış bağımsız.

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