Thyroid Dysfunction in Exacerbation of Chronic Obstructive Pulmonary Disease

Kronik Obstrüktif Akciğer Hastalığı Alevlenmesinde Tiroid Disfonksiyonu

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (copd) is a devastating lung disease which could be related with systemic consequences. Chronic comorbidities either develop independently or in association with systemic manifestation could lead increase morbidity or mortality in copd. thyroid gland dysfunctions are also a comorbidity that can accompany copd patients. This study was undertaken to study to show the distribution of thyroid hormone dysfunction in the setting of exacerbation in patients with Copd.
Methods:A group of 105 hospitalized copd patients were included to this cross-sectional study to evaluate the thyroid hormone dysfunction in the setting of exacerbation in patients with Copd.
Results: We Included 105 patients to the study,but 26 individuals were excluded due to the effect of steroid use on thyroid functions and one for sick euthyroid syndrome with low t4 serum levels.the patients were stratified into 2 subsets according to tsh concentrations:sick euthyroid syndrome and normal euthyroid function.32% of patients had normal euthyroid function,68% of them were sick euthyroid syndrome.We observed significant decrease of both po_2 and pco_2 in sick euthyroid syndrome patients(po_2: 53.35mmhg±10.55 vs. and 61.24mmhg±12.36 patients with normal thyroid function;p=0,022; pco_2: 39.35mmhg±8.08 vs. and 47,88mmhg±13.96 patients with normal thyroid function; P=0,017).
Conclusion: We found low pO_2 and pCO_2 in patients with NTIS compared to patients with normal thyroid function.This results are some similarities with the arterial blood gas values of patients with hypothyroidism.pO_2 was low in both hypothyroidism and NTIS .But we found lower pCO_2 which was different from hypothyroid COPD patients.Lowering pCO_2 can be the compansation of the body from hypoxic conditions.

Key words: Chronic obstructive pulmonary disease, thyroid function, exacerbation.

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ÖZET

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH) sistemik sonuçları olabilen progressive seyirli bir hastalıktır. Komorbiditeler, bağımsız olarak ya da sistemik belirtileri ile birlikte KOAH'ta morbidite ve mortaliteye sebep olabilir. Bu çalışmada, KOAH'lı hastalarda alevlenme döneminde tiroid hormon disfonksiyonunun dağılımını ve etkilerini göstermek hedeflenmiştir.
Yöntem: KOAH'lı hastalarda alevlenme döneminde tiroid hormon disfonksiyonunu değerlendirmek amaçlı bu kesitsel çalışmaya hastanede yatan 105 KOAH hastası dahil edilmiştir.
Bulgular: Çalışmaya 105 hasta dahil edildi ancak steroid kullanımının tiroid fonksiyonlarına etkisi nedeni ile 26 hasta ve T_4 düşüklüğü olan 1 hasta ötiroid sendromu nedeni ile çalışma dışı bırakıldı. Hastalar, TSH değerlerine göre hasta ötiroid sendromu ve normal tiroid fonksiyonu olan 2 gruba ayrıldı. Hastaların %32'si normal tiroid fonsiyon testine sahip iken, %68'i hasta ötiroid sendrom idi. Hasta ötiroid sendromlu hastalarda hem pO_2 hemde pCO_2 değerlerinde anlamlı düşüş saptandı (pO_2: 53.35mmHg±10.55 ve 61.24mmHg±12.36 (normal tiroid fonksiyonu olan hastalar));p=0,022; pCO_2: 39.35mmHg±8.08 ve 47,88mmHg±13.96 (normal tiroid fonksiyonu olan hastalar); p=0,017).
Sonuç: Normal tiroid fonksiyonu olan hastalara kıyasla non-tiroid hasta sendromu olan hastalarda istatistiksel olarak anlamlı daha düşük pO_2 ve pCO_2 değerleri saptandı. Bu sonuçlar hipotiroidili hastaların arter kan gazı değerleri ile benzerlik göstermekte idi. pO_2 değeri hem hipotiroidli hastalarda hem de non-tiroid hasta sendromu olan hastalarda düşük saptandı. Ancak hipotiroidili KOAH hastalarından farklı olarak pCO_2 değeri daha düşük saptandı. pCO_2 değerinin düşük olması hipoksik koşullara kompansasyon olarak yorumlandı.

Anahtar Sözcükler: Kronik obstrüktif akciğer hastalığı, tiroid fonksiyonları, atak

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a devastating lung disease which could be related with systemic consequences(1). Chronic comorbidities either develop independently or in association with systemic manifestation could lead increase morbidity or mortality in COPD (2). Thyroid gland dysfunctions are also a comorbidity that can accompany COPD patients. Thyroid hormones regulate the metabolism of proteins, lipids and carbohydrates, and control the activity of membrane-bound enzymes(3).

Some illnesses are associated with abnormal thyroid hormone concentration following acute or chronic stimulus that is not associated with intrinsic thyroid gland dysfunctions (4).This is now called Non-thyroidal illness syndrome (NTIS). The mechanism behind NSIT the activation of the hypothalamic-pituitary-thyroid axis due to related diseases. This is typically associated with low levels of total triiodothyronine (T_3). Sick patients with low serum T_3 had been defined as" low T_3 syndrome" and called widely as "Euthyroid sick syndrome" in the past. The pathogenesis of the NTIS is not well understood. It is not known whether the abnormal hormones are an adaptation to acute or chronic stress or need for replacement (4). Low T_3 is the mildest form of NTIS however in moderate to severe NTIS, TSH and T_4 could be altered. While TSH is considered as being the most sensitive and specific thyroid function test in the acute hospital setting 3% of the patients could have low TSH which would be attributed mostly to NTIS or the use of glucocorticosteroids (4).

In organic illnesses despite the presence of low T_3 and T_4, the rise of TSH would be failed due to an alteration of hypothalamic-pituitary axis that cause central hypothyroidism. In this case TSH usually is over 0.01 mU/l. However,in almost all hyperthyroidism patients TSH values become <0.01 mU/l (4).

Although, the alteration in thyroid function tests are common in COPD,it is difficult to interpret the alterations. Most probably, the reason of the alterations is due to NTIS in particularly in the setting of exacerbation during respiratory distress with hypoxemia, intense inflammation and intense glucocorticoid usage. Although NTIS is considered to be a compensatory reaction of the body to offset catabolism and protein break down. It is not exactly known if the NSIT is benefited by hormone therapy or if this is related with certain outcomes or the alteration of COPD outcomes(3,5,6).

Thyroid function test abnormalities could be present in the stable phase of the disease as well as the exacerbation. Besides NSIT, abnormalities due to thyroid gland could be present as subclinic hypo or hyperthyroidismor overt hypo or hyperthyroidism(3).

Very limited data is present on the prevalence of thyroid disease in COPD. The most common type is NSIT with 20% in stable COPD and 70% in exacerbation (6). However, we do not know exactly the prevalence of subclinic or overthypothyroidism, and hyperthyroidism.

Subclinical hypothyroidism (ScH) is evaluated in two categories: 1) mild: TSH levels between 4.5 to 10 microUI/ml values with normal value of free T_4) or severe: TSH levels > 10 microUI/ml values with normal value of free T_4) . Overt hypothyroidism (TSH values >10 microUI/ml with low values of free T_4), and subclinic hyperthyroidism (SHyper); (grade 1: TSH: 0.1-0.39 mIU/l), and (grade 2 SHyper; TSH<0.1 mUI/ml) with normal values of T_4 and overt hyperthyroidism (TSH<0.1 microUI/ml with high values of free T_4) (7,8).

The incidence of ScH varies between 4-10% depending on the gender, age and population studied (7). The impact of ScH including whether it increases the risk of cardiovascular risk or mortality, whether it negatively influences the metabolic parameters or whether it should be treated with L-thyroxine is not known (7).

Hyper is mostly due to Graves' disease, toxic adenoma and toxic multinodular goiter. The prevalence is between 0.6 to 16% depending on diagnostic criteria, age, sex, the TSH assay used and iodine intake. It is relatively frequent in iodine-deficient regions, and the prevalence is being as high as 15% (8). SHyper was recognized recently that associated with increased risk of coronary artery disease mortality, incident atrial fibrillation, heart failure, fractures and excess mortality (8). Therefore, now in patients with older than 65 years with grade 2 Shyper is considered as an indication for treatment (8).

Although it is known that subclinical or overt thyroid dysfunctions could be related with several outcome parameters of COPD due to impact on respiratory drive, arrhythmia, respiratory muscle functions, impaired exercise capacity, sleep disorders,and the cardiovascular comorbidities(3), it is not thoroughly investigatedand it is not certainly known if these parameters need extensive correction and this intervention is related with improvement in related outcomes.

This study was undertaken to study to show the distribution of thyroid hormone dysfunction in the setting of exacerbation in patients with COPD. The relation with abnormalities with the several parameters of exacerbation has been investigated.

MATERIAL and METHODS

Subjects and Study Design

From January 2010 to June 2013 105 hospitalized COPD patients were included to this cross-sectional study to evaluate the thyroid hormone dysfunction in the setting of exacerbation in patients with COPD. We excluded 26 patients from the study due to the effect of steroid use on thyroid functions and one for sick euthyroid syndrome with low T4 serum levels.

A complete medical history was obtained at baseline and patients were physically examined. For all patients, demographic data of the index admission, pre-bronchodilator pulmonary function tests (PFTs); comorbidities, the exacerbation history of previous year, the usage of long-term oxygen treatment (LTOT) or noninvasive mechanic ventilator (NIMV), the etiology of worsening symptoms, the Anthonisen's type of infectious exacerbation, C-reactive protein (C-RP), erythrocyte sedimentation rate (ESR), arterial blood gas analysis, hematocrit, hemoglobin were collected from the patients' records and the electronic database of the hospital.

Ethical approval was given by the Gazi University Clinical Research Ethics Committee (30.12.2016/15).

Diagnosis, Definitions and Evaluation Tools

The clinical diagnosis of COPD is obtained according to the Global Initiative for Obstructive Lung Disease (GOLD) Guideline. A patient who has dyspnea, chronic cough or sputum production and a history of exposure to risk factors for the disease with the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms with spirometry is diagnosed as COPD (1).

Pulmonary function tests; were performed with Sensor Medics Vmax20 Spirometer in sitting position while wearing a noseclip. Three full inspiration and forced expiration maneuvers were performed according to the American Thoracic Society and European Respiratory Society standardization of spirometry 2019 update statement. The recorded values were taken from the best of three forced expiratory measurements (9).

Thyroid hormones; including serum levels of TSH, free T_3(f T_3) and free T_4(f T_4) were assessed by Chemiluminescent Competitive Enzyme Immunoassay method.

Anthonisen's Criteria are used to define infectious exacerbations. According to this definition, exacerbation is characterized with at least one of the following three symptoms; increased dyspnea, increased sputum volume and sputum purulence(10,11).There are three type exacerbation. In type I exacerbation (severe) all of the three symptoms;in type II (moderate) two of the three symptoms and in type III (mild) only one of the three symptoms are present (10).

Statistical Analysis

Statistical analyses were performed using the SPSS software demo version 20. All variables were evaluated by using visual (histograms, probability plots) and analytical methods (Kolmogorov Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses for continuous variables were presented as mean± standard deviations or median(min-max)according to the distribution of variables. Categorical variables were given as count and percentage. Parametric tests (Student's t test) were used to compare normally distributed variables; non-parametric tests (Mann - Whitney U test, chi-square test) were conducted for non-normally distributed and ordinal variables. Pearson or Spearman coefficients were usedfor measuring linear correlation between variables. Statistical differences were considered significant with p values lower than 0.05.

RESULTS

We included 105 patients to the study, but 26 individuals were excluded due to the effect of steroid use on thyroid functions and one for sick euthyroid syndrome with low T4 serum levels. The patients were stratified into 2 subsets according to TSH concentrations:Sick euthyroid syndrome and normal euthyroid function. A total of 78 patients evaluated for the study.

Seventy (89,7 %)of the patients were men. The mean age was 68.60±10.43 years. The majority of the patients were ever smokers(88,5%) and the median pack/year was 57.50. The mean FEV_1 was 39.73 ± 18.55. The mean pO_2 was 58.21±12.22. The baseline demographic, clinical, functional and laboratory parameters were summarized in Table 1 and 2.

Table 1. Demographic and clinical data of patient

Age (Mean±SD) years	68.60±10.43
Sex (%)	
Female	8(10.3)
Male	70(89.7)
Body Mass Index (BMI) (kg/m²) (Mean±SD)	25.65±5.47
Smoking Ever	69(88.5)
Cigarette(pack/year) (Median(min-max))	57.50(10-200)
Duration of COPD(years) (Median(min-max))	7(1-28)
The number of comorbidities (Median(min-max))	2(0-7)
Number of patients who had more than 3 comorbidities (%)	24(30.7)
Number of exacerbation in the previous year	1.50(0-8)
Readmission rate in one month after discharge (% of patients)	20(25.6)
Duration of hospitalization in the exacerbation period (day)	11(3-60)
Number of patients who are on LTOT (%)	43(38.7)
Number of patients who are on NIMV (%)	

Table 2. Functional and laboratory parameters of patients

Variables	Mean±SD/Median(Min-Max)
fT_3	2.39±0.603
fT_4	1.15±0.225
TSH	0.94 (0.01-4.20)
FEV_1/FVC ratio	53.15±12.09
FEV_1%	33 (15-99)
FVC%	50 (31-110)
pO_2 (mmHg)	58.21±12.28
pCO_2(mmHg)	44.60±12.66
Hemoglobin gr/dL	13.90±2.13
Hematocrit %	41.02±8.58
C-Reactive Protein (CRP)	11.55 (0-284)
Erythrocyte Sedimentation Rate (ESR)	20 (0-90)

We found a negative correlation between age and TSH, fT_3(respectively p=0,001, r=-0,356; p<0,001, r=-0,355 Table 3). Also there were weak positive correlations between BMI and fT_4; $pO_2$and fT_3(respectively p=0,020, r=0,232; p=0,027, r=0,261) and weak negative between fT_3 and FEV_1, FEV_1/FVC (respectively p=0,008, r=-0,275; p=0,011, r=-0,264). 32 % of patients(n= 25) had normal euthyroid function. 68 % of them(n=53) were sick euthyroid syndrome.Table 4 shows significantly lower age in sick euthyroid syndrome patients compared with patients who have normal thyroid functions(72.92±8.93 vs. and 66.57±10.53 patients with normal thyroid function, p=0,011) Also, we observed significant decrease of both pO_2 and pCO_2 in sick euthyroid syndrome patients(pO_2: 53.35mmHg±10.55 vs. and 61.24mmHg±12.36 patients with normal thyroid function; p=0,022; pCO_2: 39.35mmHg±8.08 vs. and 47,88mmHg±13.96 patients with normal thyroid function; p=0,017). Conversely, FEV_1/FVC was significantly raised in sick euthyroid syndrome patients (57.81±10.84 vs. 51.02±12.14 patients with normal thyroid function; p=0,032)

Table 3. Correlations between thyroid functions and functional / laboratory parameters

	TSH			**fT_4**			**fT_3**		
	n	**Correlation coefficient**	**p**	**n**	**Correlation coefficient**	**p**	**n**	**Correlation coefficient**	**p**
Age	78	**-0,356**	**0,001**	104	0,017	0,866	103	**-0,355**	**<0,001**
Body Mass Index(BMI)	74	0,014	0,907	100	**0,232**	**0,020**	99	-0,108	0,287
Cigarette(pack/year)	70	-0,047	0,702	94	0,071	0,499	93	-0,042	0,692
Duration of COPD(years)	74	0,212	0,069	74	0,212	0,069	99	-0,075	0,462
Comorbidty number	75	0,028	0,811	75	0,028	0,811	99	-0,067	0,510
Number of exacerbation in the previous year	66	0,034	0,784	90	-0,016	0,880	89	0,055	0,611
Duration of hospitalization in the exacerbation period (day)	63	-0,148	0,246	89	0,155	0,148	89	0,137	0,200
FEV_1/FVC	67	-0,197	0,111	93	-0,120	0,253	92	**-0,264**	**0,011**
FEV_1%	67	-0,160	0,196	93	0,067	0,523	92	**-0,275**	**0,008**
FVC%	67	-0,060	0,632	93	0,004	0,969	92	-0,159	0,131
PO_2	52	0,117	0,410	73	-0,011	0,929	72	0,081	0,498
PCO_2	52	-0,019	0,893	73	-0,076	0,524	72	**0,261**	**0,027**

Table 4. The features of patients with normal thyroid function and sick euthyroid syndrome

	Sick euthyroid syndrome	Normal	
	Mean±SD/ Median(Min-Max)	Mean±SD/ Median(Min-Max)	***p***
Age[a]	72.92±8.93	66.57±10.53	**0.011**
Body Mass Index(BMI)[a]	26.46±6.45	25.23±4.92	0.900
Cigarette(pack/year)[b]	52.5(10-116)	60(20-200)	0,767
Duration of COPD(years)[b]	7(1-40)	9(1-28)	0,357
Number of comorbidity[b]	1.5(0-6)	2(0-7)	0,478
Number of exacerbation in the previous year[b]	1(0-4)	2(1-6)	0,797
Duration of hospital stay in admission (day)[b]	10(3-30)	12(3-42)	0,131
Number of patients who had readmission (%)[c]	6(28.6)	15(40.5)	0,362
FEV_1/FVC[a]	57.81±10.84	51.02±12.14	**0,032**
$FEV_1\%$[b]	36(21-69)	29(15-65)	0,068
FEV_1;(ml)	1102±326.12	966.26±375.04	0,071
FVC%[b]	49(31-86)	46(31-88)	0,589
FVC;(ml)	1812±402.26	1785±596.56	0,612
PO_2 [a]	53.35±10.55	61.24±12.36	**0,022**
PCO_2[a]	39.35±8.08	47,88±13.96	**0,017**

a: comparison was performed with t test. b: comparison was done with Mann-Whitney U test. c: Comparison was performed with chi-square test

DISCUSSION

COPD is a systemic disease which can effect on various organ/systems. The relationship between COPD and endocrine system is under evaluation for a few years. In this study, we investigated the NTIS in hospitalized COPD patients.

Relationship between thyroid and lung functions have been investigated. Siafakas et al. investigated the lung functions in hyperthyroid patients before and after treatment and compare them with lung functions of control subjects. They found that maximal lung pressures and lung volumes were reduced during hyperthyroidism as well as they were normalized after treatment (12). The same group also studied the lung function of hypothyroid patients. They found that PImax, PEmax , VC FEV_1, and FVC were increased after treatment of hypothyroidism. In both study there were no difference of FEV_1/FVC between groups.

A few study targeted the lung functions of COPD patients with thyroid dysfunction. Terzano et al. compare lung functions between hypothyroid, euthyroid, hyperthyroid patients with COPD. They found that hypothyroid COPD patients had lower pO_2, MIP and MEP than euthyroid COPD patients. Although not statistically significant, pCO_2 levels were higher in hypothyroid group. They did not found any difference between hyperthyroid and euthyroid group (13). Okutan et al. compare lung functions between euthyroid patients with stable COPD and control subjects. They found all of the lung function tests were negatively correlated with fT_3 except pCO_2 which was positively correlated with fT_3 (14). In the study of Dimopoulou et al., TT_3/TT_4 were positively correlated with pO_2 in severe stable COPD patients (15). They concluded that hypoxemia is important in the peripheral metabolism of thyroid hormones. On the other hand both Banks et al. and Gow et al. did not found any correlation between thyroid hormone levels and arterial blood gas measurements in patients with COPD (16,17).

NTIS can be defined as the abnormalities of thyroid hormone levels in starvation and serious illnesses. The abnormalities includes low T_3 levels or both low T_3 and low T_4 levels especially in more severe diseases. It is believed that NTIS is a compansatory way of the body to spare energy in serious conditions. It is controversial to give thyroid hormone replacement in patients with NTIS. Most of the studies could not show advantage or disadvantage of thyroid hormone replacement in NTIS.

There were two studies considering NTIS in COPD patients. Karadag et al. included 103 patients with COPD (83 patients were in stable state and 20 patients were in acute exacerbation) and 20 control subjects. They found that %20 of patients with stable COPD and %70 of patients with COPD acute exacerbation have NTIS. pO2 was positively correlated with TT_3, pCO2 was negatively correlated with TSH in stable COPD while pO_2 was positively correlated withfT_4 in acute exacerbation period of COPD(6). Yasar et al. included 125 patients with COPD who were admitted to ICU. 61 of the patients had NTIS. They found that patients with NTIS had high risk for prolonged weaning in the ICU setting(5).

We found low pO_2 and pCO_2 in patients with NTIS compared to patients with normal thyroid function. This results are some similarities with the lung functions of patients with hypothyroidism. $pO_2$was low in both hypothyroidism and NTIS. But we found lower pCO_2which was different from hypothyroid COPD patients. Lowering pCO_2 can be the compansation of the body from hypoxic conditions. This point is important at the discussion of giving thyroid hormone replacement in NTIS.

As our study did not aim to explain cause and effect relationship, we could not speculate whether pO_2 was decreased because of NTIS or NTIS occurred because of hypoxemia. In a rat study local deiodinase activity was increased after hypoxic-ischemic injury in neuronal and hepatocyte cell lines which was resulted reduction of T_3(18). Pulmonary deiodinase activity was found in lung cells. The relationship between hypoxia and pulmonary deiodinase activity needs further investigation.

Conflict of interest

No conflict of interest was declared by the authors.

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