Thyroid dysfunction and inflammatory biomarkers in chronic obstructive pulmonary disease: Relation to severity and exacerbation

Amira Shoukry [a,*], Nagwa S. Said [a], M.N. Ayman Abd-Elrahman [a], Tamer Saber [a], M. Amany Fawzy [b], Sally Shalaby [c]

[a] Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
[b] Chest Department, Faculty of Medicine, Zagazig University, Egypt
[c] Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Egypt

Abstract   *Background:* Thyroid dysfunction or non-thyroidal illness syndrome (NTIS) is frequently detected in chronic, systemic diseases. The systemic manifestations of chronic obstructive pulmonary disease (COPD) include a number of endocrine disorders. The severity of hypoxia and airway obstruction in COPD patients might cause alterations in thyroid function.

The aim of this study is to assess serum levels of thyroid hormones and the inflammatory biomarkers; IL-6, TNF-α in COPD patients during stability and acute exacerbation of the disease, and also to assess the relation between severity of COPD and levels of thyroid hormones.

Subjects and methods: Forty stable COPD patients and twenty COPD patients with acute exacerbation were included in this study as patient groups and twenty healthy age-matched non smoker subjects with normal pulmonary function as a control group. The diagnosis of COPD and acute exacerbation of COPD were established according to GOLD (2011) criteria. Stable COPD patients were further subdivided into Mild-to-moderate COPD patient group (FEV1 ⩾ 50% of predicted value, which included 14 patients) and Severe COPD patient group (FEV1 < 50% of predicted value, which included 26 patients). All enrolled patients were subjected to measurements of pulmonary function tests (FEV1%, FVC% and FEV1/FVC ratio), arterial blood gases (ABGs) (PaO_2, $PaCO_2$, pH), serum levels of thyroid hormones (TSH, total T3, total T4, free T3 and free T4) and the inflammatory biomarkers IL-6 and TNF-α on the first day of admission to RICU or first visit to the outpatient clinics.

* Corresponding author. Mobile: +20 01004540265.
E-mail address: amiramedicine@yahoo.com (A. Shoukry).

Results: There was a significant decrease in serum total T3 and free T3 levels in stable COPD patients when compared to control subjects. Also, there was a significant decrease in serum total T3, free T3, TSH levels and TT3/TT4 ratio in the COPD exacerbation patient group when compared to control subjects and when compared to stable COPD patients. There were no statistically significant differences in serum levels of total T4, free T4 between the studied groups. Regarding disease severity, serum total T3, free T3 levels and TT3/TT4 ratio were significantly decreased in severe COPD patients when compared to mild-to-moderate COPD patients. There were significant positive correlations between PaO_2 and both serum total T3 and TT3/TT4 ratio in the stable COPD group. Serum IL-6 and TNF-α levels were significantly increased in both stable and exacerbation phase COPD patient groups when compared to control subjects.

Conclusion: COPD is a systemic disease that may produce significant alterations in serum levels of thyroid hormones, especially in severe COPD patients and during exacerbation phases of COPD where NTIS is more evident. There was a significant decrease in serum total T3 and free T3 levels in stable COPD patients and this decrease was more significantly evident with a superadded significant decrease in serum TSH levels during the exacerbation phase of COPD. The hormonal alterations are especially related to severity of the disease and hypoxemia. Serum IL-6 and TNF-α levels were increased even in stable COPD and this rise is magnified with increased disease severity and during exacerbation phases of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with low grade systemic inflammation that may be responsible for the systemic effects of the disease; malnutrition, muscle wasting, osteoporosis, cardiovascular disease, type II diabetes mellitus, anemia and depression [1]. COPD is no longer considered to affect only the lungs and airways but also the rest of the body. The systemic manifestations of COPD include a number of endocrine disorders such as those involving the pituitary, thyroid, gonads, adrenals and pancreas [2]. The thyroid hormone enhances mitochondrial oxidation, and thus, augments metabolic rate .This effect on metabolic rate is probably responsible for the association between the thyroid hormone and respiratory drive [3]. The terms "Non-thyroidal Illness Syndrome (NTIS)" and "Euthyroid Sick Syndrome (ESS)" have been used to describe alterations in thyroid function tests in critical illness, such as starvation, sepsis, surgery, myocardial infarction, and also in chronic, systemic diseases including chronic heart failure, chronic liver or hematologic diseases, cancer, diabetes, connective tissue diseases and COPD [4]. Proinflammatory cytokines, especially IL-6, IL-1β, TNF-α and IFN-γ have inhibiting effects on peripheral thyroid hormone metabolism [5,6].These mediators may also be involved in the pathogenesis of NTIS [4].

Limited data on the prevalence of thyroid diseases among patients with COPD are available [4,7], yet, several characteristics of patients with COPD could potentially increase their likelihood of developing hypothyroidism and hyperthyroidism [2]. Also the severity of airway obstruction in these patients is associated with impairment of thyroid gland function [8].

The aim of this study is to assess serum levels of thyroid hormones and the inflammatory biomarkers IL-6 and TNF-α in COPD patients during stability and acute exacerbation of the disease, and also to assess the relation between the severity of COPD and levels of thyroid hormones.

Subjects and methods

This cross-sectional prospective study was conducted between October 2011 and February 2013 at Internal medicine, Chest and Medical Biochemistry Departments, Zagazig University Hospitals.

This study comprised 40 stable COPD patients and 20 COPD patients with acute exacerbation as patient groups and 20 healthy non smoker age-matched subjects with normal pulmonary function as a control group.

Stable COPD Patients (had been clinically stable for at least 3 months) were recruited from the outpatient clinics of Chest and Internal Medicine Departments. Patients with acute exacerbation of COPD (had clinical signs of COPD exacerbation as increased dyspnea, increased cough and sputum, wheezing and chest tightness, fever. tachycardia and tachypnea) were admitted to the respiratory intensive care unit (RICU). In both patient groups, all males were ex-smokers, but females were non smokers. The diagnosis and acute exacerbation of COPD were established according to Global Initiative for Chronic Obstructive Lung Disease (GOLD 2011) criteria [9].

Spirometric classification of disease severity in stable COPD patients (Stage I "mild", Stage II "moderate", Stage III "severe" and Stage IV "very severe") was done according to GOLD criteria [9].

Stable COPD patients were further subdivided into Mild-to-moderate COPD patient group (Stage I and Stage II, FEV1 ⩾ 50% of predicted value, $n = 14$) and Severe COPD patient group (Stage III and Stage IV, FEV1 < 50% of predicted value, $n = 26$).

Stable COPD patients had been receiving inhaled bronchodilator therapy in the form of long-acting β2-agonists and/or anticholinergic agents. Severe/very severe COPD patients were on inhaled corticosteroids.

Exclusion criteria

Patients on systemic glucocorticoid therapy or who use drugs known to affect thyroid function such as amiodarone or iodine-containing contrast media. Patients with clinical evidence of thyroid disease (hypo/or hyperthyroidism) or coexistence of other diseases altering thyroid function tests. Pituitary hypothalamic disease, sepsis, malignancy, significant cardiac, renal, hepatic, metabolic or endocrine disturbances were excluded.

All subjects gave written informed consent to participate in the study.

All enrolled individuals were subjected to the following:

1 – Thorough medical history and full clinical examination. Anthropometric measurements were taken and body mass index (BMI) was calculated as weight/height^2 (kg/m^2).
2 – Plain chest X-ray (postero-anterior and lateral views).
3 – Routine laboratory investigations (CBC, liver and kidney functions).
4 – Pulmonary function tests: were done on the first day of admission or in the outpatient clinic for stable COPD patients. Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured with ZAN-100 Flow Handy Π Pulmonary Function Apparatus. patients with FEV1 ⩾ 80% of predicted value were considered mild, those with 50% ⩽ FEV1 < 80% of predicted value were considered moderate, those with 30% ⩽ FEV1 < 50% of predicted value were considered severe and patients with FEV1 < 30% of predicted value were considered very severe [9].
5 – *Arterial blood gases (ABG) analysis:* was done on the first day of admission or in the outpatient clinic for stable COPD patients to check arterial oxygen tension (PaO$_2$), arterial carbon dioxide tension (PaCO$_2$) and arterial pH. Arterial blood samples were drawn while the subjects were breathing room air and analyzed immediately using a blood gas analyzer (ABL-330-Radiometer Copenhagen).
6 – *Thyroid hormones measurement*: serum levels of total triiodothyronine (total T3), Total thyroxine (total T4), free triiodothyronine (free T3), free thyroxine (free T4) and thyroid stimulating hormone (TSH) were determined by using the commercial Roche Elecsys reagent kits (Roche Diagnostica USA), Measurements were performed using the Chemiluminescence method by COBAS E 411 Roche Hitashi Apparatus. The ratio of TT3/TT4 was calculated. (Reference values for thyroid function tests: TSH: 0.27–4.2 μIU/ml; total T3: 0.8–2.0 ng/ml; total T4: 5.1–14.1 μg/dl; free T3: 2.0–4.4 pg/ml; free T4: 0.93–1.7 ng/dl).
7 – *Interleukin 6 (IL6) and Tumor necrosis factor-alpha (TNF-α) measurement:* serum TNF-α was measured by a solid phase sandwich enzyme-linked immunosorbent assay (ELISA) using hTNF-α kit (BioSource International Inc., CA, USA).

Serum IL-6 was measured with enzyme-linked immunosorbent assay (ELISA) kits (Biosource International Inc., CA, USA).

For patients, blood samples were collected at the first day of RICU admission (for COPD exacerbation patients) or in the outpatient clinic (for stable COPD patients). After centrifugation, sera were kept frozen at −80 °C until assayed.

Statistical analysis

Statistical analysis of the results was performed using SPSS software version 16.0 (statistical package for social science, SPSS inc. Chicago, USA). Continuous variables were expressed as means ± standard deviation (SD). Comparison between two sets of patients was performed by unpaired Student's t test, but more than two sets of patients were compared by one-way ANOVA. Categorical variables were expressed as percent, and compared by chi-square (χ^2) test. Correlation coefficient "r" was used to describe the association between serum levels of thyroid hormones and the variables of interest. *p* Values < 0.05 were considered statistically significant.

Results

Demographic characteristics, pulmonary function tests and arterial blood gases analysis of stable and exacerbation period COPD patients and control subjects enrolled in the study are shown in Table 1.

Age, gender and BMI were not found to be statistically different between the studied groups. There was a statistically significant difference in FEV1% of predicted, FVC% of predicted, FEV1/FVC, PaO$_2$ and PaCO$_2$ between stable COPD patients, COPD patients with acute exacerbation and control subjects.

Serum thyroid hormones, IL6 and TNF-α levels of stable and exacerbation period COPD patients and control subjects are shown in Table 2.

Mean serum levels of total T3 and free T3 were significantly lower in stable COPD patients when compared to control subjects ($p = 0.01$, $p = 0.004$, respectively), whereas there were no statistically significant differences in mean serum levels of total T4, free T4 and TSH between the two groups.

In the COPD exacerbation group, mean serum levels of total T3, free T3 and TSH were found to be significantly lower when compared to control subjects ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively), but levels of total T4 and free T4 did not differ significantly between the two groups.

When stable and exacerbation COPD groups were compared, serum levels of total T3, free T3 and TSH were found to be significantly lower in exacerbation COPD patients ($p = 0.001$, $p < 0.001$, $p < 0.001$, respectively), TT3/TT4 ratio was significantly decreased in the COPD exacerbation group when compared to control subjects ($p = 0.02$) and also when compared to stable COPD patients ($p = 0.04$), but did not differ significantly between stable COPD and control groups.

Serum IL-6 and TNF-α levels were significantly higher in both stable ($p = 0.02$, $p = 0.01$, respectively), and exacerbation phase ($p = 0.007$, $p < 0.001$, respectively) COPD patient groups than control subjects.

Table 1 Demographic characteristics, pulmonary function tests and arterial blood gases analysis of the studied groups.

	Stable COPD No. 40		COPD Exacerbation No. 20		Control Subjects No. 20		*p	**p	***p
Age (years)	54.5 ± 7.6		56.8 ± 8.3		53.6 ± 8.2		0.67	0.22	0.28
Sex									
Male	35	87.5%	18	90%	17	85%	0.9	1.0	0.9
Female	5	12.5%	2	10%	3	15%			
BMI (Kg/m^2)	24.8 ± 3.4		25.2 ± 2.5		24.3 ± 1.58		0.44	0.18	0.64
Pulmonary functions									
FEV1 (% predicted)	54.8 ± 14.5		44.6 ± 11.9		94.7 ± 12.6		<0.001	<0.001	0.009
FVC (% predicted)	84.6 ± 23.4		51.9 ± 12.7		97.3 ± 14.5		0.03	<0.001	<0.001
FEV1/FVC	53.5 ± 13.8		43.5 ± 12.7		86.4 ± 6.7		<0.001	<0.001	0.009
Arterial blood gases									
pH	7.4 ± 0.06		7.32 ± 0.08		7.38 ± 0.04		0.19	0.005	<0.001
PaO_2 mmHg	67.2 ± 14.5		51.4 ± 8.2		94.5 ± 6.9		<0.001	<0.001	<0.001
$PaCO_2$ mmHg	45.8 ± 11.6		59.3 ± 12.4		38.3 ± 2.9		0.006	<0.001	<0.001

* *p*-Value is obtained by comparison of Stable COPD patients and control subjects.
** *p*-Value is obtained by comparison of COPD exacerbation patients and control subjects.
*** *p*-Value is obtained by comparison of Stable COPD and COPD exacerbation patients.

Table 2 Thyroid hormones, IL6 and TNF-α of the studied groups.

	Stable COPD No. 40	COPD Exacerbation No. 20	Control Subjects No. 20	*p	**p	***p
TSH (μIU/ml)	1.6 ± 0.9	0.61 ± 0.48	1.18 ± 0.6	0.65	0.002	<0.001
Total T3 (ng/ml)	1.03 ± 0.22	0.78 ± 0.35	1.2 ± 0.26	0.01	<0.001	0.001
Total T4 (μg/dl)	8.58 ± 1.6	8.6 ± 1.4	8.57 ± 1.5	0.98	0.95	0.96
Free T3 (pg/ml)	2.44 ± 0.65	1.82 ± 0.48	2.98 ± 0.68	0.004	<0.001	<0.001
Free T4 (ng/dl)	1.17 ± 0.24	1.28 ± 0.48	1.14 ± 0.32	0.69	0.29	0.34
TT3/TT4 ratio	0.12 ± 0.06	0.09 ± 0.03	0.14 ± 0.09	0.31	0.02	0.04
IL6 (pg/ml)	63.87 ± 59.42	72.57 ± 61.37	29.7 ± 26.2	0.02	0.007	0.59
TNF-a (pg/ml)	11.34 ± 9.82	19.4 ± 16.43	5.33 ± 4.32	0.01	<0.001	0.02

* *p*-Value is obtained by comparison of stable COPD patients and control subjects.
** *p*-Value is obtained by comparison of COPD exacerbation patients and control subjects.
*** *p*-Value is obtained by comparison of stable COPD and COPD exacerbation patients.

Also, there was a significant increase in serum TNF-α level in exacerbation phase COPD patients when compared to stable COPD patient ($p = 0.02$) but the difference was statistically non-significant as regards serum IL-6 level between both groups.

Serum thyroid hormones, IL6 and TNF-α levels of mild-to-moderate and severe stable COPD patients are given in Table 3.

Levels of total T3 and free T3 and TT3/TT4 ratio were significantly lower in severe COPD patients compared to mild-to-moderate COPD patients ($p < 0.001$, $p < 0.001$ and $p = 0.03$, respectively), but the difference was statistically non-significant as regards serum total T4, free T4 and TSH levels between both groups.

Also, there was a significant increase in serum TNF-α level in severe COPD patients when compared to mild-to-moderate COPD patients ($p = 0.006$), but the difference was statistically non-significant as regards serum IL-6 level between both groups.

Correlation tests between serum levels of thyroid hormones (TSH, total T3. total T4 free T3 and free T4) and FEV1% predicted, PaO_2, $PaCO_2$, IL-6 and TNF-α were made in stable and exacerbation phase COPD patients. In the stable COPD group, there was a significant positive correlation between TT3/TT4 ratio and PaO_2 ($r = 0.92$; $p < 0.001$). Similarly serum total T3 levels also showed a significant positive correlation with PaO2 ($r = 0.76$; $p < 0.001$) {Figs. 1 and 2}. No other correlations were found between serum levels of thyroid hormones and these various variables in both stable and exacerbation phase COPD patient groups.

Discussion

The non-thyroidal illness syndrome, also known as euthyroid sick syndrome, describes a condition characterized by abnormal plasma levels of thyroid hormones encountered in patients with a variety of acute or chronic systemic illnesses [10,11]. Several conditions are described, the most important of which is the low T3 syndrome [12], which is characterized by reduced plasma levels of triiodothyronine (T3) due to impaired activity of specific 5′ monodeiodinases converting thyroxine (T4) to T3 in peripheral tissues, with normal or low levels of T4 and either normal or slightly suppressed thyroid-stimulating hormone (TSH) levels [11,13]. The changes in serum thyroid hormone levels in the critically ill patient seem to result from alterations in the peripheral metabolism of the thyroid hormones, in TSH regulation, in the binding of thyroid hormone to transport-proteins and in receptor binding and intracellular uptake.

Table 3 Pulmonary functions, arterial blood gases, thyroid hormones and IL6 and TNF-α of Mild-to-moderate and Severe COPD patients.

	Mild-to-moderate COPD No. 14	Severe COPD No. 26	p-Value
FEV1 (% predicted)	64.72 ± 9.38	45.82 ± 7.63	< 0.001
FEV1/FVC	60.43 ± 8.52	46.53 ± 9.45	< 0.001
PaO_2 mmHg	78.32 ± 6.42	55.85 ± 7.93	< 0.001
$PaCO_2$ mmHg	41.63 ± 4.73	48.92 ± 8.52	0.005
TSH (μIU/ml)	1.8 ± 0.85	1.4 ± 0.95	0.19
Total T3 (ng/ml)	1.2 ± 0.19	0.86 ± 0.25	< 0.001
Total T4 (μg/dl)	8.56 ± 1.5	8.64 ± 1.7	0.88
Free T3 (pg/ml)	2.79 ± 0.45	2.09 ± 0.33	< 0.001
Free T4 (ng/dl)	1.19 ± 0.18	1.15 ± 0.32	0.67
TT3/TT4 ratio	0.14 ± 0.08	0.1 ± 0.03	0.03
IL6 (pg/ml)	58.29 ± 51.64	69.45 ± 67.35	0.59
TNF-α (pg/ml)	5.21 ± 4.19	17.54 ± 15.48	0.006
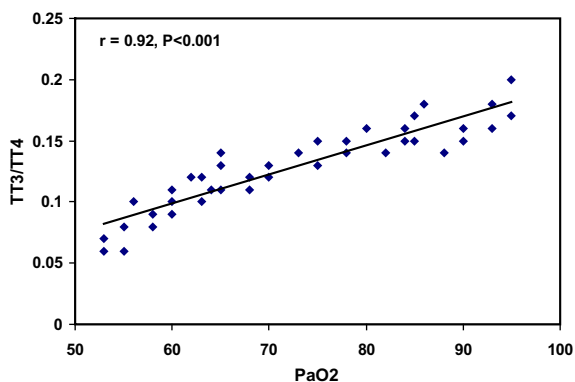
Figure 1 Correlation between PaO_2 and TT3/TT4 ratio in stable COPD group.
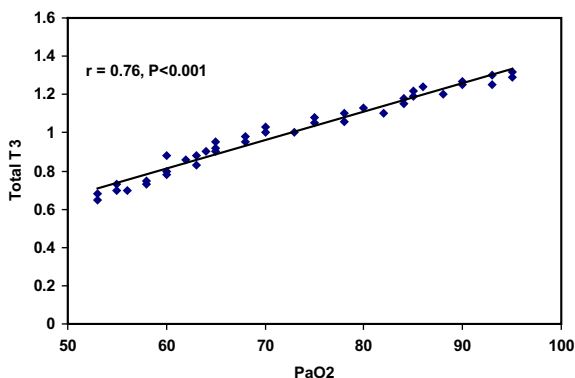
Figure 2 Correlation between PaO_2 and total T3 in stable COPD group.

Medications also have a very important role in these alterations [11].

Systemic response to chronic disease in COPD patients might cause hormonal imbalance which in turn affects the severity of the disease. The severity of hypoxia and airway obstruction in COPD patients is associated with impairment of thyroid gland function and/or alterations in thyroid func-

tion tests [8,14] The presence of thyroid dysfunction may vary according to the phases of COPD.

The present study was performed to assess serum levels of thyroid hormones and the inflammatory biomarkers IL-6, TNF-α in COPD patients during stability and acute exacerbation of the disease, and the relation between severity of COPD and levels of thyroid hormones.

In the present study serum levels of total T3, free T3 and TSH were significantly decreased in the COPD exacerbation group when compared to control subjects ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively),and also when compared to stable COPD patients ($p = 0.001$, $p < 0.001$, $p < 0.001$, respectively), also serum levels of total T3 and free T3 were significantly decreased in stable COPD patients when compared to control subjects ($p = 0.01$, $p = 0.004$, respectively) whereas TSH levels did not differ significantly between the two groups.

In our study the mean serum levels of thyroid hormones in COPD patients were within normal limits, but mean serum total T3 and free T3 levels were slightly decreased below the lower limits of reference values in the COPD exacerbation group.

Also, in our study, regarding disease severity, there was a statistically significant decrease of serum total T3 and free T3 levels ($p < 0.001$) in the severe COPD patient group than that in the mild-to-moderate COPD patient group, but the difference was statistically non significant as regards serum total T4, free T4 and TSH levels between both groups.

Our results are in consistence with Karadag et al. [7] who found that total T3 and free T3 levels were lower in the COPD group than the control and the difference was more significant for free T3. Besides, there was significant difference in TSH, total T3, free T3 levels and TT3/TT4 ratio between exacerbation, stable, and control groups. They also revealed that hormonal changes during follow-up after exacerbation period seemed parallel to changes in PaO_2 and $PaCO_2$ and hormonal alterations improved as the arterial blood gas values improved during the recovery period of exacerbation. The increase in TSH levels when hypoxia was improved and the disease become stable denotes delayed pituitary response to TRH secondary to hypoxia.

When they evaluated the relation between pulmonary function tests and thyroid hormones, they found out that serum total T3 was lower in severe COPD compared to moderate COPD. Moreover, TSH, total T3, free T3 levels were lower

in patients with severe hypoxemia ($PaO_2 < 60$ mmHg) when compared to patients with milder hypoxia. They concluded that the decrease in total T3, free T3 while T4 remains unchanged in patients with severe airflow obstruction and patients in the exacerbation period with severe hypoxemia indicating that hypoxemia and severity of COPD affect peripheral metabolism of thyroid hormones.

Madhuri et al. [15] found that mean level of free T3 was significantly lower among patients with acute exacerbation of COPD due to having critical illness, and suggested that the existence of non-thyroidal illness syndrome among those patients is more prevalent as compared to stable COPD and healthy controls.

Akbas et al. [16] also found low free T3 and TSH levels in critically ill COPD patients which increased when they recovered from critical illness.

Dimopoulou et al. [4] have demonstrated that in stable COPD patients, baseline thyroid hormones are within normal limits; however, in severe COPD, a certain degree of thyroid dysfunction was evident.

Semple et al. [17] measured serum total T3 and total T4 levels in 16 patients with stable COPD having a mean FEV1 below 40% of predicted and did not find any difference among hypercapnics, normocapnics and controls.

The same investigators [18] performed thyroid stimulation tests in eight hypoxic, stable patients with severe COPD in a subsequent study and found that their basal thyroid hormone levels were normal, but two patients showed a delayed response to TRH. They concluded that hypoxemia causes a minor change in the hypothalamic–pituitary–thyroid axis at the hypothalamic–pituitary (central) level. However, the study group is too small to generalize these findings.

Okutan et al. [19] found that thyroid hormone concentrations were within normal limits in all COPD cases. But in contrary to our results, they found that free T3 concentration was higher in stable COPD patients than the control group,.

Contrary to our results Uzun et al. [20] studied thyroid function tests only in patients with acute exacerbation COPD and found significant difference according to the percentage of cases with TSH less than minimum values and free T3 higher than maximum values between COPD and control groups. They demonstrated that both clinical and subclinical hyperthyroidism were higher in patients with COPD exacerbations than cases without COPD. They suggest that severe airway obstruction and excessive respiratory muscle load affect thyroid hormone levels in patients with COPD.

Coşkun et al. [14] reported no significant difference in TSH and free T3 between the stable COPD group and healthy controls but when classified according to severity, significant differences were observed between mild, moderate and severe stable COPD patients with respect to free T3. They also found that free T4 levels were significantly higher in the stable COPD group than healthy control whereas in our study there were no statistically significant differences in Mean serum levels of total T4, free T4 between the studied groups.

TT3/TT4 ratio has been proven to be a useful tool in studying the peripheral conversion of thyroxine to the metabolically active triiodothyronine in various disease states. In the present study TT3/TT4 ratio was significantly decreased in the COPD exacerbation group when compared to control subjects ($p = 0.02$) and also when compared to stable COPD patients ($p = 0.04$),

also TT3/TT4 ratio was significantly decreased in the severe COPD patient group than that in the mild-to-moderate COPD patient group ($p = 0.03$), this is supported by Karadag et al. [7] who found similar results in their study. Our results revealed a significant positive correlation between TT3/TT4 ratio and PaO_2 in stable COPD patients ($r = 0.92$; $p < 0.001$) which is supported by Dimopoulou et al. [4] who found the same correlation but only in the severe stable COPD group.

In consistence with Karadag et al. [7], our results revealed a significant positive correlation between serum total T3 levels and PaO_2 in stable COPD patients ($r = 0.76$; $p < 0.001$).

In our study, with the exception of the previous correlations, no other correlations were found between serum levels of thyroid hormones (TSH, total T3. total T4 free T3 and free T4) and FEV1% predicted, PaO_2, $PaCO_2$, in both stable and exacerbation phase COPD patient groups which is supported by many previous studies [15,20].

Gow et al. [8] investigated thyroid function in 20 patients with exacerbation, having severe COPD (highest FEV1 40% of predicted). They did not find any correlation between arterial blood gas measurement and thyroid hormone concentrations in patients with COPD. Also, Banks and Cooper. [21] measured thyroid hormones of 25 COPD patients with various degrees of hypoxemia and hypercapnia and they found no relation between thyroid hormones and pH, PaO_2 or $PaCO_2$, these results match our study results.

Whereas, contrary to our results, Coşkun et al. [14] found a negative correlation between FEV1 and free T4 in the stable COPD group, and Okutan et al [19] demonstrated that there was a negative correlation between pulmonary function tests, PaO_2 and free T3 in COPD patients.

Karadag et al. [7] found a positive correlation between PaO_2 and free T4 in the COPD exacerbation group and a negative or inverse correlation between $PaCO_2$ and TSH in stable COPD patients that is why they consider hypercapnia may play a role in thyroid dysfunction besides hypoxemia.

Several previous studies suggested that the underlying factors for alterations in thyroid hormones in COPD are hypoxemia, hypercapnia and severe airway obstruction [7,18,19].

However, the alterations in thyroid hormones in COPD might also be related to factors other than hypoxia and hypercapnia. TNF-α was demonstrated to be a mediator of several diseases leading to hypothalamo–pituitary dysfunction. Several previous studies investigated the effects of administering TNF-α and IL-1β to experimental animals and humans and confirmed a possible role for them in the pathogenesis of NTIS, and lowering of serum T3 [6,22,23].

Both cytokines also induce IL-6 production [4], which is known to exert regulatory effects upon many endocrine systems, either independently, or acting with other cytokines. Moreover elevated serum IL-6 concentrations are related to alterations in circulating thyroid hormones in non-thyroidal illness (NTI) secondary to various medical conditions [24,25].

Stouthard et al. [25] demonstrated that IV administration of IL-6 induced an acute decrease in T3 and TSH. However, during prolonged sc administration of IL-6, these effects seemed to be transient. After 1 week of daily administration of IL-6, thyroid hormones returned to baseline values. Therefore they concluded that acute elevations of IL-6 may at least in part mediate the development of the NTIS, whereas factors other than IL-6 contribute to the persistence

of changes in thyroid hormone concentrations during chronic illness.

In the present study serum IL-6 and TNF-α concentrations were significantly higher in both stable ($p = 0.02$, $p = 0.01$, respectively), and exacerbation phase ($p = 0.007$, $p < 0.001$, respectively) COPD patient groups than control subjects, no correlations were found between Serum levels of thyroid hormones and TNF-α or IL-6 in both groups. Our results are in agreement with Karadag et al. [7], But on the contrary, they found that IL-6 was correlated with total T3 in the stable COPD group.

Increased levels of IL-6 and TNF-α and other several pro-inflammatory cytokines have been reported in the lungs and circulation of patients with COPD in many studies [26–28].

Our study demonstrated that COPD is a systemic disease that leads to alterations in serum levels of thyroid hormones especially in severe COPD patients and during exacerbation phases of COPD where NTIS is more evident; The pattern of hormonal changes suggests that hypoxemia acts not only at the central level of the hypothalamic–pituitary–thyroid axis, but also interferes with the peripheral metabolism and turn-over of thyroid hormones.

Considerable controversy still exists on whether NTIS in COPD or other critical illness is a useful compensatory protective mechanism to counteract excessive catabolism and protein breakdown and represents a physiologic adaptive response to systemic illness by which it lowers tissue energy requirements; or conversely is an unfavorable maladaptive state which induces a damaging hypothyroid state at tissue level [7,29].

It is not clear if these patients with NTIS are biochemically euthyroid or hypothyroid. A normal serum TSH in most NTIS patients with low T3 may indicate that they are metabolically euthyroid. On the other hand, several studies demonstrate abnormalities in the synthesis, secretion, glycosylation, regulation and/or effectiveness of TSH in NTI [13].

Moreover; other studies reported that the transient increase in serum TSH during recovery from NTI suggests that TSH is suppressed during the illness [30,31].

Overall, although patients with NTI may be euthyroid because of short duration of NTIS, those with a prolonged NTI may be biochemically hypothyroid and may benefit from thyroid hormone replacement therapy [13]. However, studies evaluating T3 replacement treatment in NTIS yielded either no benefit, or appreciable improvement [32–34].

Lastly, as there are significant alterations of thyroid hormones in COPD patients, they should not be evaluated for thyroid disease by assessment of thyroid functions during acute exacerbation of COPD, and thyroid function alterations during stable phase of the disease should be considered cautiously, since thyroid function abnormalities in non-thyroidal illness may mimic or mask biochemical abnormalities observed in true thyroid disease.

Conclusion

There were significant alterations in serum levels of thyroid hormones in COPD especially in severe COPD patients and during exacerbation phases of COPD where NTIS is more evident. There was a significant decrease in serum total T3 and free T3 levels in stable COPD patients and this decrease was more significantly evident with a superadded significant decrease in serum TSH levels during the exacerbation phase of COPD. The hormonal alterations are especially related to severity of the disease and hypoxemia. Serum IL-6 and TNF-α levels were increased even in stable COPD and this rise is magnified with increased disease severity and during exacerbation phases of COPD.

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