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RESEARCH ARTICLE

Evaluation of Thyroid dysfunction in patients with chronic obstructive pulmonary disease in medical intensive care unit of Zagazig University Hospitals

Osama A. Khalil [1], Monkez M. Yousif [1], Ayman M.E.M. Sadek [1], Ashraf Khalifa [1], Ghada M. Samir[1], M.S. Fawzi [2]

1. Internal Medicine Departments, Zagazig University, Egypt
2. Medical Biochemistry Departments, Zagazig University, Egypt

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Corresponding Author

Osama A. Khalil

Abstract

Background: Thyroid abnormalities in some studies are frequent among patients with chronic obstructive pulmonary disease (COPD) admitted to intensive care unit with acute exacerbation especially with more severe cases. Other studies reported no significant thyroid dysfunction in those patients. Mortality was increased in COPD patients with exacerbation who got thyroid abnormalities. ***Aim of the work:*** To assess; the frequency and different patterns of thyroid dysfunction, risk factors and its correlation with thyroid abnormalities, and the impact of thyroid dysfunction on short term outcome of COPD patients with acute exacerbation admitted to Zagazig University Hospitals medical intensive care unit (MICU). ***Patients and Methods:*** This cohort study had been included 48 COPD patients with acute exacerbation determined by the Institutional Review Board (IRB); who were admitted to the MICU of Zagazig University during the period of 6 months; with exclusion of patients with known thyroid disease or under thyroxin therapy. All patients were subjected to thorough history and complete clinical examination, assessment of severity score system in the ICU unit using APACHE II score, routine laboratory investigations including complete blood count, liver function tests and kidney function tests**,** arterial blood gases (ABG) and Specific investigations that include assay of serum level of Thyroid Stimulating Hormone (TSH), free T_3 (FT_3), and free T_4 (FT_4). According to thyroid dysfunction, patients were classified into two groups; group I included patients with thyroid abnormalities & group II included patients with euthyroid function. Patients were followed and observed during their hospital stay until discharge (2 weeks). ***Results:*** The frequency of thyroid dysfunction in patients with COPD admitted with acute exacerbation was 25%**.** All patients with thyroid dysfunction in the study population had decreased FT_3 level with normal FT_4 and TSH (Sick euthyroid syndrome). Sick euthyroid group was characterized by significant increase in APACHE II score than the euthyroid group. FT_3 and FT_4 were negatively correlated with APACHE II score and partial pressure of carbon dioxide ($PaCO_2$) while FT_3 was positively correlated with partial pressure arterial oxygen (PaO_2). In univariate and multivariate logistic regression analysis regarding the potential predictors of thyroid dysfunction; male sex, increased age, prolonged duration of the disease, increased hematocrit, increased blood urea, increased $PaCO_2$, increased bicarbonate (HCO_3) and decreased PaO_2 were predictors of thyroid dysfunction. Relative risk of thyroid dysfunction was increased with; $PaO_2 < 60$ mmHg, $PaCO_2 > 45$ mmHg, $HCO_3 > 24$ mEq/L, APACHE II score > 14; by 6.43 fold, 2.75 fold, 1.2 fold, 1.7 fold respectively. In univariate logistic regression analysis regarding the potential predictors of mortality; APACHE II score was the

most independent predictors of mortality in sick euthyroid group. Relative risk of mortality in sick euthyroid group was increased by 2.1 fold than euthyroid group. ***Conclusion:*** Thyroid abnormalities are frequent among COPD patients with acute exacerbation admitted to MICU of Zagazig University Hospitals. Sick euthyroid syndrome was solely identified in those patients especially with more severe cases. Mortality was significantly increased in COPD patients with acute exacerbation who got thyroid abnormalities. Further studies are needed to assess the benefit from thyroid hormone replacement therapy on decreasing mortality in COPD patients with acute exacerbation.

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INTRODUCTION

COPD is characterized by significant chronic inflammation not only in the pulmonary compartment, but also in systemic circulation and this disorder is associated with clinically significant systemic alterations in biochemistry and organ function. [(1)]

Abnormalities in thyroid hormone regulation in acute exacerbation of COPD are encountered frequently in non-thyroidal diseases. Low circulating levels of thyroid hormones, low or normal TSH, diminished TSH pulsatility, and implied presence of central hypothyroidism characterize this syndrome. [(2)] Karadag et al., found increased T_4 levels [(3)], while Okutan et al., reported increased T_3 levels[(4)],

and Coskun et al., found that T_3, T_4, and TSH levels were changed[(5)]. Karadag et al., demonstrated that T_3 levels were lower, but they did not evaluate the relations among other biochemical analysis out of arterial blood gases [(3)].

Only the study by Dimopoulou et al., reported that there was no difference in thyroid hormone levels in COPD patients compared to a healthy control group. [(6)]

Several factors such as hypoxemia, exacerbation, drugs, malnutrition may lead to endocrinological changes in COPD. [(1)]

Alterations in thyroid function tests are common 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. [(6)]

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. Non-thyroidal illness syndrome or euthyroid sick syndrome is observed in wide variety of patients in the intensive care unit. [(2)]

NTIS is an adaptive process that promotes survival during life-threaten illnesses by reducing metabolic rate and energy cost. [(7)] 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. Multiple, complex, usually reversible, and incompletely understood mechanisms are involved in these abnormalities such as disturbances in the hypothalamo–pituitary–thyroid axis, thyroid hormone binding to serum proteins, tissue uptake of thyroid hormones, and/or thyroid hormone metabolism. [(8)]

Evaluation of these abnormalities is necessary for diagnosis of thyroid disease since thyroid function abnormalities in NTIS may mimic or mask biochemical abnormalities observed in true thyroid disease. Besides, the severity and nature of these alterations may be a prognostic indicator for the underlying disease. So, we performed this study to assess; the frequency and different patterns of thyroid dysfunction, risk factors and its correlation with thyroid abnormalities, and the impact of thyroid dysfunction on short term outcome of COPD patients with acute exacerbation admitted to Zagazig University Hospitals MICU.

Patients and Methods

This Observational cohort study had been carried out in the MICU of Internal Medicine and Medical Biochemistry Departments, Zagazig University during the period from April 2015 to October 2015.

Patients:

The present study included a total number of 48 patients with acute exacerbation of COPD who are admitted to the MICU during 6 months and this number determined by (IRB). They were diagnosed as COPD according to GOLD [9] in any individual over the age of 40 by the following: 1- Dyspnea that is progressive, worse with exercise and persistent; 2- Chronic cough; 3- History of exposure to risk factors like tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals; 4- Family history of COPD.

Assess Risk of Exacerbation: defined as an acute event characterized by a worsening of the patients respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. The best predictor of having frequent exacerbations (2 or more per year) is a history of previous treated events. The risk of exacerbations also increases as airflow limitation worsens. Hospitalization for a COPD exacerbation is associated with a poor prognosis with increased risk of death. [9] ABG may show low oxygen and/or high carbon dioxide with respiratory acidosis if pH is also decreased (pH below 7.3 is a sign of acute respiratory compromise). [10]

According to results of thyroid function tests 12 of them were grouped as COPD with thyroid dysfunction (group I) while the other 36 patients were grouped as euthyroid COPD control group (group II).

Inclusion criteria: Patients with COPD exacerbation aged ≥ 40 years old of both sex who accept participation in the study.

Exclusion criteria: Patients with previous history of thyroid dysfunction or under treatment, patients with missed data or refused to share, any autoimmune disease, patients on medications which can affect the thyroid hormone levels (thyroxine, glucocorticoids, amiodarone, heparin, oral anticoagulants, contraceptive pills, interferon and lithium) and hormone replacement therapy, patients with concomitant infection, cerebrovascular accident or any form of inflammation other than acute coronary syndrome, and patients with known renal or liver impairment.

Ethical Clearance: Proposal acceptance was obtained from the IRB of the Faculty of Medicine; Zagazig University. Written consents were obtained from the patients with COPD who participated in the study or his relative before assessing thyroid dysfunction.

Methods:

All patients of this study were subjected to the following:

I. **Thorough clinical history and physical examination including:** *A) Full history* of present illness and past history of previous hospital admission and any medical disorder with particular attention to hypertension, diabetes mellitus, cardio vascular disease, dyslipidemia, thyroid disorders and admission to chest hospital. *B) Full General Examination w*ith special attention to blood pressure measurement after patient admission, pulse examination, temperature and respiratory rate. *C) Chest examination in addition to examination of different systems of the body.*

II. **Routine laboratory investigations including:** *A)* Compelet blood picture (by automated blood counter) *B)* Liver function tests; serum bilirubin (total and direct), serum albumin, serum alanine transferees and aspartate transferees measured by kinetic method [11] *C)* Renal function tests; serum creatinine and blood urea by colorimetric method [12] *D)* Bleeding profile; INR, Prothrombine time (PT) and Partial Thromboplastin Time (PTT) *E)* Lipide profile (LDL, total cholesterol, serum triglycerides) *F)* Random blood glucose level *G)* Serum uric acid *H)* ABG *I)* Serum electrolytes (Na, K) according to standard techniques.

III. **Other routine investigations including:** ECG, **c**hest imaging, and any additional investigation as needed during staying in ICU.

IV. **Severity assessment:** This was done by using the most commonly scoring systems in ICU APACHE II SCORE (Acute Physiology and Chronic Health Evaluation). [13]

V. **Specific investigations**: Estimation of serum level of FT_4, FT_3, and TSH within 48 hours after admission by ELISA. [14]

VI. **Collection of blood samples:** 10 ml pf peripheral venous blood were taken from each subject under complete aseptic conditions and after overnight fast, the venous blood samples were collected and divided into 3 portions:-

- 5ml left for 30 minutes for spontaneous clotting then centrifuged at 3000 rpm for 5 minutes. Samples were separated and divided into 3 tubes for measurement of serum creatinine, serum albumin, and serum bilirubin, Complete blood count, serum uric acid, blood sugar assessment.
- 2ml collected on 3.8% tri sodium citrate anticoagulant in a 9:1 ratio, which is centrifuged to produce platelet poor plasma. Complete thromboplastin (typically from rabbit brain) is then measured automatically by electromechanical device to measure coagulation Profile (PT-PTT-INR).
- 3 ml of peripheral venous blood were taken from each subject left for 30 minutes for spontaneous clotting then centrifuged at 3000 rpm for 5 minutes obtain serum and stored at -70^0 c until the time of assessment of thyroid function.

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 15.0 for windows (SPSS Inc., Chicago, IL, USA) & Med Calc 13 for windows (MedCalc Software bvba). Continuous Quantitative variables e.g. age were expressed as

the mean ± SD & median (range), and categorical Qualitative variables were expressed as an absolute frequencies "number" & relative frequencies (percentage). Continuous data were checked for normality by using Kolmogorov-Smirnov test. Independent Student t test was used to compare two groups of normally distributed data & Mann-Whitney U (MW) test for two groups of non-normally distributed data. Categorical data were compared using the Chi-square ($\chi 2$) test. Spearman's rank correlation coefficient was done between thyroid hormonal profile and selected study parameters. We consider (+) sign as indication for direct correlation i.e. increase frequency of independent lead to increase frequency of dependent & (-) sign as indication for inverse correlation i.e. increase frequency of independent lead to decrease frequency of dependent, also we consider values near to 1 as strong correlation & values near 0 as weak correlation. A Univariate Logistic Regression (Enter method) analysis was used to estimate the Odds Ratio with the dependent variable being the thyroid dysfunction. All tests were two sided with $p < 0.05$ was considered statistically significant (S), $p < 0.005$ was considered highly statistically significant (HS), and $p > 0.05$ was considered none statistically significant (NS). [15]

Results

The frequency of thyroid dysfunction in patients with COPD admitted with acute exacerbation was 25%**.** All patients with thyroid dysfunction in the study population had decreased FT_3 level with normal FT_4 and TSH (Sick euthyroid syndrome).

Table 1 shows; demographic, clinical and routine Laboratory findings of the study population; and with comparison of these data between thyroid dysfunction group (group I) and euthyroid function group (group II) in ***table 2;*** it reveals that non-significant differences between groups as regarding demographic data. Patients with thyroid dysfunction had statistically significant higher level of APACHE II score, blood urea, $PaCO_2$ and HCO3 with statistically significant lower level of PaO_2 compared with patients with euthyroid function. Regarding other clinical and laboratory variables there were no statistically significant difference between the two groups.

Table 3 displays the mean values ± SD of thyroid functions of the study population. With comparison of these data between groups in ***table 4***; it shows that thyroid dysfunction group had statistically significant lower FT_3 and FT_4 levels compared with euthyroid function group but still FT_4 level in the thyroid dysfunction group within the normal level while there was no significant difference in serum TSH level in the studied two groups.

There was statistically significant positive correlation ***(table 5)*** between FT_3 level and PaO2. Significant negative correlation was found between FT_3 and APACH II, HCO_3 and $PaCO_2$. Also, significant negative correlation was found between FT_4 and APACHE II, PaO_2 and $PaCO_2$.

By calculating univariate and multivariate logistic regression analysis regarding the potential predictors of thyroid dysfunction ***(table 6 and 7)***; male sex, increased age, prolonged duration of disease, increased hematocrit, increased blood urea, decreased PaO_2, increased $PaCO_2$ and decreased HCO_3 were predictors of thyroid dysfunction. In multivariate logistic regression analysis regarding the potential predictors of thyroid dysfunction; high blood urea was the single independent predictor of thyroid dysfunction.

The decrease of PaO2 below 60 mmHg increased the relative risk of thyroid dysfunction by 6.43 folds in acute exacerbation COPD patients than those with PaO2 above 60 mmHg, while the increase of PaCO2 above 45 mmHg increased the relative risk of thyroid dysfunction by 2.75 folds in acute exacerbation COPD patients than those with PaCO2 less than 45 mmHg. The increase of HCO3 above 24 mEq/L increased the relative risk of thyroid dysfunction by 1.2 folds in acute exacerbation COPD patients than those with HCO3 less than 24 mEq/L, also APACH II more than 14 increased the relative risk of thyroid dysfunction by 1.7 folds in acute exacerbation COPD patients than those with APACH II score less than 14 ***(table 8)***.

In univariate logistic regression regarding the potential predictors of mortality ***(table 9)***; APACHE II score is the most independent predictor of Mortality in sick euthyroid group followed by smoking and $PaCO_2$.

Acute exacerbation of COPD with thyroid dysfunction increased relative risk of mortality by 2.1 folds than those COPD with euthyroid function ***(table 10)***.

Table (1): Mean values ± SD of Demographic, Clinical and Routine Laboratory findings of study population

Item		COPD patients (N=48)	
		No	%
Age (years)	≤ 65 years	25	52.1
	> 65 years	23	47.9
Sex	Male	37	77.1
	Female	11	22.9
Smoking	Non smoker	10	20.8

	Smoker	27	56.3
	Ex- Smoker	11	22.9
		Mean ± SD	
Duration of disease (years)		27.03 ± 9.52	
Systolic Blood Pressure (mmHg)		130.31 ± 29.57	
Diastolic Blood Pressure (mmHg)		77.81 ± 12.33	
Heart Rate (beat/min)		78.31 ± 11.29	
Respiratory Rate (breath/min)		46.5 ± 10.4	
APACH II score		21.71 ± 10.03	
Hematocrit (%)		43.24 ± 1.76	
Hemoglobin level (g/dl)		13.35 ± 1.17	
Urea (mg/dl)		16.65 ± 1.54	
Creatinine (mg/dl)		1.04 ± 0.24	
Serum AST (IU/L)		32.81 ± 14.16	
Serum ALT (IU/L)		48.79 ± 12.97	
PaO_2 (mmHg)		56.76 ± 10.05	
$PaCO_2$ (mmHg)		51.15 ± 11.95	
HCO_3 (mEq/L)		29.74 ± 5.40	
PH		7.38 ± 0.06	
Na (mEq/L)		143.61 ± 3.83	
K (mEq/L)		3.11 ± 0.61	

Table (2): Comparison of the mean values ± SD of Demographic, Clinical and Routine Laboratory findings between Thyroid dysfunction and Euthyroid function groups

Item		**Thyroid dysfunction (n=12) Group I**		**Euthyroid function (n=36) Group II**		**Test**	***P***
		No	**%**	**No**	**%**	**χ^2**	
Sex	Male	9	75	28	77.8	0.039	0.843 (NS)
	Female	3	25	8	22.2		
Smoking	Non smoker	2	16.7	8	22.2	0.176	0.916 (NS)
	Smoker	7	58.3	20	55.6		
	Ex-Smoker	3	25	8	22.2		
						t	
Age (years) Mean ± SD		64.28 ± 8.10		62.67 ± 7.97		0.599	0.552 (NS)
Duration of disease (years) Mean ± SD		24.83 ± 10.15		27.47 ± 9.45		0.822	0.415 (NS)
Systolic Blood Pressure (mmHg) Mean ± SD		132.08 ± 27.25		129.72 ± 30.65		-0.237	0.814 (NS)
Diastolic Blood Pressure (mmHg) Mean ± SD		78.75 ± 10.02		77.5 ± 13.12		-0.301	0.765 (NS)
Heart Rate (beat/min) Mean ± SD		77.25 ± 12.59		78.67 ± 10.99		0.373	0.711 (NS)
Respiratory Rate (breath/min) Mean ± SD		48.92 ± 11.35		45.69 ± 10.10		-0.928	0.358 (NS)
APACH II score Mean ± SD		35.17 ± 5.68		17.22 ± 6.50		-8.517	**<0.001 (HS)**
Haematocrit (%) Mean ± SD		43.46 ± 1.68		43.17 ± 1.81		-0.495	0.623 (NS)
Hemoglobin level (g/dl) Mean ± SD		13.55 ± 1.57		13.28 ± 1.03		-0.704	0.485 (NS)

Blood Urea (mg/dl) Mean ± SD	17.43 ± 1.26	16.39 ± 1.55	-2.086	**0.043 (S)**
$PaCO_2$ (mmHg) Mean ± SD	66.71 ± 6.47	44.63 ± 7.29	-9.321	**<0.001 (HS)**
PH Mean ± SD	7.36 ± 0.01	7.38 ± 0.07	1.213	0.232 (NS)
K (mEq/L) Mean ± SD	3.1 ± 0.27	3.11 ± 0.7	0.077	0.939 (NS)
			MW	
Creatinine (mg/dl) Mean ± SD	1.12 ± 0.34	1.02 ± 0.19	-0.990	0.322 (NS)
Serum AST (IU/L) Mean ± SD	34 ± 12.95	32.42 ± 14.69	-0.597	0.550 (NS)
Serum ALT (IU/L) Mean ± SD	53.25 ± 10.82	47.31 ± 13.41	-1.680	0.093 (NS)
PaO_2 (mmHg) Mean ± SD	47.23 ± 20.66	60.61 ± 8.05	-4.733	**<0.001 (HS)**
HCO_3 (mmHg) Mean ± SD	32.97 ± 4.33	28.67 ± 5.34	-2.310	**0.021 (S)**
Na (mEq/L) Mean ± SD	143.26 ± 2.98	143.73 ± 4.11	-0.861	0.389 (NS)

t: independent Student t-test. χ^2: Chi-square test. **MW:** Mann Whitney U test.

Table (3): Mean values ± SD of Specific Laboratory findings of study population

Item	**COPD patients (N=48)**	
Thyroid Functions	**Mean ± SD**	**Median (Range)**
Free T_4 (Pg/ml)	0.614 ± 0.177	0.621 (0.315 – 1.029)
Free T_3 (pg/ml)	0.794 ± 0.466	0.946 (0.046 – 2.215)
TSH (µIU /ml)	0.627 ± 0.196	0.639 (0.058 – 1.029)

Table (4): Comparison of the mean values ± SD of thyroid hormone profile between Thyroid dysfunction and Euthyroid function groups.

Thyroid hormone profile	**Thyroid dysfunction (n=12) Group I**	**Euthyroid function (n=36) Group II**	**Test**	***p***
Free T_4 Mean ± SD	0.416 ± 0.031	0.685 ± 0.153	**MW** -4.733	**<0.001 (HS)**
Free T_3 Mean ± SD	0.081 ± 0.015	1.031 ± 0.245	**t** -5.143	**<0.001 (HS)**
TSH Mean ± SD	0.575 ± 0.125	0.644 ± 0.213	**MW** -1.691	0.091 (NS)

t: independent Student t-test. **MW:** Mann Whitney U test.

Table (5): Correlation Coefficient between Thyroid Functions and different Demographic, Clinical and Routine Laboratory Data.

Item	**FT_4**		**FT_3**		**TSH**	
	R	**P**	**R**	**P**	**R**	**p**
Age (years)	+ 0.187	0.203 (NS)	+ 0.235	0.108 (NS)	+ 0.164	0.265 (NS)
Respiratory Rate (/min)	- 0.193	0.189 (NS)	- 0.039	0.792 (NS)	- 0.087	0.555 (NS)
APACH II score	- 0.532	**<0.001 (HS)**	- 0.555	**<0.001 (HS)**	- 0.093	0.529 (NS)

Haematocrit (%)	+ 0.089	0.546 (NS)	- 0.114	0.440 (NS)	- 0.051	0.730 (NS)
PaO_2 (mmHg)	- 0.442	**0.002 (HS)**	+ 0.517	**0.001 (HS)**	+ 0.107	0.334 (NS)
$PaCO_2$ (mmHg)	- 0.456	**0.001 (HS)**	- 0.532	**<0.001 (HS)**	- 0.227	0.120 (NS)
HCO_3 (mmHg)	-0.180	0.221 (NS)	- 0.293	**0.043 (S)**	- 0.074	0.618 (NS)
PH	+ 0.039	0.794 (NS)	+ 0.150	0.309 (NS)	+ 0.087	0.558 (NS)
Na (mEq/L)	+ 0.060	0.683 (NS)	- 0.018	0.906 (NS)	- 0.114	0.442 (NS)
K (mEq/L)	+ 0.048	0.747 (NS)	- 0.011	0.938 (NS)	+ 0.005	0.975 (NS)

Table (6): Univariate logistic regression of potential predictors of thyroid dysfunction in COPD patients.

Variables	β	SE	OR	95% CI	*p*
Age (years)	**- 0.017**	**0.005**	**0.983**	**(0.973 – 0.993)**	**0.001 (HS)**
Sex (male)	**- 1.135**	**0.383**	**0.321**	**(0.152 – 0.681)**	**0.003 (HS)**
Smoking	**- 0.981**	**0.677**	**0.375**	**(0.099 – 1.414)**	0.147 (NS)
Duration of disease (years)	**- 0.041**	**0.012**	**0.960**	**(0.937 – 0.984)**	**0.001 (HS)**
APACH II score	**- 0.015**	**0.012**	**0.985**	**(0.962 – 1.010)**	0.235 (NS)
Hematocrit (%)	**- 0.025**	**0.008**	**0.975**	**(0.961 – 0.990)**	**0.001 (HS)**
PaO_2 (mmHg)	**- 0.019**	**0.006**	**0.981**	**(0.969 – 0.993)**	**0.002 (HS)**
$PaCO_2$ (mmHg)	**- 0.013**	**0.006**	**0.987**	**(0.975 – 0.999)**	**0.027 (S)**
HCO_3 (mEq/L)	**- 0.010**	**0.010**	**0.981**	**(0.963 – 0.999)**	**0.042 (S)**

SE: standard error; **OR:** odds ratio; 95 % **CI:** 95% confidence interval.

Table (7): Multivariate logistic regression of potential predictors of thyroid dysfunction in COPD patients.

Variables	β	SE	OR	95% CI	p
Age (years)	**- 0.109**	**0.064**	**0.869**	**(0.790 – 1.016)**	0.088 (NS)
Haematocrit (%)	**+ 0.377**	**0.255**	**1.457**	**0.882 – 2.407)**	0.140 (NS)
Blood Urea (mg/dl)	**+ 0.597**	**0.303**	**1.817**	**(1.002 – 3.294)**	**0.049 (S)**
Creatinine (mg/dl)	**+ 3.319**	**1.886**	**27.655**	**(0.685 – 1115.4)**	0.078 (NS)
Serum GPT (IU/L)	**+ 0.045**	**0.030**	**1.046**	**(0.985 – 1.110)**	0.142 (NS)
Constant	**- 26.473**				

Overall Model Fit: Chi-square = 53.984, degree of freedom =5, p=0.040 (S). The model correctly classify 85.42 % of cases

Table (8): Relative risk of ABG and APACH II score for the occurrence of thyroid dysfunction in patients with acute exacerbation of COPD.

Item	Thyroid dysfunction (n=12) Group I	Euthyroid function (n=36) Group II	Total	Relative risk
PaO_2 (< 60 mmHg)	10	11	21	**6.43 fold**
PaO_2 (> 60 mmHg)	2	25	27	
$PaCO_2$ (>45 mmHg)	10	21	31	**2.75 fold**
$PaCO_2$ (<45 mmHg)	2	15	17	
HCO_3 (>24 mEq/L)	9	26	35	**1.2 fold**
HCO_3 (<24 mEq/L)	3	10	13	
APACH II (> 14)	10	27	37	**1.7 fold**
APACH II(< 14)	2	11	13	

Table (9): Univariate logistic regression of potential predictors of mortality in sick euthyroid function patients

Variables	β	SE	HR	95% CI	p
Age (years)	0.019	0.04	1.010	(0.928 – 1.120)	0.684 (NS)
Sex (female)	-14.44	285	0.000		0.959 (NS)
Smoking	0.143	0.064	1.154	(1.017 – 1.309)	**0.026(S)**
Disease duration (years)	0.078	0.042	1.081	(0.994 – 1.175)	0.068 (NS)
SBP (mmHg)	0.003	0.011	1.004	(0.982 – 1.026)	0.723 (NS)
DBP (mmHg)	-0.011	0.034	0.988	(0.923 – 1.057)	0.731 (NS)
HR (beat/min)	-0.004	0.029	0.995	(0.940 – 1.054)	0.887 (NS)
RR (/min)	0.053	0.039	1.055	(0.977 – 1.138)	0.171 (NS)
APACH II score	4.093	1.567	59.925	(2.821 – 1272)	**0.009 (HS)**
Haematocrit (%)	0.215	0.253	1.240	(0.756 – 2.033)	0.394 (NS)
Hemoglobin level (g/dl)	-0.005	0.199	0.995	(0.673 – 1.469)	0.979 (NS)
Urea (mg/dl)	0.226	0.250	1.254	(0.769 – 2.045)	0.366 (NS)
Creatinine (mg/dl)	0.546	1.050	1.726	(0.222 – 13.38)	0.602 (NS)
Serum GOT (IU/L)	0.035	0.027	1.036	(0.982 – 1.093)	0.192 (NS)
Serum GPT (IU/L)	0.048	0.036	1.049	(0.976 – 1.127)	0.190 (NS)
PaO_2 (mmHg)	0.021	0.064	1.021	(0.900 – 1.159)	0.741 (NS)
$PaCO_2$ (mmHg)	0.134	0.063	1.143	(1.009 – 1.271)	**0.031 (S)**
HCO_3 (mmHg)	0.083	0.085	1.086	(0.920 – 1.282)	0.327 (NS)
PH	-21.212	20.264	0.000		0.295 (NS)
Na	0.095	0.108	1.099	(0.891 – 1.357)	0.378 (NS)
K	2.326	1.596	10.241	(0.455 – 230.3)	0.145 (NS)

β: regression Coefficient **SE:** standard error; **HR:** Hazards Ratio; 95% **CI:** 95% confidence interval.

Table (10): Relative risk of thyroid disorders on mortality in patients with acute exacerbation of COPD.

Item	Deceased	Survive	Total	Relative risk
Thyroid dysfunction	**9**	**3**	**12**	**2.1 fold**
Euthyroid function	**6**	**30**	**36**	

Discussion

We performed this study to assess; the frequency and different patterns of thyroid dysfunction, risk factors and its correlation with thyroid abnormalities, and the impact of thyroid dysfunction on short term outcome of COPD patients with acute exacerbation admitted to Zagazig University Hospitals MICU.

The present study showed a high prevalence of non-thyroidal illness syndrome in 12 patients (25%) from 48 patients with acute exacerbation of COPD.

Those patients had low FT_3 than normal, normal FT_4 except one case with high FT_4 level and normal TSH level. Other 36 patients had normal FT_3, FT_4 and TSH level; we consider this group of euthyroid function as a control group.

These finding was matching with a study which found that mean level of FT_3 was significantly lower among patients with acute exacerbation of COPD, and suggested that the existence of NTIS among those patients is more prevalent as compared to stable COPD and healthy controls. Also, they found that Patients with NTIS have decreased levels of the biologically active hormone T_3, normal or decreased levels of hormone T_4 and serum levels of the TSH are usually normal. The presence of thyroid dysfunction may vary according to the phases of COPD. [16]

Also; Karadag et al., demonstrated that T_3 levels were lowered [3], as well as, Akbas et al., who finds that low FT_3 and TSH levels in critically ill COPD patients return to normal when they recovered from critical illness. [17] It was demonstrated that in sever COPD patients, a certain degree of thyroid dysfunction was evident. [6]

However, in stable COPD baseline thyroid hormones are within normal limits. The alteration in thyroid hormone levels in COPD patients with acute exacerbation is thought to be because of decreased turnover of T_4 and T_3 as an adaptive mechanism in chronic diseases. [18]

On the other hand, several studies reported that there was no difference in thyroid hormone levels in COPD patients compared to a healthy control group. [19-20] Uzun et al., studied thyroid function tests in patients with acute exacerbation COPD and found that both clinical and subclinical hyperthyroidism were higher in patients with COPD

exacerbations than cases without COPD. [21] They suggest that severe airway obstruction and excessive respiratory muscle load affect thyroid hormone levels in patients with COPD.

Also, Hefney et al., found that 4 patients (20%) had normal thyroid function and 3 patients had hypothyroidism, while only one patient had subclinical hyperthyroidism. It was found low T_3 and T_4 with high TSH concentrations in patients with COPD. [22]

This difference with Hefney et al., might be due to that they studied their subjects on prolonged mechanically ventilated COPD patients (more than 2 weeks) and their hormonal assay was done after stability of their condition. [23]

Several previous studies suggested that the underlying factors for alterations in thyroid hormones in COPD are hypoxemia, hypercapnia and severe airway obstruction. [4] However, the alterations in thyroid hormones in COPD might also be related to factors other than hypoxia and hypercapnia like TNFα that was demonstrating to be a mediator of several diseases leading to hypothalamo–pituitary dysfunction. Several previous studies investigated the effects of administering TNFα and IL1b to experimental animals and humans and confirmed a possible role for them in the pathogenesis of NTIS, and lowering of serum T_3. [24] Also IL6, TNFα and other several pro-inflammatory cytokines have been reported in the lung and circulation of patients with COPD in many studies. [25]

In our study, there was non-significant differences between COPD patients with euthyroid function and COPD patients with thyroid dysfunction as regard demographic data, clinical data except for APACH II score which exhibited statistically a high significant increase in COPD with thyroid dysfunction as compared to COPD with euthyroid function as the patients with NTIS had more sever indicators as hypoxemia and hypercapnia which worsen the condition of those patients.

This study showed that the mean value of arterial PaO_2 level decreased while the mean value of $PaCO_2$ and HCO_3 level increase in the group of COPD patients with thyroids dysfunction (non-thyroidal illness syndrome) as compared to COPD patients with euthyroid function similar result was obtained by Okutan et al., showed the values of PaO_2 were lower in the patients than the control group, but the values of $PaCO_2$ were higher. [4] Also, Terzano et al., demonstrated that patients with COPD have lower values of arterial PaO_2 level than controls and a tendency towards higher $PaCO_2$ levels. [26] Other studies have demonstrated that thyroid dysfunction is associated with reduced ventilator drive than induced hypoxemia and hypercapnia. [27]

We found statistically significant positive correlation between FT_3 and PaO_2 in COPD patients this was in consistence with Karadag et al. [3] but this wasn't matching with Uzun et al., who found a negative correlation between FT_3 and PaO_2. [21]

We also found statistically significant negative correlation between FT_3 and FT_4 and each of APACH II and $PaCO_2$ and between HCO_3 and FT_3 and this was matching with Madhuri et al., who found that FT_3 was negatively correlated with HCO_3. [16] A low FT_3 level represents a biochemical prognostic marker in pulmonary patients with respiratory failure [28] and Okutan et al., showed that FT_3 levels are positively correlated with $PaCO_2$. [4]

On the contrary, Gow et al., (1987) investigated thyroid function in 20 patients with exacerbation, having severe COPD did not find any correlation between ABG and thyroid hormones, and therefore suggested that aging and illness might be more important than hypoxemia in thyroid dysfunction, [29] also thyroid hormones was measured in 25 COPD patients with various degrees of hypoxemia and hypercapnia. [30]

Different results reported by Magd et al., who found a significant positive correlation between FT_4 and HCO_3 and a significant inverse correlation between FT_4 and PaO_2 and a highly significant positive correlation between FT_4 and $PaCO_2$. [20] A positive association was found between $PaCO_2$ and FT_3, and no association between TSH and FT_4 on the one hand, and pulmonary function tests and ABG on the other. The difference in the results may be due to our investigation of hormonal changes was during acute exacerbation of COPD. [23]

We found that hypoxia (PaO_2< 60%), hypercapnia ($PaCO_2$ > 45%) and increase HCO_3 increase the relative risk of thyroid dysfunction by 6.22, 2.75 and 1.2 fold respectively in acute exacerbation COPD patients.

Karadag et al., when they evaluated the relation between pulmonary function tests and thyroid hormones, they found out that serum total T_3 was lower in severe COPD compared to moderate COPD. Moreover, TSH, total T_3, FT_3 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 T_3, FT_3 while T_4 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. They also revealed that hormonal changes during follow-up after exacerbation period seemed parallel to the 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. Also, they found a negative or inverse correlation between $PaCO_2$ and TSH in COPD patients that is why they consider hypercapnia may play a role in thyroid dysfunction besides hypoxemia

and suggested that the underlying factors for alterations in thyroid hormones in COPD are hypoxemia, hypercapnia and severe airway obstruction. [3]

We also found that APACHE II score >14 increase the relative risk of thyroid dysfunction by 1.7 fold in acute exacerbation COPD patients than those of APACHE II < 14.

The APACHE II score is the most commonly used pedictor of mortality in intensive care patients. This score involves 12 routine physiological measurements, age and previous health status. It ranges from 0 to 71 points and correlates with the severity of illness. [34] However, this score does not consider hormonal responses to illness, particularly serum levels of cortisol and thyroid hormones, which have been shown to be highly associated with mortality in critically ill patients. [35]

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. [36]

It is not clear if these patients with NTIS are biochemically euthyroid or hypothyroid. A normal serum TSH in most NTIS patients with low T_3 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 NTIS. [37] Moreover; other studies reported that the transient increase in serum TSH during recovery from NTIS suggests that TSH is suppressed during the illness. [38] Overall, although patients with NTIS may be euthyroid because of short duration of NTIS, those with a prolonged NTIS may be biochemically hypothyroid and may benefit from thyroid hormone replacement therapy. However, studies evaluating T_3 replacement treatment in NTIS yielded either no benefit, or appreciable improvement. [39]

In the present study we found that thyroid dysfunction increase relative risk of mortality by 2.1 fold than euthyroid function in acute exacerbation of COPD patients. This was consistent with Fumagalli et al., found that exacerbations of COPD are important events in the course of disease as exacerbations negatively affect quality of life, accelerate the decline of pulmonary function, and are associated with higher socioeconomic costs and mortality. [31] Although the isolated T_3 state usually represents the mildest form of non-thyroidal illness, the magnitude of the drop in T_3 level reflects the severity of the illness. A very low serum T_3 level has been associated with increased mortality rate in patients with COPD and other systemic disease. [32]

In other studies, several factors have been implied as risk factors for increased mortality in COPD after an acute exacerbation of the disease. In a study among COPD patients comparable to our patient population, it reported severity of illness, BMI, age, prior functional status, PaO_2/fraction of inspired oxygen ratio, congestive heart failure, serum albumin level, and the presence of cor-pulmonale to be independently related to survival following acute exacerbation. [33]

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

Thyroid abnormalities are frequent among patients with COPD admitted to MICU with acute exacerbation. Sick Euthyroid Syndrome was solely identified in these patients especially with more severe cases. Mortality increased in COPD patients with exacerbation who got thyroid abnormalities. Further studies are needed to assess the benefit from thyroid hormone replacement therapy on decreasing mortality in COPD patients with acute exacerbation.

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