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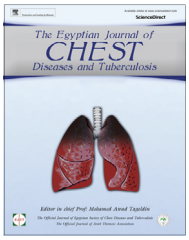

ORIGINAL ARTICLE

Thyroid function in respiratory failure patients

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KEYWORDS

Non thyroidal illness syndrome (NTIS);
Respiratory ICU (RICU);
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Euthyroid sick syndrome (ESS)

Abstract *Background:* The non thyroidal illness syndrome (NTIS) represents a risk factor for prolonged mechanical ventilation in mechanically ventilated, critically ill patients admitted to the ICU. It is unclear, whether the NTIS is only a biochemical prognostic marker or it actually contributes to the development and progression of respiratory failure.

Aim: To assess the thyroid function in patients with respiratory failure and to evaluate the impact of thyroid dysfunction as well as thyroid hormone replacement therapy on patients' outcome.

Patients and methods: The study was conducted on 100 patients (51 females and 49 males), they were divided into two groups, Group A (respiratory failure group), who were admitted to the Respiratory ICU (RICU) and group B (non-respiratory failure group) who were admitted to the Inpatient Chest Department of Zagazig University Hospitals Egypt. The respiratory failure group (Group A) included sixty-four (64) patients with respiratory failure (according to ABG parameters) 30 males and 34 females. They included 30 patients with acute exacerbation of COPD, 5 patients with acute severe bronchial asthma, 5 patients with severe pneumonia, 4 patients with acute pulmonary embolism, 8 patients with ARDS and 12 patients with acute exacerbation of IPF. This respiratory failure group included 43 patients who were on invasive mechanical ventilation and 21 respiratory failure patients who were non-mechanically ventilated. Group (B) included thirty-six (36) patients without respiratory failure according to ABG parameters as a control group (19 males and 17 females). There were 11 patients with acute exacerbation of COPD, 10 patients with

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exacerbated bronchial asthma, 6 patients with exacerbated IPF, 6 patients with pneumonia and 3 patients with acute pulmonary embolism. All patients were subjected to calculation of APACHE Π score, PaO_2/FiO_2 ratio and estimation of thyroid hormones (TSH, free T3 and free T4) at the 1st, 3rd and 10th day of admission. Those who were still having ESS at the 10th day (16 patients) and were not improving clinically, were subdivided randomly into two subgroups. Each of them comprised 8 patients. One group was given L-thyroxin replacement therapy (The replacement group) beside conventional appropriate management. The other group (8 patients) was followed by conventional appropriate management only without replacement therapy (The non-replacement group). L-Thyroxine 100 μg daily is administered for 7 weeks. At the 7th week, a fourth set of thyroid hormone estimation was done for the patients of the replacement and non-replacement groups. Patients' outcome was assessed after 7 weeks of admission and labeled as the following: 1-death, 2-successfully treated and discharged.

Results: Respiratory failure patients showed evidence of euthyroid sick syndrome (ESS) at the 1st, 3rd and 10th days of admission with a frequency of 31.2%, 79.6% and 43.7% respectively while none of the control group showed evidence of (ESS) and the difference was statistically significant. There were highly significant negative correlation between serum levels of free T3 and TSH and each of the duration of mechanical ventilation and length of ICU stay. There was significant negative correlation between APACHE Π score and serum level of freeT3 in the respiratory failure group. There was non significant impact of thyroid hormone levels on patients' outcome. There was non significant difference in the levels of thyroid hormones between replacement and non replacement groups at the 7th week of the study.

Conclusion: A state of hypothyroidism or euthyroid sick syndrome (ESS) is commonly found among patients with respiratory failure and this is related to the severity of the disease. ESS represents a risk factor for prolonged mechanical ventilation and length of ICU stay. L-thyroxin replacement therapy has no significant impact on patients' outcome.

Introduction

The thyroid hormone regulates the metabolism of proteins, lipids and carbohydrates, and controls the activity of membrane-bound enzymes. This hormone can also regulate the transcription of numerous genes encoding both myofibrillar and calcium-regulatory proteins in myofibers. 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 [1].

The non-thyroidal illness syndrome, also known as the low T3 syndrome or euthyroid sick syndrome, describes a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses. The laboratory parameters of this syndrome include low serum levels of triiodothyronine (T3) and high levels of reverse T3, with normal or low levels of thyroxine (T4) and normal or low levels of thyroid-stimulating hormone (TSH). This condition may affect 60% to 70% of critically ill patients. 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-protein and in receptor binding and intracellular uptake. Medications also have a very important role in these alterations. Hormonal changes can be seen within the first hours of critical illness and, interestingly; these changes correlate with final outcome. Data on the beneficial effect of thyroid hormone treatment, on the outcome in critically ill patients are so far controversial [2].

Aim of the work

To assess the thyroid function in patients with respiratory failure and to evaluate the impact of thyroid dysfunction as well as thyroid hormone replacement therapy on patients' outcome.

Patients and methods

This study was carried out at the intensive care unit and the inpatient section of Chest Department, Zagazig University Hospitals, Egypt in the period from October 2011 to October 2012.

Patients

The study was conducted on 100 patients (51 females and 49 males). They were divided into two groups, Group A (respiratory failure group), who were admitted to the Respiratory Intensive Care Unit (RICU) and Group B (non-respiratory failure group) who were admitted to the Inpatient Department of Chest Diseases.

- Group (A) or respiratory failure group

Sixty-four (64) patients with respiratory failure were included (according to ABG parameters) 30 males and 34 females with a mean age of 59.5 ± 6.4 years. Respiratory failure patients either due to acute or chronic respiratory diseases were diagnosed according to ABG parameters when an arterial PaO_2 less than 60 mmHg with or without increase in arterial $PaCO_2$ by more than 50 mmHg [3]. They were

classified as the following regarding their initial cause of respiratory failure:

I. *Thirty (30) patients* with acute exacerbation of chronic obstructive pulmonary disease, who were diagnosed according to (GOLD) [4] on the basis of:

(1) Symptoms of acute exacerbation of COPD (GOLD) [4]

Acute exacerbation of COPD was defined as the presence of any one of the following three major symptoms: (1) increased sputum volume, (2) increased sputum purulence, or (3) increased dyspnea. In addition, patients may have one or more symptoms of fever, Sore throat or nasal discharge within past 5 days, increased wheezing, increased cough, increased respiratory rate >20% above baseline and increased heart rate >20% above baseline. Severity of an acute exacerbation of COPD was defined as severe when patients had all three symptoms, moderate when patients had any two out of three symptoms, and mild when patients had any one out of three symptoms [4].

(2) Lung function tests

FEV1 < 1L indicate a severe exacerbation

(3) Arterial blood gases

PaO_2 < 60 mmHg and/or SaO_2 < 90% with $PaCO_2$ > 50 mmHg on room air at rest indicate respiratory failure type II and if pH 7.30–7.35 would indicate severe exacerbation. In addition, if PaO_2 < 50 mmHg, $PaCO_2$ > 70 mmHg and PH 7.30 would point toward a life-threatening episode it needs critical management.

II. *Five (5) patients* with acute severe bronchial asthma who were diagnosed according to (GINA) [5]:

- Moderate exacerbation parameters: breathless on talking, talk phrases, usually agitated, increased respiratory rate, over use of accessory muscles and suprasternal retractions, loud wheeze, pulse 100–120/min. PEF after initial bronchodilator percent of predicted or percent of personal best was 60–80%, PaO_2 (on air) > 60 mmHg and/or $PaCO_2$ < 45 - mmHg and SaO_2% 91–95% (on air).
- Severe exacerbation parameters: breathless at rest, talk words, usually agitated, increased respiratory rate > 30/min., over use of accessory muscles and suprasternal retractions, loud wheeze, pulse was > 120/min pulsus paradoxus often present > 25 mmHg (adult), PEF after initial bronchodilator was (< 100 L/min), PaO_2 (on air) < 60 mmHg and/or $PaCO_2$ > 45 mmHg and SaO_2% < 90% (on air).

III. *Five (5) Patients* with severe pneumonia who were diagnosed according to Fine et al. [6]

Features such as fever (> 38 °C), pleural pain, dyspnea, and tachypnea and signs on physical examination of the chest like diminished movement on affected side, dullness and bronchial breathing or diminished vesicular breathing were observed. CXR and/or CT show finding like consolidation and parapneumonic pleural effusion.

The patient of severe pneumonia comes usually with one or more of these signs in the word of CURB 65 (confusion, urea > 7 mmol/L, RR > 30, systolic blood pressure < 90 or diastolic blood Pressure < 60 and age > 65).

IV. *Four (4) patients with* acute pulmonary embolism

Management of a case of pulmonary embolism is by clinical probability according to the Wells Clinical Prediction Score [7].

Variable points	
DVT symptoms/signs	3.0
PE is likely or more likely than alternative diagnosis	3.0
Heart rate > 100	1.5
Immobilization/Surgery in the previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total score pretest probability	
< 2.0 Low	
2.0–6.0 Moderate	
> 6.0 High	
Dichotomized score	
#4 PE unlikely	
> 4 PE likely	

V. *Eight (8) patients* with ARDS who were diagnosed according to Mortelliti et al. [8] on the basis of:

- Identifiable associated condition. (e.g. near drowning, electric shock and others).
- Acute onset.
- Bilateral infiltrates on chest radiography.
- Acute lung injury (ALI) is present if PaO_2/FiO_2 ratio is $\leqslant$ 300.
- Acute respiratory distress syndrome is present if PaO_2/FiO_2 ratio $\leqslant$ 200.

VI. *Twelve (12) patients* with exacerbated IPF who were diagnosed according to Eric et al. [9].

Criteria of acute exacerbation of IPF:

Patients with established IPF (already known by history of progressive dyspnea, pulmonary function is restrictive and HRCT is diagnostic) satisfy the criteria for an acute exacerbation if they have: (a) acute worsening of dyspnea within the last month, (b) deterioration from baseline in measures of pulmonary function or gas exchange, (c) new infiltrates on plain chest film or CT and (d) the absence of other identifiable causes for decline.

Patients of group (A) (the respiratory failure group) were subclassified according to the need for mechanical ventilation into:

1. Group A 1

This group included the patients who were on invasive mechanical ventilation. They were 43 patients. (among those patients were 21 patients with acute exacerbation of COPD,5 patients with exacerbated IPF, 5 patients with acute severe bronchial asthma, 8 patients with ARDS, 2 patients with acute pulmonary embolism and 2 patients with severe pneumonia).

2. Group A 2

This group included 21 respiratory failure patients who were non-mechanically ventilated. There were 9 patients with acute exacerbation of COPD who did not need mechanical ventilation, 2 patients with pulmonary embolism, 7 patients with exacerbated IPF and 3 patients with severe pneumonia.

- Group (B) (non-respiratory failure group):The control group

Thirty-six (36) patients without respiratory failure according to ABG parameters as a control group (19 males and 17

females) were included. There were 11 patients with acute exacerbation of COPD, 10 patients with exacerbated bronchial asthma (moderate exacerbation), 6 patients with exacerbated IPF, 6 patients with pneumonia and 3 patients with pulmonary embolism with a mean age of 59.5 ± 4.7 years. All were already diagnosed according to the previous data which were mentioned in group A and were not in respiratory failure.

Exclusion criteria

1. Patients were excluded from the study if they had concomitant diseases such as renal failure, hepatic failure (creatinine ⩾ 3.5 and bilirubin ⩾ 6) (Normally most (80–90%) of T3 is produced by monodeiodination of 40% of circulating T4, a reaction catalyzed by 5′-monodeiodinases in organs such as the liver and kidney. The remaining (10–20%) is directly secreted by the thyroid gland) (Foteini et al.) [2]. Other patients to be excluded are those with cancer, cerebrovascular stroke, cardiogenic pulmonary edema, acute myocardial infarction, diabetic ketoacidosis, starvation, sepsis, acute pancreatitis, cardiopulmonary bypass, bone marrow transplantation and cardiac arrest.
2. Patients receiving drugs which alter thyroid function as high dose of vasopressors (They cause suppression of TSH).
3. Exclusion of any pituitary hypothalamic disease, use of iodine contrast agents in the previous 8 weeks, transfusion of plasma proteins within 48 h prior to thyroid hormone assessment.
4. Exclusion of patients with known hypothyroidism or hyperthyroidism.

Methods

• All patients were subjected to the following:

(1) Full history taking from patients or their relatives who were asked for smoking history, the principal symptoms of respiratory disease (onset and duration)

(2) Thorough clinical examination including general and local chest examination.

(3) APACHE II score was calculated.

The APACHE II score (Acute Physiology and Chronic Health Evaluation) is a system for classifying patients in the intensive care unit. Patients were evaluated by physiologic scores and evaluation of chronic health status. Physiologic scores correlate with severity of illness. The clinical status of the patients of respiratory failure in ICU was usually reflected by this score (Knaus et al.) [10].

(4) PaO_2/FiO_2 ratio was calculated:

From the ABG the following are interpreted:

– A simplified approach, used in the definition of acute lung injury and the acute respiratory distress syndrome, to calculate the PaO2/FiO_2 ratio. Acute lung injury (ALI) is present if Pao_2/Fio_2 ratio is ⩽ 300.
– Acute respiratory distress syndrome is present if Pao_2/Fio_2 ratio ⩽ 200. [8]

(5) Routine laboratory investigations including:

– Serum electrolytes, kidney function tests, liver functions tests and complete blood picture.
– D dimer whenever pulmonary embolism was suspected. It was done for 10 cases.

(6) Electrocardiogram: Identify arrhythmias, ischemia and ventricular hypertrophy.

(7) Plain chest X-ray: Previous chest X-rays were first reviewed for assessing abnormality related to the disease and new one is performed for confirmation and to assess any diseases like pneumonia, pleural effusion, lung fibrosis, pneumothorax etc.

(8) Echocardiography was done for patients with suspected corpulmonale, or pulmonary hypertension accompanied with acute pulmonary embolism.

(9) High resolution CT was revised and asked for those who have IPF (13 patients) and who were non mechanically ventilated.

(10) Magnetic Resonance pulmonary angiography (MRA): was revised for patients who were suspected of having pulmonary embolism and were non mechanically ventilated (5 patients).

(11) At the day of admission (1st day). Baseline serum TSH, free T3 and free T4 were estimated.

(12) At the third day of admission (3rd day). Serum TSH, free T3 and free T4 were re-estimated to detect any change in their levels.

(13) At 10th day another set of thyroid function was done excluding those who died.

(14) Those who still have ESS at 10th day (16 patients) and not improving clinically were subdivided randomly into two subgroups. Each of them comprised 8 patients. One group was given replacement therapy (L-thyroxin replacement) (replacement group) beside conventional appropriate management. The other group (8patients) was followed by conventional appropriate management only without replacement therapy (non-replacement group). L-thyroxine 100 μg daily is administered for 7 weeks according to Roberts and Ladenson [11].

(15) At 7th week, a fourth set of thyroid function was done for the patients of the replacement and non-replacement groups.

(16) Patients' outcome was assessed after 7 weeks of admission and labeled as the following: 1-death, 2-successfully treated and discharged.

Collection of samples and technique used for estimation of thyroid hormone levels: [12]

Device used: COBAS E 411

Free T3: Principle of the procedure: competitive analog-based immunoassay

Specimen collection and preparation: Serum samples can be prepared according to common procedures used routinely in clinical laboratory practice. Samples can be stored for 2 days at 2–8 °C or for 2 months at −20 °C. The use of ultracentrifuge is recommended to clear lipemic samples.

Volume required: 15 μL serum.

Reference value: 2.0–4.4 pg/ml

Free T4: Principle of the procedure: competitive analog-based immunoassay.

Specimen collection and preparation: Serum samples can be prepared according to common procedures used routinely in clinical laboratory practice. Samples can be stored for 2 days at 2–8 °C or for 2 months at −20 °C. The use of ultracentrifuge is recommended to clear lipemic samples.

Volume required: 15 μL serum.

Reference value: 0.93–1.7 ng/dL.

TSH: Principle of the procedure: solid-phase immunometric assay.

Specimen collection and preparation: Serum samples can be prepared according to common procedures used routinely in clinical laboratory practice. Samples can be stored for 5 days at 2–8 °C or for 1 month at −20 °C. The use of ultracentrifuge is recommended to clear lipemic samples.

Volume required: 50 μL serum.

Reference value: 0.27–4.2 μIU/mL.

(17) Statistical analysis:

Data were entered, checked and analyzed using the Epi-Info version 6 and SPSS for Windows version 8.

Data were summarized using:

1. The arithmetic mean ($\overline{X}$): as an average describing the central tendency of observations:

2. The standard deviation (SD): as a measure of dispersion of the results around the mean:

3. Analysis of variance (ANOVA of *F* test): for comparison of means of more than two groups.

4. Correlation study:

Correlation between variables was done using the correlation coefficient "*r*" this test detects if the change in one variable was accompanied by a corresponding change in the other variable or not.

5. Chi squared $(X)^2$:

Used to find the association between row and column variables.

Level of significance

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (*P*-value).

Results

Table 1 shows that 31.2% of patients with respiratory failure (Group A) have ESS at the 1st day, while none of the control group (Group B) has ESS and the difference was statistically highly significant.

Table 2 shows that 79.6% of patients with respiratory failure (Group A) show ESS at the 3rd day, while none of the control group (Group B) show ESS and the difference was statistically highly significant.

Table 3 shows that the level of TSH and FT3 was lower on the third day than the first day and the difference was statistically highly significant while there is no significant difference regarding FT4 between 1st and 3rd day among respiratory failure patients.

Table 4 shows that there is no significant difference regarding FT3, FT4, and TSH between 1st and 3rd day among non respiratory failure patients.

Table 5 and Fig. 1 show that there is a statistically highly significant difference in the number of normal and ESS patients at 1st, 3rd and10th days. The number of ESS patients was more at 3rd day (79.6%) and least at 1st day (31.2%) i.e. the 3rd day was the worst.

Table 6 shows that there is a significant negative correlation between each of FT3 and TSH and duration of MV at 3rd day of the study, while no significant correlation between FT4 and duration of MV.

Table 7 shows that there is a statistically highly significant negative correlation between mean levels of FT3, FT4 and TSH and length of stay in ICU at 3rd day in the respiratory failure group.

Table 8 shows that there is a statistically significant negative correlation between FT_3 and APACHE II score in the respiratory failure group at 1st day of ICU admission.

Table 9 shows that there is no significant impact of thyroid status on patients' outcome at the third day of ICU admission in the studied respiratory failure patients.

Table 10 and Fig. 2 show that there is no significant difference in the thyroid hormone levels at 7thweek between replacement and non-replacement groups.

Table 1 Percentage distribution of the studied patients (group A and B) regarding their thyroid status at the 1st day of admission.

Thyroid status	Group				*X*	*P*
	Group A *N* = 64		Group B *N* = 36			
	No	%	No	%		
Normal	44	68.7	36	100	12.3	< 0.001
ESS	20	31.2	0	0		
TOTAL	64	100	36	100		

Table 2 Percentage distribution of the studied patients (group AB) at the 3rd day of admission.

Thyroid status	Group				X^2	*P*
	Group A *N* = 64		Group B *N* = 36			
	No	%	No	%		
Normal	13	20.3	36	100	55.2	< 0.001
ESS	51	79.6	0	0		
Total	64	100	36	100		

Table 3 Comparison between thyroid hormone levels at the 1st and 3rd day among patients of Group A.

Day	Thyroid hormones		
	FT_3	FT_4	TSH
1st Day (Mean ± SD)	2.3 ± 0.7	1.1 ± 0.2	1.5 ± 0.9
3rd Day (Mean ± SD)	1.6 ± 0.6	1.15 ± 0.6	1.4 ± 0.9
T	5.4	1.7	4.5
P	< 0.001	> 0.05	< 0.001

Table 4 Comparison between thyroid hormone levels at the 1st and 3rd day among patients of Group B.

Day	Thyroid function		
	FT_3	FT_4	TSH
1st Day (Mean ± SD)	2.6 ± 0.4	1.2 ± 0.2	2.2 ± 0.9
3rd Day (Mean ± SD)	2.8 ± 0.5	1.2 ± 0.2	2.3 ± 0.8
T	−1.2	1.7	0.4
P	> 0.05	> 0.05	> 0.05

Table 11 shows that the initial cause of respiratory failure has no significant impact on thyroid status.

Discussion

The prevalence of NTIS is about 11–18% in records of non-selected hospitalized patients and increases up to 60–70% among patients admitted to intensive care units. Considerable controversy still exists on whether NTIS represents a physiologic adaptive response to systemic illness, by which it lowers tissue energy requirements or conversely a maladaptive state, which induces a damaging hypothyroid state at the tissue level [13].

Severe hypothyroidism has several metabolic effects that may adversely affect attempts at weaning. Although these include direct impairment of the diaphragm function and actual myxoedema of these and other muscles, probably the dominant effect is the blunting of ventilatory responses to hypoxia and hypercapnia. Thyroid hormone replacement results in significant improvement in these ventilatory control parameters [14].

In the differential diagnosis of low serum T3and T4 in the critically ill patient, intensivists should include hypothyroidism. Measurements of rT3 had been considered useful in differentiating non thyroidal illness (high rT3) from secondary hypothyroidism (low TSH), which should be associated with low rT3. Subsequent studies however showed that rT3 does not accurately distinguish the two states [13].

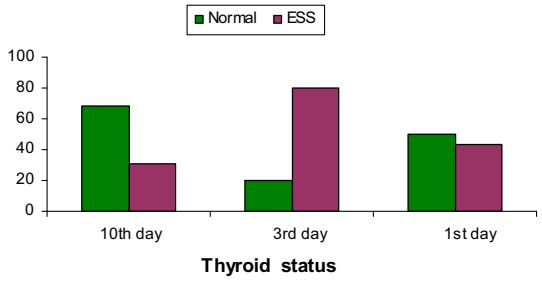

Figure 1 Percentage distribution of group A patients regarding their thyroid status at (1st, 3rd and 10th day) of the study.

To date, there are few data on thyroid function in patients with respiratory diseases due to pulmonary disorders, and there are no data available on thyroid function in respiratory failure patients needing invasive or noninvasive mechanical ventilation [15].

So the aim of this work was to study the thyroid function among patients with respiratory failure due to various etiologies to check the frequency of ESS and its effect on the prognosis of the original disease.

In this study, two groups of patients were studied: Group (A) (respiratory failure group); comprised 64 patients with respiratory failure, there were 30 males and 34 females (with a mean age of 59.5 ± 6.4 years) and they were chosen from ICU of the chest department. Another group (B) (control group or non respiratory failure patients) comprised 36 patients (with a mean age of 59.5 ± 4.7 years, 19 males and 17 females). They were chosen from general ward of the Chest Department of Zagazig University Hospitals. They were matched with the respiratory failure group regarding age and sex. They were having the same chest diseases (apart from ARDS subgroup) of group (A) but without respiratory failure.

In this work and on the initial presentation (1st day) 20 patients (31.2%) of group A (respiratory failure group) were having ESS and (68.7%) did not have ESS while none in group B (non-respiratory failure group) were having this defect. This means that the deranged blood gases and severity of the disease were mostly the main factor causing ESS. On the third day of admission to the ICU the repeated values of thyroid hormones showed that the number of ESS patients increased from 20 patients (31.2%) to 51 patients (79.6%) (Tables 1 and 2).

In agreement with our study, De Groot, (2006) [16] found in a cohort study of consecutive acutely ill, hospitalized older patients, the prevalence of NTIS was 31.9%. Also Datta and Scalise [14] found near similar results.

Bacakoglu et al. [17] found that, higher rates of thyroid function test (TFT) abnormalities (in at least one of the thyroid hormone levels mostly FT3) in what is so called ESS

Table 5 Percentage distribution of group A patients regarding their thyroid status at (1st, 3rd and 10th day) of the study.

Thyroid status	Day						X^2	*P*
	1st day		3rd day		10th day			
	No	%	No	%	No	%		
Normal	44	68.7	13	20.3	32	50	31.3	< 0.001
ESS	20	31.2	51	79.6	28	43.7		

Table 6 Correlation between thyroid hormone levels and duration of MV at 3rd day of study among patients of group (A).

Thyroid hormones	MV	
	r	*p*
FT3	−0.57	< 0.001
FT4	−0.24	> 0.05
TSH	−0.56	< 0.001

Table 7 Correlation between thyroid hormone levels and length of stay in ICU at 3rd day among patients of group (A).

Thyroid function	ICU stay	
	r	*P*
FT3	−0.50	< 0.001
FT4	−0.35	< 0.001
TSH	−0.49	< 0.001

Table 8 Correlation between FT_3 at 1st day and APACHE Π score in group (A).

	r	*P*
APACHE and FT_3	−0.34	< 0.01

Table 9 Thyroid status at the third day and outcome of studied patients in group (A).

Thyroid status	Outcome				X^2	*P*
	Normal No. = 13		ESS No. = 51			
	No.	%	No.	%		
Death	0	0	9	17.6	2.4	> 0.05
Discharged	13	100	42	82.4		

Table 10 Comparison of thyroid hormone levels at 7th week between replacement and non-replacement groups.

	Replacement group *n* = 8	Non-replacement group = 8	*t*	*P*
	Mean ± SD	Mean ± SD		
FT_3	1.1 ± 0.4	1.2 ± 0.5	−0.2	> 0.05
FT_4	1.1 ± 0.12	1 ± 0.04	1.2	> 0.05
TSH	0.7 ± 0.6	0.3 ± 0.2	0.6	> 0.05

can be detected in patients hospitalized for respiratory failure compared to those with less severe disease and no respiratory failure. Burman and Wartofsky [18], illustrated that several mechanisms can contribute to the inhibition of 5′-monodeiodination and therefore to the low serum T3 concentrations in critically ill patients with non thyroidal illness: (A) Exogenous glucocorticoid therapy. (B) Circulating inhibitors of deiodinase activity, such as free (non-esterified) fatty acids. (C) Treatment with drugs that inhibit 5′-monodeiodinase activity, such as amiodarone and high doses of propranolol. (D) Cytokines (such as tumor necrosis factor, interferon-alpha, NF-kB and interleukin-6) [18].

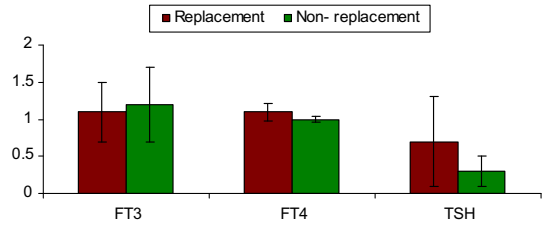

Figure 2 Comparison of thyroid hormone levels at 7th week between replacement and non-replacement groups.

The results of this work showed that, there is statistically highly significant difference in the number of normal and ESS patients at 1st, 3rd and 10th days. The number of ESS patients was more at 3rd day (79.6%) and least at 1st day (31.2%) while the number of normal patients was more at 1st day (68.7%) and least at 3rd day (20.3%) (Table 5 and Fig. 1).

Also it was found that, in group A the mean levels of TSH and FT3 were lower on the third day than the first day and the difference between the 1st and 3rd days was statistically highly significant (Tables 3)

In contrast, no significant difference regarding FT3, FT4, and TSH between 1st and 3rd day among patients of group B was observed (Tables 4).

In agreement with our results, Plikat et al. [19] studied different medical diseases with acute illness and examined thyroid laboratory values for TSH, FT3, and FT4 at days 1, 5 and 10. They found that, 44.1%, 68.4% and 34% at day 1, 5 and 10 had low serum FT3 levels indicating a NTIS, either with normal or reduced serum TSH levels.

During the chronic phase of critical illness, serum TSH levels are reduced and correlate with low serum T3 level. Normalization or a frank elevation of serum TSH may herald recovery from the critical illness [20].

Our explanation of this point is consistent with that of Mebis et al. [21] who stated that, in the acute phase of critical illness, the low serum T3 values are mainly attributed to changes in the circulation of peripheral organs such as the liver and kidney. These comprise of reduced thyroid hormone binding, reduced uptake of thyroid hormone by the cells and increased inactivation by the iodothyronine deiodinases.

The results of this study showed that there is significant negative correlation between FT3 and TSH at 3rd day of study and duration of MV (Tables 6).

In accordance with the results of the current work, Datta and Scalise [14] reported that, the patients with ESS were more frequently treated with invasive mechanical ventilation when compared to those with normal thyroid function results. Furthermore, both the period of that invasive mechanical ventilation and the in-hospital stay were higher.

Also, our findings are in agreement with those of Okutan et al. [22] who assessed thyroid function in mechanically ventilated patients and found that FT3 level was the only factor significantly associated with an increased period of invasive mechanical ventilation.

The results of this work showed that, there is a highly significant negative correlation between thyroid hormone levels at 3rd day of study and length of stay in ICU (Table 7)

Table 11 Percentage distribution of the patients of group A according to their thyroid status with special reference to the cause of respiratory failure at 1st, 3rd, 10th day.

	1st Day				3rd Day				10th Day			
	Normal		ESS		Normal		ESS		Normal		ESS	
	No	%	No	%	No	%	No	%	No	%	No	%
COPD	15	50	15	50	3	10	27	90	11	36.6	19	63.33
IPF	7	58.3	5	41.7	3	25	9	75	7	58.3	5	41.6
BA	5	100	0	0	1	20	4	80	3	60	2	40
ARDS	8	100	0	0	1	12.5	7	87.5	3	37.5	1	12.5
EMBOLISM	4	100	0	0	2	50	2	50	3	75	1	25
PNEUMONIA	5	100	0	0	3	60	2	40	5	100	0	0

$X^2 = 19.4$ P = NS ($P > 0.05$).

Near similar results were mentioned by Peeters et al. [23]. They studied patients with NTIS who had an increased length of stay in ICU. The median duration for patients with low FT3 was 6 days compared with 3 days for normal thyroid patients. Patients with low FT3 and FT4 stayed significantly longer at ICU.

In the current study there was significant negative correlation between FT3 at 3rd day and APACHE II score in the studied respiratory failure patients (Table 8).

These results match with the study done by Scoscia et al. [15] who stated that, there were negative significant correlations between, FT3 and APACHE score (inverse correlation), FT3 and the mortality rate, APACHE score and the mortality rate.

The results of our study showed that there is no significant relation between outcome and thyroid hormone levels at 3rd day in the studied respiratory failure patients (Tables 9).

In support with the result of this work, Van den Berghe [24] found that, in spite of the course of the disease (clinical conditions and length of hospital stay) it was worse in patients with reduced FT3 values but, plasma FT3 could not predict the outcome.

Also, Plikat et al. [19] found that about 44% of patients admitted in the medical intensive care unit of University Hospital of Regensburg had ESS. There was no significant correlation between FT3 and the mortality rate.

In contrary with the results of the current study, Dietrich et al. [25] reported that, during hospitalization (mean duration 10 ± 5 days), the overall cumulative death rate was 8.3%, significantly higher in patients with low T3 syndrome as compared to those without. Indeed, serum FT3 levels were significantly lower in patients who died during hospitalization with an inverse relationship between death rate and FT3 value.

Also, the findings of the present study are in contrary with those of Iervasi et al. [26] who found that, the reduced FT3 levels were the only significant predictor of death in respiratory failure patients and concluded a preliminary data that, the FT3 plasma concentration may be used as a marker of disease severity and outcome in patients with respiratory failure due to pulmonary disorder.

The results of the current work showed that, there is no significant difference in the thyroid function tests between the replacement and non-replacement group (at 7th week) (Table 10). This may be explained according to DeRuiter [27] who illustrated that when people are ill, malnourished, or have had surgery, the T4 form of thyroid hormone is not converted normally to the T3 form. Despite this abnormal conversion, the thyroid gland continues to function and to control the body's metabolic rate normally. Because no problem exists with the thyroid gland, no treatment is needed. Laboratory tests show normal results once the underlying illness resolves.

Stathatos et al. [28] concluded that, in ICU patients, who were clinically euthyroid but have the altered thyroid function tests of the sick euthyroid syndrome, there is no proven benefit in replenishing them with T4 and certainly no improvement in overall mortality.

Our study showed that the initial cause of respiratory failure has no significant effect on thyroid status at all days of the study (Tables 11). This means that the state of critical illness itself is the leading cause of ESS whatever its etiology.

In agreement with our study Uzen et al. [29] noted that there was no significant difference in mean levels of TSH, FT3 and FT4 between COPD and the control group. Serum level of TSH was lower than normal limits in 20 of 62 patients with COPD.

Conclusion

- A state of hypothyroidism (ESS) or euthyroid sick syndrome is commonly found among patients with respiratory failure and this is related to the severity of the disease.
- ESS represents a risk factor for prolonged mechanical ventilation and length of ICU stay.
- L-Thyroxin replacement therapy has no significant impact on patients' outcome.

Conflict of Interest

None declared.

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