

The Impact of Thyroid Dysfunction in ICU Patients upon the Weaning Difficulty from Mechanical Ventilation. A Case-Control Observational Study

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ABSTRACT

Background: Non-thyroidal illness syndrome has been associated with diverse manifestations of critical illness in the ICU; it correlates significantly with severity of illness in clinically unstable patients.

Objectives: The aim of the current work was to clarify the impact of thyroid dysfunction on weaning difficulty from mechanical ventilator in critically ill patients.

Patients and Methods: This case –control observational study included a total of 50 patients received invasive mechanical ventilation (MV) with age > 18 years, attending at Internal Medicine & Critical Care and Anesthesia ICU departments, Faculty of Medicine, Assiut University Hospitals. This study was conducted between October 2020 to September 2021. Full history taking and all routine laboratory investigations including complete thyroid panel were done at the time of mechanical ventilation.

Results: Out of the studied patients; 33 (66%) patients were males. The most common causes of ICU admission were cardiogenic shock (30%) and toxicity (30%); the mean simplified acute physiology score (SAPS-II) among enrolled patients was 65.18 ± 17.92 . Based on thyroid function, it was found that majority (70%) of patients have normal thyroid status while 15 (30%) has euthyroid sick syndrome (ESS) and all of them have low T3. Patients with ESS had significantly higher body mass index and SAPS-II. ($p=0.001;0.06$ respectively) Also, diaphragmatic dysfunction was significantly higher among patients with ESS ($P=0.02$) who showed longer duration of mechanical ventilation ($p=0.03$) and hospital stay($p=0.02$).

Conclusion: It could be concluded that critically ill patients who are admitted to intensive care units are vulnerable to develop euthyroid sick syndrome. ESS can increase the difficulty of weaning from mechanical ventilation and affect the outcome.

Keywords: Thyroid function test, Euthyroid Sick Syndrome, Critical Care.

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) exhibit profound inflammation, overwhelming fluid overload with renal failure, and ultimately, significant malnutrition with sarcopenia ⁽¹⁾.

The initial response to acute stress is to decrease serum triiodothyronine levels (T3) to counteract biochemical catabolism. However, in those with prolonged critical illness, the normal physiologic response of the hypothalamus-pituitary-thyroid (HPT) axis is altered, leading to low levels of both T3 and thyrotropin (TSH) ⁽²⁾.

Non-thyroidal illness syndrome has been associated with various manifestations of critical illness in the ICU. Hypothyroidism can adversely affect respiratory function by blunting the body's response to hypercapnia and hypoxia, impairing skeletal muscle/diaphragm function, and contributing to the development of pleural effusions and obstructive sleep apnea (OSA) ⁽³⁾. It was previously reported that thyroid dysfunction particularly hypothyroidism in critically ill patients is a considerable cause of failure to wean in patients receiving mechanical ventilation ⁽⁴⁾.

This study was aimed to clarify impact of thyroid dysfunction on difficulty of weaning from mechanical ventilator in critically ill patients.

PATIENTS AND METHODS

This case –control observational study included a total of 50 patients received invasive mechanical ventilation (MV) with age > 18 years, attending at Internal Medicine & Critical Care and Anesthesia ICU departments, Faculty of Medicine, Assiut University Hospitals. This study was conducted between October 2020 to September 2021.

Ethical Consideration:

This study was ethically approved by the Hospital's Ethics Committee (ID-1000450) and according to the principles of the Declaration of Helsinki. The purpose of the study was explained to all participants and written informed consent was obtained. The study was registered on *clinicaltrials.gov* with identification number of NCT0343145.

Exclusion criteria included patient with known previous intrinsic thyroid hypothalamic pituitary axis disease, usage of iodine contrast agents in the past 8 weeks, pregnancy, or history of pregnancy within the previous 6 months, any hormonal therapy except insulin use or taking drugs causing hypothyroidism like oral amiodarone, palpable thyroid nodule and or goiter, and patient's refusal.

Patients were subjected to full history taking and clinical examination included causes of admission to ICU. Investigations included complete blood picture (CBC), blood urea nitrogen, serum creatinine, serum electrolytes, liver function tests, international randomized ration (INR) and arterial blood gases. Thyroid function tests were done on the time of mechanical ventilation. These tests included free triiodothyronine (FT3), free thyroxin (FT4) and thyroid stimulating hormone (TSH).

Based on the results of thyroid function tests, patients were euthyroid, hypothyroid, or hyperthyroid or to have euthyroid sick syndrome as follows: -

Euthyroid: normal TSH level (0.45 - 4.50 mu/L), FT4 (0.70-1.9 ng/dl) and FT3 (2-4.4 pmol/L) within the normal ranges. Typical non-thyroid illness (NTI) findings are T4 level within the reference range, low T3 level, slightly reduced or reference range level of TSH, elevated rT3 level, and a free T4 level that is within the reference range or is elevated. In severe NTI, the findings are low T4, low T3, reduced TSH, elevated rT3, and free T4 that is within the reference range or is diminished ⁽⁵⁾.

Patients were categorized into ESS or normo-thyroid patients and compared accordingly.

The difficulty of weaning was determined as follows:

Simple weaning means successful weaning from the 1st trial, difficult weaning means failed three spontaneous breath trials or the need of up to 7 days to wean, and prolonged weaning means the need of > 7days after the 1st weaning trial to wean ⁽⁶⁾.

Chest ultrasound was performed for all patients to assess the presence of diaphragmatic dysfunction. With the use of Sonoscape SSI6000 (equipped with a 3.5 MHz curvilinear and 8 MHz linear probes, Nanshan, China), examination was performed. The lateral decubitus position was used to examine posterior lung regions in the participants. M-mode was used to evaluate the diaphragmatic excursion of each hemidiaphragm after initial evaluation in the B-mode by the same operator. During the respiratory cycle, diaphragmatic curve was freezed during the respiratory cycle, then, the distance from the base of the curve to its apex was used to attain the excursion ⁽⁷⁾.

The main outcome included primarily as the successfulness of weaning; secondary outcomes included the length of ICU stay and mortality rate of the included patients.

Statistical analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Quantitative data are expressed as mean (SD) and compared with Student t test while nominal data are given as number (n) and percentage (%). Chi2 test was implemented on such data. Predictors of difficult weaning were determined by multivariate regression analysis. Effect of thyroid status on overall survival was determined by Kaplan Meier analysis. Level of confidence was kept at 95% and hence, *P* value was considered significant if < 0.05.

RESULTS

Table (1) shows the main demographic and clinical characteristics of the participants. Out of the studied patients, 33 (66%) patient was males. The most frequent causes of ICU admission were cardiogenic shock (30%) and toxicity (30%) including organophosphorus poisoning in 10 (20%) and aluminum phosphide poisoning in the other 5 (10%) patients. Other causes included ten hypovolemic shock, pulmonary embolism, and acute kidney injury present.

Based on thyroid function, it was founded that majority (70%) of patients had normal thyroid status while 15 (30%) patients had euthyroid sick syndrome (ESS). Also, diaphragmatic dysfunction was detected in only seven (14%) patients.

Table (2) shows that most of ESS patients have low T3 (100%) and 77% have low TSH. Low T4 was present in only 20% of ESS patients.

Table (3a) shows insignificant differences between the two groups regarding baseline data with exception of patients with ESS who have significantly higher BMI and significantly lower creatinine. Also, diaphragmatic dysfunction was significantly higher among patients with ESS.

It was found that patients with ESS have significantly longer duration of mechanical ventilation and hospital stay. Majority (68.6%) of patients with normal thyroid function had successful weaning while majority (73.3%) of those with ESS had difficult weaning (**Table 3b**).

Kaplan Meier survival analysis revealed that both groups of patients either with ESS or normal thyroid status have insignificant differences regarding the overall survival and in hospital mortality where 12 (34.3%) patients of those with normal thyroid status and 6 (40%) patients with ESS were alive (**Fig. 1**).

Table 4 shows that the predictors of difficult weaning among studied patients were diaphragmatic dysfunction (odd's ratio= 2.30) and ESS (odd's ratio= 3.40).

Table (1): Baseline demographic, clinical and laboratory data of patients:

	N= 50
Age (years)	56.64 ± 16.97
Range	18-90
Sex	
Male	33 (66%)
Female	17 (34%)
Body mass index (kg/m²)	22.47 ± 3.99
Causes of admission	
Cardiogenic shock	15 (30%)
Toxicity	15 (30%)
Organophosphorus poisoning	10 (20%)
Aluminum phosphide	5 (10)
Hypovolemic shock	10 (20%)
Pulmonary embolism	5 (10%)
Massive embolism	4 (8%)
Segmental embolism	1 (2%)
Acute kidney injury	5 (10%)
SAPS-II	65.18 ± 17.92
Thyroid status	
Normal	35 (70%)
ESS	15 (30%)
Diaphragmatic dysfunction	7 (14%)

Data expressed as frequency (percentage), mean (SD). SAPS: simplified acute physiology score; INR: international randomized ratio; TSH: thyroid stimulating hormone; ESS: euthyroid sick syndrome.

Table (2): Pattern of thyroid function among patients with ESS

	N= 15
Free triiodothyronine (T3) (pmol/L)	15 (100%)
Low TSH (mIU/L)	10 (66.7%)
Free thyroxin(T4) (ng/dl)	5 (20%)

Data expressed as mean (SD). TSH: thyroid stimulating hormone; ESS: euthyroid sick syndrome

Table (3a): Baseline data of enrolled patients based on thyroid status

	Thyroid status		P value
	Normal function (n= 35)	ESS (n= 15)	
Age (years)	57.80 ± 17.18	53.93 ± 16.73	0.47
Sex			0.39
Male	24 (68.6%)	9 (60%)	
Female	11 (31.4%)	6 (40%)	
Body mass index (kg/m ²)	21.44 ± 3.41	24.87 ± 4.32	< 0.001
Causes of admission			0.14
Cardiogenic shock	8 (22.9%)	7 (46.7%)	
Toxicity	10 (28.6%)	5 (33.3%)	
Hypovolemic shock	10 (28.6%)	0	
Pulmonary embolism	3 (8.6%)	2 (13.3%)	
Acute kidney injury	4 (11.4%)	1 (6.7%)	
Alanine transaminase (U/L)	39.80 ± 4.46	36.87	0.06
Aspartate transaminase (U/L)	39.42 ± 23.44	32.73 ± 14.09	0.31
Bilirubin (mg/dl)	0.57 ± 0.08	0.40 ± 0.05	0.06
Albumin (g/L)	37.20 ± 3.86	36.60 ± 3.24	0.60
Creatinine (mg/dl)	1.33 ± 0.79	0.99 ± 0.59	0.01
Urea (mg/dl)	4.57 ± 1.99	4.01 ± 0.71	0.29
International randomized ratio	1.05 ± 0.06	1.03 ± 0.05	0.22
Hemoglobin (g/dl)	12.75 ± 2.93	11.97 ± 1.92	0.23
Leucocytes (10 ³ /ul)	10.94 ± 3.21	11.13 ± 2.16	0.83
Platelets (10 ³ /ul)	218 ± 52.26	199.40 ± 41.80	0.19
Sodium (mmol/l)	138.97 ± 4.93	136.67 ± 5.53	0.15
Potassium (mmol/l)	3.92 ± 0.25	3.97 ± 0.35	0.55
Random blood sugar (mg/dl)	118.60 ± 45.64	108.06 ± 31.16	0.42
pH	7.36 ± 0.08	7.36 ± 0.11	0.92
PaCO ₂	61.71 ± 16.77	55.93 ± 16.51	0.26
PO ₂	37.95 ± 8.87	38.27 ± 8.02	0.90
SO ₂	64.74 ± 14.64	67.13 ± 15.18	0.60
HCO ₃	33.65 ± 8.56	31.27 ± 8.14	0.36
Lactate (mmol/L)	4.36 ± 0.26	5.57 ± 1.90	0.10
SAPS-II	68.37 ± 8.15	57.73 ± 5.45	0.06

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. ESS: euthyroid sick syndrome

Table (3b): Outcome of enrolled patients based on thyroid status

	Thyroid status		P value
	Normal function (n= 35)	ESS (n= 15)	
Duration of MV (days)	6.54 ± 3.40	9.27 ± 4.77	0.03
Type of weaning			< 0.001
Successful	24 (68.6%)	4 (26.7%)	
Difficult	11 (31.4%)	11 (73.3%)	
Hospital stay (days)	12.54 ± 3.40	15.26 ± 4.17	0.02
Diaphragmatic dysfunction	2 (5.7%)	5 (33.3%)	0.02
2ry Outcome			0.47
Alive	12 (34.3%)	6 (40%)	
Died	23 (65.7%)	9 (60%)	

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. ESS: euthyroid sick syndrome; MV: mechanical ventilation

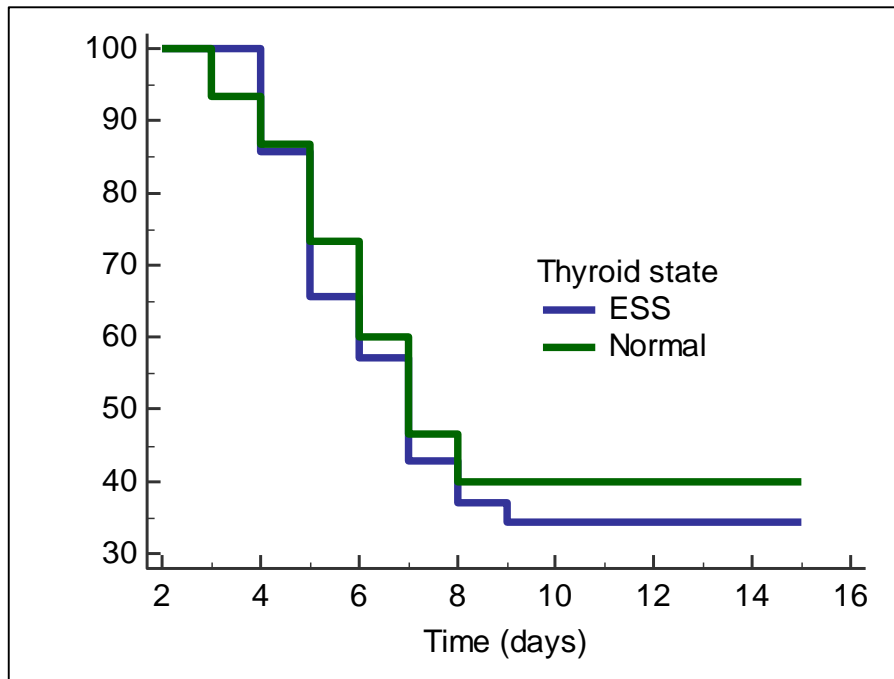


Figure (1): Kaplan Meier survival in the current study

Table (4): Multivariate regression analysis for prediction of difficulty weaning

Variables	Odd's ratio	95% confidence interval	P value
Age (years)	0.45	0.22-1.21	0.10
Body mass index (kg/m ²)	1.01	0.98-1.90	0.22
Diaphragmatic dysfunction	2.30	1.50-4.33	0.02
ESS	3.40	2.67-6.90	< 0.001

ESS: euthyroid sick syndrome

Discussion:

ESS is related to the severity of illness in critically ill patients. As a result, total T3 and T4 levels drop dramatically; this condition is known as the low-T3 syndrome or ESS, and it has a poor prognosis. Patients with low or undetectable TSH levels have a higher morbidity and mortality rate. It has been found a link between hypothyroxinemia and mortality in critically ill patients with sepsis⁽⁸⁾.

In the current study we aimed to clarify role of thyroid dysfunction on difficulty weaning from mechanical ventilator in critical care setting. A total of 50 patients were recruited in the study and majority of them were males.

In line with the current study, **Qari⁽³⁾ and Biegelmeier et al.⁽⁹⁾** conducted studies which enrolled 340 and 345 patients with mean age of 56 and 60.5 years respectively. In contrast to our study, majority (55.3%; 50.7%) of their patients was females. This discrepancy could be mainly attributed to different sample size and different population.

In the current study, based on thyroid function, it was found that majority (70%) of patients had normal thyroid status while 15 (30%) patients had ESS. **Qari⁽³⁾** found that in a total of 520 patients; normal thyroid function, hypothyroidism, hyperthyroidism and ESS were present in 320 (61.5%), 75(14.4%), 21(4%), and 86(13%) patients, respectively. The author founded that

ESS was documented in 16% of medical ICU patients compared with the 19.3% of surgical ICU cases. Also, **Mohammed et al.⁽¹⁰⁾** studied a total of 40 patients: 21 males (52.2%) and 19 females (47.5%). Their age ranged from 21 to 91 years, and all of them were selected from critically ill patients. The authors founded that 24 (60%) patients had normal thyroid function while 16 (40%) patients were classified to have thyroid dysfunction.

In the current study, we founded that all patients with ESS had low T3, while low TSH and T4 were present in 10 (66.7%) and 5 (20%) patients, respectively. Low T3 syndrome reflects alterations in thyroid hormone levels without modification in the pituitary-thyroid axis. These alterations occur in approximately 50% of patients with several chronic or acute diseases, but the mechanisms behind them are poorly understood⁽¹¹⁾.

In comparison between those with ESS and those with normal thyroid function, we founded that patients with ESS had significantly higher body mass index, diaphragmatic dysfunction and longer duration of hospital stay and mechanical ventilation. Also, patients with ESS had higher frequency of difficult weaning. But both groups had insignificant differences as regard the outcome.

It is well known that hypothyroidism is associated with respiratory failure, and it is a cause of ventilator dependence. Impairment of normal ventilator responses

to hypercapnia and hypoxia, diaphragmatic and skeletal muscle dysfunction, pleural effusions, and obstructive sleep apnea are assumed to be the major causes of respiratory failure in hypothyroidism. Correction of hypothyroidism was reported to be beneficial in weaning these patients from mechanical ventilation⁽¹²⁾.

Studies on thyroid hormones and mortality in euthyroid individuals are controversial and the results are contradictory. **Pearce et al.**⁽¹³⁾ demonstrated that low FT3 level was associated with all-cause mortality. **Mohammed et al.**⁽¹⁰⁾ founded that patient in thyroid dysfunction group showed significantly higher APACHE II score and CRP but lower GCS. They also needed more mechanical ventilation with longer duration. There was no significant difference between the 2 study groups as regard cardiovascular complication.

In the current study, Kaplan Meier survival analysis revealed that both groups of patients either with ESS or normal thyroid status had insignificant differences regarding the overall survival and in hospital mortality. In contrast, previous study found that low T3 was associated with low survival rate and higher frequency of overall mortality. This discrepancy may be secondary to different population, sample size and study design⁽¹⁴⁾.

During long-term follow-up of chronically ill patients, **Ataoglu et al.**⁽¹⁵⁾ founded that low free T3 can be associated with a 56.1–122.4% increase in mortality. They found that non-survivors had significantly lower T3 in comparison to survivors (2.27 ± 0.50 vs. 2.63 ± 0.60 ; $p < 0.001$).

In the current study, patients with difficult weaning had significantly higher frequency of ESS, diaphragmatic dysfunction, and significantly lower thyroid hormones with longer duration of hospital stay. The predictors for difficult weaning were diaphragmatic dysfunction and ESS. Similarly, it was previously reported that diaphragmatic dysfunction is common in mechanically ventilated patients at an early stage during their ICU stay and is responsible for delayed weaning as well as increased days of MV and mortality⁽¹⁶⁾. Consistently, **Qian et al.**⁽¹⁷⁾ found that that diaphragmatic dysfunction was associated with an increased risk of weaning failure. **Qari**⁽³⁾ showed that there were an association between ESS and ICU mortality. A major risk factor for difficult weaning in mechanically ventilated, critically ill patients may be attributed to thyroid dysfunction. Also, previous study found that hypothyroidism was a cause of failure to wean in patients receiving prolonged mechanical ventilation with an incidence of 3%. Prolonged MV may result in diaphragmatic muscle weakness, leading to difficulty in weaning and a longer duration of MV. Previous studies have focused on thyroid dysfunction as a risk factor for difficulty in weaning from MV. According to **Yasar et al.**⁽¹⁸⁾ ESS was an independent predictor of prolonged weaning in patients with COPD admitted to the ICU. **Bello et al.**⁽¹⁹⁾ also reported ESS as a risk factor for prolonged MV⁽¹⁹⁾.

The main limitations of the current study included relatively small size; this small sample size could be attributed to lockdown and decreased flow to the hospital secondary to worldwide pandemic COVID-19 infection during the study period.

Short term follow up is the second limitation. Also, we didn't perform follow up thyroid hormones among those patients. The study recruited patients with different etiologies for ICU's admission and this may have different impact on thyroid hormones. But, to our knowledge this is the first study that discussed such issue in our locality.

Conclusion:

It could be concluded that critically ill patients are vulnerable to develop euthyroid sick syndrome. ESS can increase the difficulty of weaning from mechanical ventilation and affect the outcome. Future studies with larger number of patients and long term follow up are warranted. Clinical trials about use of thyroid hormones among those patients and its effect on the outcome should be further investigated.

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