

## The Serum Thyroid Hormone Profile in Mechanically Ventilated Children: Does Euthyroid Sick Syndrome Exist?

Tarek A. Abdelaziz<sup>1\*</sup>, Mohamed Mahmoud. Romih<sup>1</sup>, Weam Ibrahim. Ismail<sup>2</sup>,  
Khadija AL Mabrouk Emhalhal<sup>1</sup>, Eman Gamal Baz<sup>1</sup>

<sup>1</sup>Pediatric and <sup>2</sup>Clinical Pathology Departments, Faculty of Medicine, Zagazig University, Egypt.

\*Corresponding author: Tarek A. Abdelaziz, Email: tareklatef43@gmail.com

### ABSTRACT

**Background:** The term "euthyroid sick syndrome" refers to alterations in thyroid function testing during critical illness. Mechanically ventilated children's thyroid hormone levels may be altered, although the reason for this remains a mystery.

**Objective:** This study was aimed to evaluate thyroid hormone profile in mechanically ventilated children and their correlation with mortality.

**Patients and Methods:** Thirty-four mechanically ventilated children were enrolled in a prospective cohort study. On the first and third days of mechanical ventilation, serum TSH, FT3, FT4 and reverse T3 were measured.

**Results:** The mean age of the studied patients was of  $31.06 \pm 35.94$  months. After three days of mechanical ventilation, the serum levels of FT3 and FT4 in the blood were significantly lower than the serum levels on the first day. The serum reverse T3 levels increased significantly on the third day of mechanical ventilation compared to the first day. There was a statistically significant increase in the number of patients with low FT3 and FT4 serum levels on the third day compared to the first day. Twenty-two patients (64.7%) died, and the frequency of low FT3 among dead patients was significantly higher than among surviving patients.

**Conclusions:** It could be concluded that the mechanically ventilated children had signs of euthyroid sick syndrome, shown by low levels of FT3 and FT4 and a rise in rT3 without a compensatory rise in TSH. Serum FT3 and FT4 decreased, but reverse T3 increased, on the third day of mechanical ventilation compared to the first day. Patients who had low FT3 levels died at a higher rate.

**Keywords:** Euthyroid sick syndrome, Thyroid profile, Reverse T3, Mechanically ventilated children

### INTRODUCTION

Euthyroid sick syndrome refers to abnormalities in thyroid function tests in children admitted to the pediatric intensive care unit during critical illness. Seventy five percent of hospitalized patients with this condition had abnormalities in the hypothalamic-pituitary-thyroid axis. As a result of acute critical illness, calorie restriction, and major surgery, many children suffer from this syndrome. Normal T4 and TSH and low TT3 and FT3 levels are the hallmarks of euthyroid sick syndrome's hormonal pattern <sup>(1)</sup>.

Several hormones, protein messengers, and a complex system of injury-induced stimuli that stimulates the central nervous system can be triggered by injury, trauma, or sepsis. As a result, the hypothalamic anterior pituitary axis is altered, including the adrenal gland, the somatotrophic, the thyrotrophic, and the gonado-lactotrophic. The CNS also stimulates catecholamine secretion via the peripheral sympathetic nervous system <sup>(2)</sup>.

The alteration in thyroid hormone levels in mechanically ventilated children remains unclear. There is little evidence to suggest overt pathology in this setting.

The aim of the current work was to evaluate thyroid hormone profile in mechanically ventilated children and their correlation with mortality.

### PATIENTS AND METHODS

This prospective cohort study included a total of 34 mechanically ventilated patients, attending at Pediatric Intensive Care Unit (PICU) and Clinical Pathology Department, Zagazig University Hospitals.

#### Inclusion criteria:

This study included all mechanically ventilated patients aged between 1 month and 16 years admitted to the PICU during the study period.

#### Exclusion criteria:

Patients who died within 48 hours of PICU admission and those with the decision are made to provide only palliative care were excluded from the study. Also, we excluded patients with a history of thyroid disorders.



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-SA) license (<http://creativecommons.org/licenses/by/4.0/>)

### **Data collections:**

A complete history, clinical examination, including age, gender, body weight, height, head circumference, Weight-for-Height Z-Score (WHZ), and laboratory findings were recorded for each patient. Thyroid hormones were assayed, including thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), and reverse T3 (rT3) on days 1 and 3 of the mechanical ventilation. The outcome of the studied patients was recorded.

### **Hormonal assay:**

TSH, FT4, and FT3 were immunoassayed on Cobas 8000 autoanalyzer (Roche; Germany) by electrochemiluminescence. Serum rT3 was measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit. Kit was provided from Shanghai Sunred Biological Technology Co., Ltd; Catalogue No. 201-12-0006. The kit measures serum rT3 levels using a double-antibody sandwich ELISA.

### **Ethical Consideration:**

**An approval of the study was obtained from Zagazig University academic and ethical committee and the parents of patients who were enrolled in this study signed an informed consent form before they were allowed to participate. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

### **Statistical analysis**

The statistical analysis of the data was performed using SPSS for Windows 20.0. It was necessary to present numerical data in terms of its median value, mean, standard deviation, and range. The absolute frequencies of categorical variables were used to describe them. We utilized a variety of statistical tests, including the following: Paired Wilcoxon and McNemmar tests. Chi-square (X<sup>2</sup>) was employed to

find out if two qualitative characteristics in different groups were related. If the p-value was equal to or less than 0.05, we considered the difference statistically significant.

### **RESULTS**

The mean age of the studied patients was 31.06±35.94 months, and 61.8% of them were males. Regarding Weight-for-Height Z-Score (WHZ), the prevalence of malnutrition was 26.5%, including one patient with moderate acute malnutrition (MAM) as well eight patients with severe acute malnutrition (SAM). The most common causes of admission to the PICU were pneumonia (32.3%), status epilepticus (20.6%), and encephalitis (8.8%). Comorbidities were found in 79.4% of the studied patients, and the most common comorbidities were CHD and IEM, followed by cerebral palsy and chronic kidney disease. Twenty-two patients (64.7%) died, and 26 patients (76.5%) had sepsis (**Table 1**).

On the first day of mechanical ventilation, the median TSH serum level was 2 µIU/L, the median FT3 was 2.15 ng/dl, the median FT4 was 13 ng/dl, and the median reverse T3 was 1214 pg/ml. On the third day of mechanical ventilation, the median TSH level was 1.24 µIU/L, the median FT3 was 2 ng/dl, the median FT4 was 11 ng/dl, and the median reverse T3 was 1802 pg/ml. In comparison to the first day's serum levels, there was a statistically significant drop in FT3 and FT4 serum concentrations on the third day. On the third day of mechanical ventilation, there was a statistically significant increase in blood levels of reverse T3 compared to the first day (**Table 2**).

Compared to the 1st day, the frequency of patients with low FT3 and FT4 serum levels significantly increased on the 3rd day (**Table 3**).

Twelve (35.3%) of the studied patients survived, and 22 patients (64.7%) died. The frequency of low FT3 among dead patients was significantly higher than among surviving patients (**Table 4**).

**Table (1): Clinical characteristics of the studied patients**

Variable	(N=34)
<b>Age (months)</b>	
Mean ± SD	31.06 ± 35.94
Median (Range)	15 (1 – 144)
<b>Sex</b>	
Male	21 (61.8%)
Female	13 (38.2%)
<b>Weight (kg)</b>	
Median (Range)	8.75 (3.5 – 32)
<b>Hight (cm)</b>	
Median (Range)	72.5 (49-150)
<b>Head circumference (cm)</b>	
Mean ± SD	45.76± 6.89
(Range)	(34-68)
<b>Weight-for-Height Z-Score</b>	
Normal	25 (73.53%)
MAM	1 (2.94%)
SAM	8 (23.53%)
<b>Co-morbidity</b>	
<b>No</b>	7(20.6%)
<b>Yes</b>	27(79.4%)
CHD	5
IEM	4
CP	2
CKD	2
Brain atrophy	1
Brain hygroma	1
Cystic fibrosis	1
Epidermolysis bullousa	1
Epilepsy	1
Guillain-Barre syndrome	1
Hydrocephalus with V.P shunt	1
Idiopathic thrombocytopenia	1
Leucodystrophy	1
Microcephaly with cerebellar atrophy	1
Osteogenesis imperfecta	1
Osteopetrosis	1
SCID	1
Skeletal dysplasia	1
<b>Cause of admission</b>	
Pneumonia	11(32.3%)
Status epilepticus	7 (20.6%)
Encephalitis	3 (8.8%)
Complicated gastroenteritis	2 (5.9%)
Guillain-Barre syndrome	2 (5.9%)
Septic shock	2(5.9%)
Acute pulmonary oedema	1(2.9%)
Acute bronchiolitis	1(2.9%)
Congestive heart failure	1(2.9%)
DKA	1(2.9%)
Intracranial haemorrhage	1(2.9%)
Severe sepsis	1(2.9%)
MIS-c	1(2.9%)
<b>Sepsis</b>	
No	8 (23.5%)
Yes	26 (76.5%)
<b>Outcome</b>	
Died	22 (64.7%)
Survived	12 (35.3%)

CHD: congenital heart disease; CKD: chronic kidney disease; CP: cerebral palsy; DKA: diabetic ketoacidosis; IEM: inborn error of metabolism; MAM: moderate acute malnutrition; MIS-c: multisystem inflammatory syndrome in childhood; SAM: severe acute malnutrition; SCID; severe combined immunodeficiency.

**Table (2): Serum thyroid hormone levels of the studied patients on the 1<sup>st</sup> day and 3<sup>rd</sup> day of mechanical ventilation**

Serum levels of thyroid hormones	1 <sup>st</sup> day of mechanical ventilation (n=34)	3 <sup>rd</sup> day of mechanical ventilation (n=34)	W	P
TSH (µIU/L) Median (Range)	2 (0.11-8.7)	1.24 (0.11-9)	1.42	0.16 (NS)
FT3 (ng/dl) Median (Range)	2.15 (0.5-69.9)	2 (0.5-65.6)	<b>3.67</b>	<b>&lt;0.001** (HS)</b>
FT4 (ng/dl) Median (Range)	13 (1.42-100.8)	11 (0.4-100)	<b>2.98</b>	<b>0.003* (S)</b>
rT3 (pg/ml) Median (Range)	1214 (9.83-3943)	1802 (455-4812)	<b>4.67</b>	<b>&lt;0.001** (HS)</b>

W: Paired Wilcoxon test NS: non-significant (P>0.05) \*: Significant (P≤0.05) \*\*: highly significant (P<0.001)

**Table (3): Thyroid hormone abnormality among the studied patients on the 1<sup>st</sup> day and 3<sup>rd</sup> day of mechanical ventilation**

Thyroid hormones		1st day of mechanical ventilation (n=34)		3 <sup>rd</sup> day of mechanical ventilation (n=34)		Mc	P
		No	%	No	%		
TSH	Low level	5	14.7	7	20.6	3.01	0.22 (NS)
	Normal level	26	76.5	25	73.5		
	High level	3	8.8	2	5.9		
FT3	Low level	15	44.1	20	58.8	<b>4.12</b>	<b>0.03* (S)</b>
	Normal level	19	55.9	14	41.2		
FT4	Low level	15	44.1	20	58.8	<b>4.12</b>	<b>0.03* (S)</b>
	Normal level	19	55.9	14	41.2		

P: McNemmar test NS: non-significant (P>0.05) \*: Significant (P≤0.05)

**Table (4): Relation between survival and thyroid hormone abnormality among the studied patients**

Thyroid hormones		Survived (n=12)		Dead (n=22)		χ <sup>2</sup>	P
		No	%	No	%		
TSH: 1 <sup>st</sup> day	Low level	3	60	2	40	2.98	0.23 (NS)
	Normal level	9	34.6	17	65.4		
	High level	0	0	3	100		
T3: 1 <sup>st</sup> day	Low level	3	20	12	80	<b>3.48</b>	<b>0.04* (S)</b>
	Normal level	9	47.4	10	52.6		
T4: 1 <sup>st</sup> day	Low level	5	33.3	10	66.7	0.05	0.83 (NS)
	Normal level	7	36.8	12	63.2		
TSH: 3 <sup>rd</sup> day	Low level	3	42.9	4	57.1	0.48	0.79 (NS)
	Normal level	8	32	17	68		
	High level	1	50	1	50		
T3: 3 <sup>rd</sup> day	Low level	6	30	14	70	0.60	0.44 (NS)
	Normal level	6	42.9	8	57.1		
T4: 3 <sup>rd</sup> day	Low level	5	25	15	75	2.25	0.14 (NS)
	Normal level	7	50	7	50		

χ<sup>2</sup>: Chi square test NS: Non significant (P>0.05) \*: Significant (P<0.05)

## DISCUSSION

In this study, the mechanically ventilated children had signs of the euthyroid sick syndrome, shown by low levels of FT3 and FT4 and a rise in rT3 without a corresponding rise in TSH.

In our study, the mean age of the studied patients was 31.06 months, and 61.8% of them were males. In a similar study conducted by **Beenish et al.** <sup>(3)</sup>, the median age of ventilated patients was 36 months, and 59.6% of them were males. **Sayarifard et al.** <sup>(4)</sup> enrolled thirty-five patients, including 19 (54.3%) females and 16 (45.7%) males, with a mean age of 2 years.

Our study showed that the median weight among the studied patients was 8.75 Kg, the median height was 72.5 cm, and the mean head circumference was 45.76 cm. Regarding Weight-for-Height Z-Score (WHZ), 73.5% of the studied patients were normal, and the prevalence of malnutrition was 26.5%, including one patient with moderate acute malnutrition (MAM) as well eight patients with severe acute malnutrition (SAM). **Grippa et al.** <sup>(5)</sup> reported that 18.6 % of critically sick children admitted to the PICU were malnourished, which is consistent with our findings.

Pneumonia was shown to be the most common reason for hospitalization in our research (32.3 percent), then status epilepticus (20.6%) and encephalitis (8.8%). Pneumonia is the most common illness affecting infants and children globally <sup>(6)</sup>.

Regarding the thyroid function tests on the 1st and 3rd days of mechanical ventilation among the studied patients, we found that there was a statistically significant decrease in FT3 and FT4 levels on the 3rd day compared to the 1st day, but no significant difference as regards TSH levels. Additionally, rT3 increased significantly on the third day in comparison to the first day. The number of patients with low FT3 and FT4 on the third day was statistically higher than on the first day.

Similar to our study results, **Yanni et al.** <sup>(7)</sup> 71.2 % and 51.2 %, respectively, reported a reduction in T3 and T4 hormone levels on the first day of admission. Those with low levels of T3 hormone were reduced to 61.2% on the third day of admission, while patients with low levels of T4 hormone were raised to 56.35 %.

**Galusova et al.** <sup>(8)</sup> revealed that all critically ill patients had normal baseline TSH and FT4, but FT3 levels were lower in 33% of ICU patients on the first day of admission. On the 7th day, TSH had a tendency to increase, however it did not reach statistical significance and FT4 significantly decreased.

Peripheral thyroid hormone inactivation is crucial in the early stages of severe disease <sup>(9)</sup>. In the euthyroid ill syndrome, increased deiodination, the primary mechanism of peripheral thyroid hormone metabolism, results in higher levels of physiologically inactive (rT3) while free T3 levels fall <sup>(10)</sup>.

Regarding the outcome of our studied patients, we found that 22 patients (64.7%) died and 12 patients

(35.3%) survived. The high mortality rate may be explained by the high prevalence of comorbidities, sepsis, and patient characteristics because we included only the mechanically ventilated patients.

**Yanni et al.** <sup>(7)</sup> reported a comparable mortality rate (52.5%). On the other hand, **Sayarifard et al.** <sup>(4)</sup> reported a lower mortality rate compared to our study (28.4%).

In the current study, the frequency of low FT3 among dead patients was significantly higher than among surviving patients.

**Chaudhari and Slaughter** <sup>(11)</sup>, stated that in infants, the low levels of T3 are considered an adaptive stress response that saves energy, lowers the metabolic rate, and protects the body from the high catabolism rate caused by illness. An infant with a low total T3 value may have a worse prognosis for survival and is more metabolically adaptive with a low T3 value. Following a rise in TSH, serum T3 should rise as well.

The euthyroid sick syndrome may reflect the body's attempt to conserve energy in response to stress. Protein synthesis would also be modulated by the alterations in thyroid hormones characteristic of euthyroid sick syndrome. There is a difference between euthyroid sick syndrome and hypothyroidism. The latter can happen occasionally in patients who take dopamine and high-dose corticosteroids, both of which inhibit TSH. It can be difficult to tell the difference between critical nonthyroidal illness and hypothyroidism if both T4 and TSH levels are low in the patient. Conversely, hypothyroidism is diagnosed when T4 levels are low and TSH levels are elevated <sup>(12)</sup>.

## CONCLUSION

It could be concluded that the most common causes of admission to the PICU were pneumonia, status epilepticus, and encephalitis. There is a high prevalence of comorbidities, sepsis, and malnutrition among mechanically ventilated children. The mechanically ventilated children had signs of the euthyroid sick syndrome, shown by low levels of FT3 and FT4 and a rise in rT3 without a compensatory rise in TSH. On the third day of mechanical ventilation, FT3 and FT4 levels decreased while reverse T3 levels increased in comparison to the first day. Patients with low levels of FT3 had a high mortality rate.

**Financial support and sponsorship:** Nil.

**Conflict of interest:** Nil.

## REFERENCES

1. **Ganesan K, Wadud K (2021):** Euthyroid Sick Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK482219/>
2. **Orellana R, Coss-Bu J (2021):** Metabolic alterations in the critically ill child. *Pediatr Med.*, 4:8-12.
3. **Mukhtar B, Siddiqui N, Haque A (2014):** Clinical Characteristics and Immediate-Outcome of Children

- Mechanically Ventilated in PICU of Pakistan. *Pak J Med Sci.*, 30(5):927-30.
4. **Sayarifard F, Yaghmaie B, Sayarifard A *et al.* (2018):** Thyroid Function Tests in Critically Ill Children; Any Correlation with Disease Severity or Outcome?. *Iranian Journal of Pediatrics*, 28(6): 1-4.
  5. **Grippa R, Silva P, Barbosa E *et al.* (2017):** Nutritional status as a predictor of duration of mechanical ventilation in critically ill children. *Nutrition*, 33:91-95.
  6. **Walker C, Rudan I, Liu L *et al.* (2013):** Global burden of childhood pneumonia and diarrhoea. *Lancet*, 381(9875):1405-1416.
  7. **Yanni G, Destariani C, Lubis A *et al.* (2019):** Thyroid Hormone Profile in Children with Sepsis: Does Euthyroid Sick Syndrome Exist? *Open Access Maced J Med Sci.*, 7(7):1110-1113.
  8. **Galusova A, Pauliny M, Majek M *et al.* (2015):** Dynamic neuroendocrine changes in critically ill patients with polytrauma. *Neuro Endocrinol Lett.*, 36(5):498-503.
  9. **Peeters R, Wouters P, Kaptein E *et al.* (2003):** Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab.*, 88(7):3202-11.
  10. **den Brinker M, Joosten K, Visser T *et al.* (2005):** Euthyroid sick syndrome in meningococcal sepsis: the impact of peripheral thyroid hormone metabolism and binding proteins. *J Clin Endocrinol Metab.*, 90(10):5613-20.
  11. **Chaudhari M, Slaughter J (2018):** Thyroid Function in the Neonatal Intensive Care Unit. *Clin Perinatol.*, 45(1):19-30.
  12. **Peeler K, Agus M (2018):** The Endocrine Response to Critical Illness. In *Pediatric Endocrinology*. Springer, Cham. Pp. 847-861. [https://doi.org/10.1007/978-3-319-73782-9\\_38](https://doi.org/10.1007/978-3-319-73782-9_38)