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Thyroid Dysfunction in Critically ill Patients

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ABSTRACT

Background: Thyroid hormones play an important role in maintenance of body growth by modulating metabolism and immune system. Critical illness decreases 5'deiodenase activity, thereby decreasing T4 to T3 conversion and rT3 clearance. Increased metabolic clearance of T4 in critical illness further diverts T4 to form inactive isomer of rT3. Therefore, T3 decreases and rT3 increases. Thyroid dysfunction is associated with increased mortality of patients admitted to ICU. This study was done to evaluate prognostic value of free T3, total T3, TSH, free T4 and total T4 in ICU patients. Aims and Objective: 1) Identify critically ill patients and grade them clinically according to Acute Physiology and Chronic Health Evaluation II (APACHE II) severity scale. 2) Evaluate thyroid function tests (TFTs) and to document outcome and relate APACHE II severity scale with TFTs. **Methods:** It was an observational prospective study conducted on 100 patients who were admitted to ICU/CCU of BLDE(DU) Shri B M Patil Medical College and Hospital with critical illness were included in this study. Patients were selected based on the inclusion and exclusion criteria. APACHE Ⅱ score was calculated on the day of admission and total T3, Total T4, TSH, free T3 & free T4 were sent on the day of admission and outcome were noted and statistically analysed. This study was conducted between December 2017 to July 2019. **Results:** In this study, out of 100 patients 45 patients (45%) had low free T3. Patients with low T3 had mean APACHE II score 24.9±6.9 and had higher rate of mortality. **Conclusion:** Non Thyroidal illness syndrome is a common occurrence in critically ill patients and low T3 level correlates with poor outcome in terms of mortality. Therefore, estimation of T3 level in a critically ill patient may help in predicting the outcome.

Keywords: Non Thyroidal Illness Syndrome (NTIS); Euthyroid Sick Syndrome (ESS); Critically Ill.

INTRODUCTION

The endocrine response to critical illness is complex. The physiological rationale behind these changes is to help body maintain homeostasis and is associated with the morbidity and mortality of patients.[1] The care of a critically ill patient is very important and at the same time it is very challenging for a physician. Predicting the outcome of a critically ill patient is as important as patients care because, complete resolution of the underlying illness or cure is not possible in every case and the outcome of treatment may vary from each patient and it is the duty of the treating physician to answer the questions posed by the patients' attendants regarding the prognosis of a critically ill patient. At times it is a very challenging task for the physician to explain about the disease and its prognosis. Changes in the levels of thyroid hormones, sex hormones, and corticosteroids are the predominant changes in critical illness.[2] During critical illness, changes in circulating hormone levels are a common phenomenon. These alterations are correlated with the severity of morbidity and the outcomes of patients in ICUs. Thyroid hormones play a key role in the maintenance of body growth and in modulating metabolism and the immune system. In the 20th century, studies found that thyroid dysfunction is associated with the increased morbidity and mortality of patients admitted to Intensive Care Unit (ICU).[3] These alterations in thyroid hormone levels are referred by various terms such as euthyroid sick syndrome, sick euthyroid syndrome, nonthyroidal illness syndrome, and low triiodothyronine (T3) low thyroxine (T4) syndrome. It is characterized by low serum levels of free and total T3 and high levels of reverse T3 (rT3) accompanied by normal or low levels of T4 and thyroid-stimulating hormone (TSH)[4],[5] .Subsequent studies confirmed the association between non thyroidal illness syndrome (NTIS) and adverse outcomes in patients with sepsis, multiple trauma, acute respiratory distress syndrome, respiratory failure and mechanical ventilation, as well as in ICU and medical emergency ward patients admitted for other causes A few studies have reported that alterations in thyroid hormone levels during nonthyroidal illness syndrome can act as independent predictors of mortality and morbidity in critically ill patients, thus proposing the inclusion of thyroid profile in these scoring systems of critically ill patients.[3,6] In this study, we tried to find out the relationship between critical illness (based on the

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Acute Physiology and Chronic Health Evaluation II [APACHE II] score) and thyroid dysfunction and outcome.

MATERIALS AND METHODS

It was a prospective observational study. 100 Patients included in the study were aged more than 18years who were critically ill, admitted to medical emergency ward and CCU/ICU of BLDE (DU) Shri B M Patil Medical College and Hospital, Vijayapur between December 2017 to July 2019. After obtaining written informed consent from patients or their legal guardian, who fulfil the inclusion criteria, details of the patients were recorded on a pretested structured proforma which included the demographic details, detailed case history, and APACHE II score.

Exclusion criteria

1. Thyroid swelling detected by physical examination at the time of admission or previous history of thyroid diseases.
2. Patients on hormonal therapy or taking drugs which affect thyroid function (e.g. amiodarone) except insulin.
3. Pregnancy within past 6 months.
4. Patients with a history of ICU admission within previous 6 months.

Investigations sent were Complete Blood Count, Urine Routine, Serum urea, serum creatinine, serum electrolytes, Thyroid assay - T3, T4, TSH, free T3, free T4, Arterial Blood Gas analysis.

The thyroid hormone assay (TSH, T3 and T4) was done by Chemiluminescence Immuno Assay (CLIA) using ADVIA Centaur equipment. FT3 and FT4 were measured by Enzyme Linked Immuno Sorbent Assay (ELISA) using Accubind ELISA kits.

APACHE II score (Acute Physiology and Chronic Health Evaluation Score) was estimated for all subjects and the predicted mortality in order to know the severity of the subject's illness was calculated.

Table 1: Reference range for serum thyroid hormones.[7]

Total T3	**0.77– 1.35 ng/dL**
Total T4	5.4 – 11.7 µg/dL
TSH	0.34-4.25 mIU/L
Free T3	3.7-6.5 pmol/L
Free T4	9-16 pmol/L

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square ($\chi 2$) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

If the p-value was < 0.05, then the results were statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23.0. and Microsoft office 2007.

RESULTS

Out of the total 100 patients, 66 were males and 34 were females.

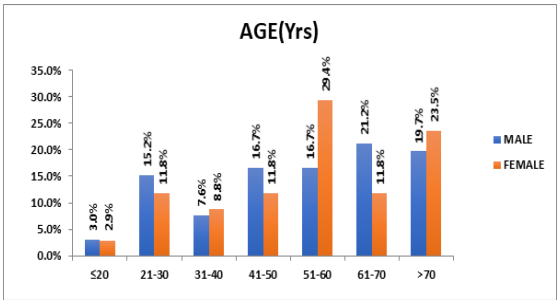

Figure 1: Distribution of cases according to age and sex

Table 2: Mean study parameters between died and survivors

Parameters	Died		Survived		p value
	Mean	SD	Mean	SD	
APACHE II	25.9	7.2	18.0	6.4	<0.001*
Total T3	0.6	0.3	1.0	0.3	<0.001*
Total T4	6.0	2.5	6.5	3.3	0.446
TSH	1.5	2.1	3.4	12.7	0.38
Free T4	18.1	4.5	17.0	4.5	0.239
Free T3	4.7	1.4	5.5	2.3	0.103

This table shows relation between APACHE II score and mortality in all the cases of studied groups, there was significant statistical differences between died and survived groups as regarding APACHE II score (p value <0.001). The table shows relation between thyroid profile and mortality in all the cases of studied groups, there was significant statistical difference between died and survived groups as regarding total T3 (P < 0.001), while there were non-significant statistical differences as regarding total T4, TSH, FT3 and FT4.

Mortality according to total T3 and free T3

In our study, among 100 patients, 45 patients had low T3, of that 30 patients died (78.9%) p value of <0.001 which is statistically significant.

In this study, 17 patients had low free T3, of that 11 patients died (31.4%) and 6 patients survived (10.3%) which is statistically significant (p value 0.044).

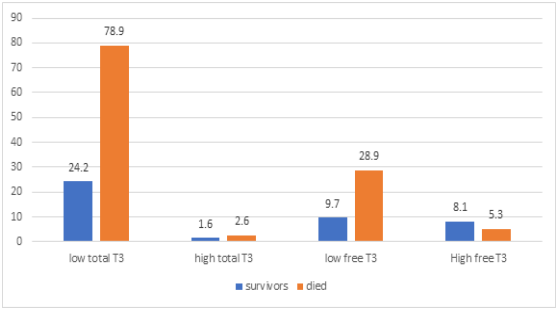

Figure 2: Mortality according to total T3 & free T3

Mean predicted mortality % by thyroid dysfunction
In our study, patients with deranged total T3 had a mean predicted mortality % of 47.3(p<0.001) statistically significant and with normal T3 had 25.7. Patients with deranged free T3 had mean predicted mortality % 47.8(p value 0.003) which was statistically significant.

Table 3: Mean predicted mortality % by thyroid dysfunction

Mean predicted mortality % by thyroid dysfunction	Dysfunction		Normal		p value
	Mean	SD	Mean	SD	
Total T3	47.3	21.7	25.7	18.7	<0.001*
Total T4	25.4	16.2	37.9	23.4	0.043*
TSH	37.7	19.8	35.2	23.8	0.64
Free T4	39.3	23.5	35.7	22.7	0.597
Free T3	47.8	21.3	32.3	21.9	0.003*

Note: *significant at 5% level of significance (p<0.05)

DISCUSSION

In our study, we found that the levels of T3, FT3 and TSH levels were generally reduced in patients with NTIS. TT3 or FT3 levels were found to be better than TSH and T4 level (or FT4 level) for predicting ICU outcomes. The T3 or T4 levels were affected by the concentration of thyroxin-binding globulin (TBG) and the binding ability of TBG, which is affected by many health conditions like acute hepatic dysfunction and liver disease and by commonly used drugs in ICU like glucocorticoids, nonsteroidal anti-inflammatory drugs, furosemide and heparin. Conversely, FT3 levels were not affected by these factors. Thus FT3 may be better than T3 levels for predicting ICU outcomes.

We found that, 66% were males and remaining 34% were females. 60% subjects were inthe age group of more than 50 years. Depending upon the changes in T3, T4, free T3, free T4 and TSH, thyroid hormone alterations were categorized into low T3, low T4, low TSH, high TSH, low FT3, high FT3 and high FT4. Majority of the subjects had low T3(45%), low FT3(18.3%). TSH was reduced in 20% and elevated in 6% patients.

In this study, patients with low total T3 had a mean predicted mortality % of 47.3(p<0.001). Patients with low free T3 had mean predicted mortality % 47.8(p 0.003). T3 and FT3 levels were significantly lower in non survivors compared to survivors (P value <0.001 and 0.044 respectively). Although TT4 and TSH were lower in non survivors than in survivors, it was not statistically significant (P values 0.727 and 0.216 respectively). Hence, estimation of T3 and FT3 levels in a critically ill patient may help in predicting the outcome. Low T3 level is associated with poor outcome in terms of mortality. Mortality rate was higher in subjects with thyroid dysfunction, than in the subjects without thyroid dysfunction.

A study was conducted in India at Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar by Zargar and it was noted that severity of illness correlated with decrease in T3 and T4. A low T3 and T4 with low or undetectable TSH were associated with increased mortality. At the onset of acute illness low T3 was seen in 113 (29.6%, low T3 -low T4 in 50 (13.1%), high T4 in 28 (7.3%) lowT3-lowT4-low TSH in 10 (2.6%) and low T4 alone in 4 (1%) patients. T3 (mean) was significantly reduced at the onset of illness compared to that in the controls. Although serum TSH showed noticeable fall and rise in some individuals, no significant difference in mean TSH was observed during any period of illness compared to that in the controls.[8]

In a study done by Feilong wang, at Shanghai, a total of 480 consecutive patients without known thyroid diseases were screened and followed up during their ICU stay. It was found that among the thyroid hormones, FT3 had the greatest power to predict ICU mortality, could independently predict primary outcome. 23 (4.79%), 53 (11.04%), 261 (54.38%) and 48 (10.00%) patients had low T3, low T4, low FT3 and low FT4 levels, respectively, and 17 (3.54%) and 30 (6.25%) patients had high TSH and rT3 levels, respectively. A total of 91 patients (19.13%) died during their ICU stay. The levels of TT3, TT4, FT3, FT4, TSH and T3/rT3 were lower in non survivors than in survivors (all P < 0.01). Compared with survivors, Non survivors were older and had higher APACHE II scores (19.49 ± 6.85 vs 11.38 ± 5.60, P< 0.0001).[9]

Low T3 was seen in critically ill patients because the conversion of T4 to T3 is inhibited by deiodinase in the present study.

CONCLUSION

Mortality rate was higher in subjects with thyroid dysfunction than in subjects without thyroid dysfunction. Patients with low T3 and low free T3 had more mean predicted mortality in non survivors than in survivors. T3 and free T3 levels were lower in non survivors than survivors. Hence, in our study of critically ill patients, we had common occurrence of low T3 and free T3 level that correlates with poor outcome in terms of mortality. Therefore, estimation of T3 and free T3 level in a critically ill patient may help in correlating the outcome.

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