ORIGINAL ARTICLE

Correlation of Thyroid Hormone Profile with the Acute Physiology and Chronic Health Evaluation II Score as a Prognostic Marker in Patients with Sepsis in the Intensive Care Unit

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Abstract

Objectives: Thyroid hormones regulate metabolism and homeostasis, and variations in thyroid hormone levels are common in chronically ill patients. Thyroid dysfunction, especially in critically ill patients admitted to the intensive care unit (ICU), is associated with adverse outcomes. This study was conducted to find a correlation between thyroid profile and sepsis and associate it with the acute physiology and chronic health evaluation II (APACHE II) score.

Methods: A cross-sectional study was conducted from January 2015 to December 2015 at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Center, Belagavi. A total of 100 patients aged 18 years or more fulfilling the sepsis criteria were included in the study. Patients were subjected to clinical examination followed by systemic examination. The clinical severity as well as the prediction of outcome was assessed by APACHE II score. Based on the outcome, the patients were divided into two groups, namely survivors and nonsurvivors. The data obtained were coded and entered into Microsoft excel spreadsheet and analyzed using SPSS 21. Continuous data were compared using independent sample t-test. The correlation of free triiodothyroxine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) with APACHE II score was done using Pearson's correlation coefficient. At 95% confidence interval, $p < 0.05$ was considered as statistically significant.

Results: Out of 100 patients, 57 patients were men and 43 were women. The mean age of patients was 48.55 ± 18.09 years. Type 2 diabetes mellitus was the most common[29] comorbid condition. Pneumonia was the primary diagnosis noted in 31patients followed by pyelonephritis.[20] Most[18] of the patients had APACHE II scores between 15 and 19. The mean APACHE II score was higher in nonsurvivors as compared to survivors (30.5 ± 7.24 vs. 16.92 ± 8.11; $p < 0.001$). In the study, 68 patients survived, while 32 of them died. Among nonsurvivors, APACHE II was inversely correlated with fT3 and fT4 levels, while TSH was positively correlated.

Conclusion: In ICU patients with sepsis, thyroid profile in combination with the APACHE II score may prove to be a better indicator of ICU morbidity and mortality more accurately than the APACHE II score alone.

Introduction

Sepsis is a complex syndrome and is defined as the body's systemic inflammatory response to infection.[1] It results in systemic manifestations, hypoxia and tissue hypoperfusion, and eventually death.[2] Sepsis affects the endocrine system causing alterations in the thyroid function. The abnormal thyroid activity is referred to as euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS), which is often observed in critically ill patients with no history of intrinsic thyroid disease. Patients present with low serum levels of free triiodothyronine (fT3) and thyroid-stimulating hormone (TSH), and low or normal levels of free thyroxine (fT4).[3] Also, high levels of reverse T3 (rT3) are observed in nonthyroidal illness due to the reduced conversion of rT3 to diiodothyronine (T2) due to the inhibition of 5'-monodeiodinase activity.[4]

Critically ill sepsis patients admitted to the intensive care unit (ICU) exhibit thyroid dysfunction, which is associated with morbidity and mortality. Thyroid hormones modulate the metabolism and immune system in the body[5,6] and, the magnitude of the thyroid dysfunction depends on the duration and severity of the disease.[7] Based on the previous research studies, fT3 levels are significantly reduced in nonsurvivors when compared to survivors. Reports were also published in which there no association between fT3 and outcome was observed in ICU patients. Hence, there are several conflicting results regarding the association of thyroid hormones with the morbidity and mortality in ICU sepsis patients.[8-10]

The acute physiology and chronic health evaluation II (APACHE II) scoring system is a widely accepted method to determine the outcomes in ICU patients with an accuracy level of 77%.[11] It is a point score system based on the initial values of 12 routine physiologic measurements, age, and previous health status, which provide a measure of severity of the disease. APACHE II is the preferred method, as it involves simple calculations and the

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Table 1: Clinical profile of study population

Variable	Mean ± SD	Range
Pulse rate (per min)	118.14 ± 10.87	100–150
Respiratory rate (per min)	37.35 ± 7.44	24–66
Systolic BP (mm Hg)	79.9 ± 11.76	40–100
Diastolic BP (mm Hg)	59.56 ± 9.01	40–70
Temperature (F)	101.35 ± 0.80	99–103
Mean BP (mm Hg)	62.85 ± 14.59	16–80
pH arterial	7.18 ± 0.15	6.8–7.45
Oxygenation (%)	81.14 ± 15.93	9–100
Serum sodium (mmol/L)	136.15 ± 6.40	108–157
Serum potassium (mmol/L)	4.15 ± 0.94	2.22–7.13
Serum creatinine (mg/dL)	3.52 ± 12.87	0.51–129
Hemocrit (%)	33.35 ± 8.79	9–54
WBC (cells/mm^3)	19072 ± 8590.68	1200–58400
Glassgow coma score	11.93 ± 2.73	4–15
APACHE II score	21.26 ± 10.07	2–46
Free T3 (ng/dL)	1.81 ± 0.68	0.08–3.17
Free T4 (ng/dL)	1.76 ± 1.65	0.55–10.3
TSH (mIU/L)	1.79 ± 1.51	0.1–10.8
Hospital stay (days)	7.05 ± 3.98	1–20

WBC, White blood cell; *APACHE II*, Acute physiology and chronic health evaluation II; *fT3*, Free triiodothyroxine; *fT4*, Free thyroxine; *TSH*, Thyroid stimulating hormone

best calibration technique to accurately predict mortality.[12] It does not include hormonal responses, such as thyroid function in critical illness, although the levels of hormones are highly associated with mortality.[13] However, the APACHE II scores, when combined with an accurate description of the disease, provide a prognostic profile of the critically ill patients.[12]

Role of thyroid hormones in predicting the outcome in sepsis patients is still debatable. In India, correlation of metabolic parameters with the APACHE II score in sepsis patients is nonexistent. Hence, this study was designed to find a correlation between thyroid profile and sepsis and associate it with APACHE II score.

Methodology

Study Design and data collection

The study was conducted at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. It was a 1-year cross-sectional study conducted from January 2015 to December 2015.

A total of 100 patients aged 18 years and more admitted to the intensive care unit (ICU) were enrolled in the study. Patients fulfilling sepsis criteria were included in the study. The criteria include hypothermia, leukocytosis or leucopenia, tachypnea or tachycardia, systemic inflammatory response syndrome (SIRS), and proven infection. Patients with known cases of thyroid disorder, adrenal insufficiency, and patients not fulfilling the criteria predefined for sepsis were exempted from the study. Before the commencement of study, ethical clearance was obtained from the Institutional Ethical Committee. After explaining the purpose of the study, a written informed consent was obtained from all the participants before data collection. The data were recorded in a predesigned and pretested proforma.

Table 2: APACHE II scores and thyroid profile in survivors and nonsurvivors

Variable	Survivors (Mean ± SD)	Nonsurvivors (Mean ± SD)
APACHE II	16.92 ± 8.11	30.5 ± 7.24***
fT3 (ng/dL)	1.88 ± 0.66	1.67 ± 0.70†
fT4 (ng/dL)	1.59 ± 1.20	2.14 ± 2.31†
TSH	1.90 ± 1.71	1.56 ± 0.93†
Pearson's correlation coefficient		
fT3	− 0.38***	− 0.21†
fT4	0.18†	− 0.29†
TSH	− 0.07†	0.10†

***$p < 0.001$; †nonsignificant ($p > 0.05$); *APACHE II*, Acute physiology and chronic health evaluation II; *fT3*, Free triiodothyroxine; *fT4*, Free thyroxine; *TSH*, Thyroid stimulating hormone

Statistics and data analysis

Selected patients underwent clinical examinations followed by systemic examinations. They were evaluated for body temperature, blood pressure, pulse rate, respiratory rate, and impairment of consciousness on the Glasgow coma scale. The various investigations performed included arterial blood gas analysis, thyroid profile (fT3, fT4, and TSH), complete blood count, liver function test, renal function test, chest x-ray, and ultrasonography. The clinical severity and the prediction of outcome were assessed by APACHE II score. Based on the outcome, the patients were divided into two groups, namely survivors and nonsurvivors. The data obtained was coded and entered into a Microsoft excel spreadsheet and analyzed using SPSS 21. The categorical data were expressed in terms of rates, ratios, and percentages and the continuous data were expressed in terms of mean ± standard deviation. Continuous data were compared using independent sample t-test. The correlation of fT3, fT4, and TSH with APACHE II score was done using Pearson's correlation coefficient. At 95% confidence interval, a $p < 0.05$ was considered as statistically significant.

Results

A slight male predominance[57] was observed in the study population. Maximum patients[23] were in the age-group of 18–30 years followed by 20 in 31–40 years age-group with a mean age of 48.55 ± 18.09 years. The most common[29] comorbid condition was type 2 diabetes mellitus (DM) followed by ischemic heart disease with type 2 DM,[12] and hypertension with type 2 DM.[11] Right ventricular dysplasia (RVD), RVD with type 2 DM, and cerebrovascular accident (CVA) with type 2 DM were observed in 1 patient each. Remaining patients[45] were devoid of any comorbid conditions. The clinical profile of the study population is shown in Table 1. Mean respiratory rate (37.35 ± 7.44/min) was high in the study population and mean diastolic blood pressure was as low as 59.56 ± 9.01 mm Hg. A high WBC count was observed in the study population with a mean of 19072 ± 8590.68 cells/mm^3. The mean hospital stay was 7.05 ± 3.98 days.

Maximum number of the patients[18] had an APACHE II score between 15 and 19 with a mean of 21.26 ± 10.07. The thyroid profile revealed low fT3 levels in majority of the patients,while low fT4 and TSH was observed in 11 and 18 patients, respectively. Improvement in the outcome was observed in most of the patients, whereas mortality was observed in few of the patients in the study population. The primary diagnosis was pneumonia followed by pyelonephritis[20] in the patients.

Analysis of outcome with APACHE II scores revealed a statistically significant difference between mean values of APACHE II scores in survivors and nonsurvivors ($p < 0.001$) wherein, the APACHE II score was significantly high in the nonsurvivors as compared to the survivors (30.5 ± 7.24 vs 16.92 ± 8.11, $p < 0.001$; Table. 2).

In survivors, the APACHE II was negatively correlated with fT3 ($r = -0.38$) and TSH ($r = -0.07$) levels, whereas, fT4 ($r = 0.18$) level was positively correlated. In nonsurvivors, APACHE II score was

inversely correlated with fT3 ($r = -0.21$) and fT4 ($r = -0.29$) levels, whereas TSH ($r = 0.10$) level was positively correlated (Table 2).

Discussion

The present study aimed at evaluating the correlation between thyroid profile and ICU mortality predictability scoring system—APACHE II score. It revealed that fT3 levels were reduced in majority of the patients. A marked correlation was established between the APACHE II score and thyroid profile. The analysis of the study population showed slight male predominance with a male to female ratio of 1.32:1. Most of the patients were aged between 18–30 years with a mean age of 48.55 ± 18.09 years. The gender and age distribution pattern observed in this study was consistent with the study conducted by Kumar et al.14 in which 52% of the patients were men and 48% were women. The mean age was 58.7 ± 16.9 years. Most of the patients had APACHE II scores between 15 and 19 with a mean APACHE II score of 21.26 ± 10.07. Also, the majority of the patients had low fT3 levels; however, low fT4 and TSH levels were observed in few of the patients only. The results were similar to the study conducted by Kumar et al.,[14] who reported low fT3, fT4, and TSH levels in 61%, 14% and 7% of the patients, respectively.

In the present study, a marked difference in the thyroid hormone levels and the APACHE II score was observed in the survivors and the nonsurvivors. In the nonsurvivors, a significant increase in the APACHE II score ($p < 0.001$) was observed when compared to the survivors. Among the circulating thyroid hormones, mean fT3 and TSH levels were reduced in nonsurvivors as compared to survivors, with increased mean fT4 levels in the nonsurvivors.

In the survivors, APACHE II score was inversely correlated with the fT3 and TSH levels, whereas fT4 levels showed a direct correlation with APACHE II score. On the other hand, in the nonsurvivors, the APACHE II score was inversely correlated with fT3 and fT4 levels. Also, a positive correlation was observed between APACHE II score and TSH levels in the nonsurvivors. The positive correlation between APACHE II score and TSH level indicates initial recovery phase in the sepsis patients with central hypothyroidism. A significant negative correlation between APACHE II and fT3 level indicates that fT3 level measurement might prove beneficial in the assessment of morbidity and eventual mortality in critically ill patients with sepsis. So, in this study among the thyroid profile parameters, the fT3 can be considered to be linearly correlated as a independent indicator of ICU morbidity.

In a study conducted by Zaid et al,[13] similar results were observed with a significantly increased APACHE II score in nonsurvivors as compared to survivors (20.71 ± 6.65 vs 13.04 ± 6.06). Researchers in previous clinical studies found that low fT3 level has a negative prognostic effect in critically ill ICU patients with poor cardiac function, indicating the development of cardiac dysfunction.[15-17] Wang et al., conducted a study to investigate the relation between APACHE II score and thyroid profile in 480 critically ill patients including sepsis. They reported significant correlation ($p < 0.001$) between fT3 level and APACHE II score and also as a good indicator of mortality in ICU patients.[6] In a similar study conducted by Ture et al.[18], levels of fT3 were markedly decreased in nonsurvivors, and reported a significant and negative correlation between fT3 and ICU mortality scores—APACHE II score ($p < 0.0005$) and SOFA score ($p < 0.0005$). The findings reported by Elvio et al,[19] reveal that the fT3 was significantly lower in nonsurvivors when compared to survivors. Hosny et al,[5] in a study including 80 critically ill patients assessed the predictive value of thyroid hormone in septic patients and reported fT3 level as a better predictor of mortality among other thyroid profile parameters.

The reason behind the decreased fT3 levels in majority of the critically ill patients with nonthyroidal illness is the inhibition of 5′-monodeiodinase which leads to decreased conversion of T4 to T3.[20,21] Several factors are involved in the inhibition of 5′-monodeiodinase including cytokines,[22,23] circulating deiodenase inhibitors (free fatty acids),[24] and glucocorticoid therapy.[25] In prolonged illness the hypothalamic-pituitary suppression leads to reduced secretion of TSH, decreased production of T4 from the thyroid gland, and eventually reduced fT4 levels. The reduced levels of TSH and fT4 are a sign of severe chronic illness and a prognostic marker of poor outcome.[26,27]

As the illness progresses, reduced TSH secretion leads to low total and free T4 eventually resulting in reduced fT3 levels. The decreased TSH, fT4 and fT3 contribute in the development of central hypothyroidism.[28] This is one of the self-protective mechanisms adopted by the body during chronic illnesses such as sepsis. The normalization of the thyroid hormones is indicative of the recovery phase in the critically ill patients with sepsis, which is observed by the initial increase in the TSH levels followed by the normal levels of fT4.[29] Also, the fT3 and fT4 levels are not affected by the binding ability of thyroxine-binding globulin (TBG), liver disease, pregnancy, and commonly used drugs such as nonsteroidal anti-inflammatory drugs, heparin and furosemide. Thus, fT3 and fT4 levels are considered better than total T4 and total T3 as well.[6] Therefore, inclusion of the fT3, fT4 and TSH in the APACHE II scoring system will provide an early assessment of morbidity and mortality in patients with sepsis.

When compared to other studies the present study included patients without previous history of thyroid dysfunction, which did not interfere with the study outcomes and proves to be the strength of the study. The patients in the ICU are administered with several drugs that can interfere with thyroid functioning which can be a limitation of the study. Because, in critically ill patients it is difficult to adjust this factor, the blood samples were collected on the admission day of the patients. And also fT3 and fT4 are not affected by various drugs, so fT3 and fT4 can be used as indicators for morbidity and mortality in ICU patients.

Conclusion

The present study revealed an inverse relationship between low fT3 levels with high APACHE II scores. Higher APACHE II scores were associated with higher mortality rate. In sepsis patients, thyroid profile in combination with APACHE II score in ICU patients predicts the outcome more accurately than the APACHE II score alone. The inclusion of thyroid profile in the APACHE II scoring system can

significantly improve the outcome analysis in the ICU patients. Further studies involving a large number of patients with multicentric design are required to unravel the role of thyroid hormones in patients with sepsis.

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