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Stress Induced Changes in Insulin and Thyroid Level in Seriously Ill Patient in Intensive Care Unit and Their Influence in Final Outcome

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Abstract: ***Background: Stress is an important cause of hormonal imbalance. Alteration in hormones is observed in critically ill patients admitted to ICU. We observed the changes in thyroid profile and glycemic status of patients on admission and analyzed the correlation with their final outcome. Material And Methods: In this cross sectional study, patients admitted to ICU were subjected for complete physical examination and a single fasting blood sample was obtained at admission for analyzing the biochemical parameters of thyroid and glycemic profile. The severity of illness was scaled using APACHE II scoring system.The patients were divided into two groups: Group 1 – survivors (discharged from the hospital) and Group 2 – non-survivors (patient succumbed to their illness inside hospital). The final outcomes of the patients were compared to their hormonal balance. Results: The baseline demographic profile was comparable between survivors and non- survivors. The mean age of participants was 50.4 ±19.77 years and the mean duration of ICU stay was 3.3±3.1 days. A total of 22 patients survived, whereas remaining 18 succumbed to their illness. Non survivors had low free T3 when compared with survivors (0.87± 0.65 vs. 1.84 ±1.18, p = 0.002) and a high APACHE II score (20±6.85 vs. 14±8.96, p= 0.028).Conclusion: The study showed that low free T3 and high APACHE II score is an important marker of mortality in critically ill patient.***

Keywords: APACHE II; ICU; Stress hormones; Insulin; free T3

1. Introduction

Critical illness is a life-threatening multisystem process that can result in significant morbidity or mortality. In most patients, critical illness is preceded by a period of physiological deterioration; but evidence suggests that the early signs of this are frequently missed [1].

Critical illness is characterized by hypermetabolic state associated with increased mortality.The metabolic support of the critically ill patient is a relatively new target of active research and yet little is known about the effects of critical illness on metabolism. Critical stress on our body is a reason for an elevated level of stress hormones to compensate and maintain the physiological status of our body. The primary hormones elevated during stress are called stress hormones which includes ADRENOCORTICOTROPIC HORMONE, CATECHOLAMINES, ANTI DIURETIC HORMONE, GLUCAGON, and GROWTH HORMONE [2].

Stress makes our body more vulnerable for the occurrence of hyperglycemia because of enhanced glucose production and peripheral insulin resistance. Insulin resistance is a physiological condition in which peripheral cells fail to respond to the normal action of insulin, therefore inspite of raised insulin levels the body witnesses hyperglycemia. Insulin also plays an important role in keeping other stress hormones like thyroid in balance, but the exact action is still unkown [3].

The nonthyroidal illness syndrome, also known as the low T3 syndrome or euthyroid sick syndrome, is described as a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illness. Euthyroid sick syndrome is one of the commonest changes encountered in critically ill patients [4].The laboratory parameters seen in this syndrome includes: low levels of serum triiodothyronine (T3) and high levels of reverseT3, with normal or low levels of thyroxine (T4) and normal or low levels of thyroid stimulating hormone (TSH) in blood. This condition may affect 60 to 70% of critically ill patients [5].

Successful outcome of an ICU patient is reflected by the ability with which his body can combat stress which principally is determined by the equilibrium of his hormonal profile. Good outcomes on the part of a doctor relies upon rapid identification and diagnosis of the illness with definitive treatment filling the body deficit, that will help the patient to maintain normal physiological equilibrium during the stress. Therefore assessment of the critically ill patient should be undertaken by an appropriately trained clinician and the severity of illness should be scaled upon following a standardized structural format, of which APACHE II scoring is currently the most commonly used. This facilitates correction of life-threatening problems by priority and provides a standardized approach between professionals.

Several research works done earlier have correlated the outcome of ICU patients with respect to hormonal balance and APACHE II scoring individually but very few significant studies have correlated these parameters together to predict the outcome of ICU patients. This study stands unique in respect that it correlates both the thyroid profile

and glycemic status of the patient along with APACHE II grading of the illness severity, together to predict the outcome of ICU patients. This study if able to establish a correlation between the critical illness and hormonal balance,will add to the APACHE system of scoring which is an amalgamation of 12 different factors taken independently and hence more complicated and costlier. This study also tries to find the significance of thyroid and glycemic status of the patient in prognostication to the case further increasing the predictive capacity of APACHE II grading system.

2. Literature Survey

Many research have been done in the past decades to determine the correlation between hormonal imbalance and prognosis of critically ill patients. But the previous attempts to correct these hormonal imbalances did not yield beneficial results in clinical trials [6-8].Few studies have reported that the low thyroid hormones are independent predictors of mortality in patients admitted to ICU, suggesting the inclusion of the thyroid profile in scoring systems like APACHE II. [9-11].The most common thyroid hormonal changes reported in critically ill patients is reduced serum free T3 level.[12] There appears a continuum of changes in critically ill patients , starting with low free triiodothyronine(T3), followed by low free thyroxine (T4), and lastly followed by thyroid stimulating hormone(TSH) [13].

In a recent study of 206 patients, a logistic regression model incorporating a well established clinical measure of ICU patients evaluation, free T3 and TSH values were shown to add to the prognostic value of APACHE II in patients with acute respiratory distress syndrome (ARDS) [14]. In the aforementioned study no patients with trauma were included. In another recent study of 113 ICU patients of non-traumatic history , the addition of TSH and total T3 improved the prognostic value of APACHE II [15]. An older study of 260 ICU patients correlation of TSH, T4, and cortisol was a better predictor of survival than APACHE II score [16]. Interestingly, TSH value in earlier studies of fewer ICU patients with trauma were mostly low [17] or suppressed[18] but were not associated with survival [19, 20].

Studies in India (Uttar Pradesh) have also shown that low serum free T3 is an important marker of mortality in critically ill patient but level of free T4 and TSH did not vary between survivors and non survivors [21]. But similar studies in regions of Maharashtra among pediatric age group have shown that T3 level reflects the patient's clinical status ,while T4 level can predict survival [22].

Recent studies have reported that blood sugar level with serum insulin levels are independent markers in predicting the outcome of ICU patients. In a retrospective study on 1826 consecutive patients in intensive care unit stay at The Stamford Hospital in Stamford, it was found that hospital mortality increased progressively as glucose values increased, reaching 42.5% among patients with mean glucose values exceeding 300 mg/dL [23].

In one more study on 2030 consecutive adult admitted in ICU, Atlanta , it was seen that patients with new hyperglycemia had a higher in-hospital mortality (16%) compared with patients with a known history of diabetes (3%) and normoglycemia (1.7%; both $P < 0.01$) [24]. Another recent study done on 54 ICU patients showed that the levels of blood glucose and fasting insulin were found to be elevated with the increase in APACHE II score of more than 10, and in contrast insulin sensitivity was greatly reduced in those patients with higher APACHE II scoring. ($P<0.05$) [25].

Several researches done earlier have correlated the outcome of ICU patients with respect to hormonal balance and APACHE II scoring but very few significant studies have correlated both thyroid and insulin together with APACHE II to predict the outcome of ICU patients. This study stands unique in respect to correlate both the thyroid profile and glycemic status of the patient to predict the outcome of ICU patients.

This study also aims to find the significance of thyroid and glycemic status of the patient in prognostication to the case further increase the predictive capacity of APACHE II grading system.

3. Methodology

This cross sectional study was done keeping KLES DR. PRABHAKAR KORE HOSPITAL as the source for patients. The hospital system was selected for an easy access to the ICU patients and maintaining their follow up records from the time of admission till their final outcome. The sample population size was calculated by estimating the admission rate in the ICU and correlating it with the time span of the study which was of 2 months from June 2014 to July 2014. Therefore the study sample size was taken as 40.

Ethical committee's permission was obtained before starting the research. The protocol of the research procedure was formulated and followed till the end.

After admission in the ICU informed written consent was obtained from the patients or their relatives in case of unconscious patients. The detailed history was taken followed by thorough general and systemic examination. Then 10ml of blood was withdrawn from mid cubital vein after 8 hrs of fasting in a clot retractor bulb following strict antiseptic measures. In case of difficulty from mid cubital any other accessible vein was used.Then the blood sample was taken for biochemical analysis to the Basic Science Laboratory, KLE University. In the laboratory the sample was centrifuged for 15mins at rate of 2000 rpm to separate the serum from the sample and the serum was stored at -80©. The sugar profile, insulin profile, and thyroid profile was obtained from the serum sample. The blood sugar profile was done by kinetic method using AUTO ANALYSER. The insulin profile was done by ELISA. The thyroid profile was done by CHEMILUMINESCENCE.

The normal ranges for biochemical analysis taken were as:
Serum Free T3 : 2.4- 4.2 pg/ml
Serum Free T4 : 0.86- 1.76ng/dl

Serum TSH : 0.34 – 4.25 µIU/ml
Random blood sugar (RBS) : 70 – 125 mg/dl
Serum Insulin : 0.7- 9.0 µIU/ml

The normal ranges were chosen as prescribed in the kits used which were of Merilisa Pvt Ltd. The physical assessment of the patient was done with other parameters along with APACHE II grading system. Then a complete follow up of the patient was recorded till the end point which was either mortality or discharge of the patient from the Intensive Care Unit. The course of the disease and their outcomes as specified above was then correlated with hormonal status and APACHE II scoring. Suitable statistical methods was adopted for calculation of the final outcomes (SPSS software 16th edition (trial version), Z test , Chi Square test, Fischer Exact test). Software access was done were ever required.

All patients admitted to the ICU of KLES DR. PRABHAKAR KORE HOSPITAL, above the age of 18years and who willfully consented for the study were included into the study group.

Patients who did not consent for the study and patients who were already on exogenous thyroxine medication or diabetic patients who were already on insulin therapy were excluded from the study group.

4. Results

A total of 40 patients admitted to the ICU were analyzed. The baseline profile of study population is given in, Figure 1. The mean age of study population was 50.4± 19.77 years (range, 20-86 years) and average duration of ICU stay was 3.3±3.1 days (range, 1-18days). Out of them, 22 patients survived and discharged from the hospital whereas remaining 18 succumbed to their illness. The clinical diagnosis of patients is in Figure 2.

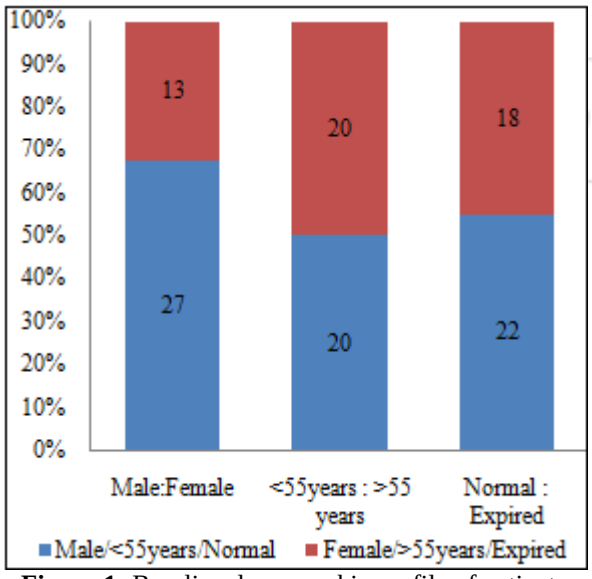

Figure 1: Baseline demographic profile of patients

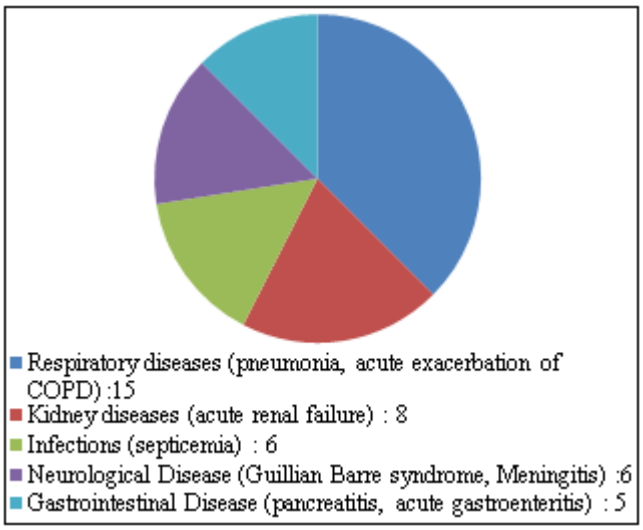

Figure 2: Clinical diagnosis of study population

COPD : chronic obstructive pulmonary disease.

In our study there was no significant correlation with the demographic details of the patients with their final outcomes. The patients were divided into two age groups one <55yrs and other > 55yrs, considering the mean age of the population. We observed that there was no significant difference among the patients with respect to their age as most of them were of same age group Table 1. Similarly in this study sex of the patient didn't play an important role in deciding the outcome as p value = 0.435(>0.05), Table 2.

Table 1: Correlation of outcome with age of patients

Age	*Expired*	*Normal*	*Total*
≤55	9(45%)	11	20
>55	9(45%)	11	20
Total	18	22	40
p value = 1			

Table 2 : Correlation of outcome with sex of patients

Sex	*Expired*	*Normal*	*Total*
Female	7(53.8%)	6	13
Male	11(40.7%)	16	27
Total	18	22	40
p value = 0.0435			

Patients were divided into 3 categories observing the prescribed range of biochemical parameters given in the kit into normal, lower and higher range. A total of 30 patients had low free T3(<2.4 pg/ml) and out of them 8 patient also had low free T4(<0.86 ng/dl). Out of 30 patients with low T3 only 17 succumbed to death and out of 10 patients having normal T3 level only 1 succumbed to death, Table 3. There was no significant difference observed in profile between survivors and non survivors with respect to FreeT4 and TSH, Table 4 and Table 5 respectively.

Table 3: Correlation of outcome with sr. free T3 level of patients

Free T3(pg/ml)	*Expired*	*Normal*	*Total*
<2.4	17(56.7%)	13	30
2.4-4.2	1(10%)	9	10
Total	18	22	40
p value = 0.028* (significant p=<0.05)			

Table 4: Correlation of outcome with sr. free T4 level of patients

Free T4(ng/dl)	*Expired*	*Normal*	*Total*
<0.86	3(37.5%)	5	8
0.86 – 1.76	6 (40%)	9	15
>1.76	9(52.9%)	8	17
Total	18	22	40
p value = 0.682			

Table 5: Correlation of outcome with sr. TSH level of patients

Sr. TSH(µIU/ml)	*Expired*	*Normal*	*Total*
<0.34	6 (46.2%)	7	13
0.34 – 4.25	7(36.5%)	12	19
>4.25	5(62.5%)	3	8
Total	18	22	40
p value = 0.471			

In the study RBS and Sr. Insulin level of patients also did not predict the mortality outcome in ICU Table 6 and Table 7 respectively. The p value observed was non significant (>0.05). It was seen that out of 24 patients having high level of sr. insulin 13 (54.2%) patients succumbed to death.

Table 6: Correlation of outcome RBS level of patients.

RBS (mg/dl)	*Expired*	*Normal*	*Total*
<70	2(50%)	2	4
70 – 125	4(36.4%)	7	11
>125	12(48%)	13	25
Total	18	22	40
p value = 0.793			

Table 7: Correlation of outcome with sr. insulin level of patients

Sr. Insulin(µIU/ml)	*Expired*	*Normal*	*Total*
<0.7	1(25%)	3	4
0.7 – 9	3 (27.3%)	8	11
>9	13(54.2%)	11	24
Total	18	22	40
p value = 0.241			

A total of 23 patients had an APACHE II scoring of more than 14 out of which 14(60.9%) patients succumbed to death, Table 8 with a significant p value.

Table 8: Correlation of outcome with APACHE II score of patients.

APACHE II	*Expired*	*Normal*	*Total*
≤14	4(23.5%)	13	17
>14	14(60.9%)	9	23
Total	18	22	40
p value = 0.019* (significant p=<0.05)			

Correlating the two significant parameters of Free T3 and APACHE II , out of 30 patients who had a low Free T3 level 22 patients also had an APACHE II score of >14 , reducing the p value further significantly to 0.002, Table 9.

Table 9: Correlation of Free T3 with APACHE II score of patients.

APACHE II	*T3 (<2.4pg/ml)*	*T3(2.4- 4.2pg/ml)*	*Total*
≤14	8(47.1%)	9(52.9%)	17
>14	22(95.5%)	1(4.3%)	23
Total	18	22	40
p value = 0.002* (significant p=<0.05)			

The comparison of the parameters studied where compared among the 2 group of patients, the survivors and the non-survivors. The data analyzed is given in, Table 10. It was found that free T3 and APACHE II had a significant p values.

Table 10: Comparison of the mean values of study parameters among patients

Parameters	*Expired*	*Normal*	*t*	*degree of freedom*	*P*
Free T3	0.87±0.65	1.84±1.18	3.273	38	0.002*
Free T4	4.64± 5.21	2.44± 2.62	1.625	38	0.117
Sr. TSH	2.68± 4.05	1.65±2.03	0.993	38	0.331
RBS	148.27±66.10	147.9±65.03	0.018	38	0.986
Sr. Insulin	34.51±59.88	20.18±20.56	1.051	38	0.300
APACHE II	20±6.85	14±8.96	2.280	38	0.028*
*= p value <0.05 is significant					

5. Discussion

In this study of patients admitted to ICU survival prediction was not related to demographic details of the patient as a whole like age and sex. As these factors were comparable in most of the study participants of this study the age and sex of the patients were not found to be confounding factors in this study. This is the strong point of the study as our subjects had a matched population in the comparison groups. Age and sex plays a significant role in outcomes especially

the extremes of age, but this effect was not a player in our study.

Our study demonstrated that low T3 is an important marker of the severity of the illness and predicts mortality in ICU, as 17 (56.7%) out of 30 patients having serum free T3 less than 2.4 succumbed to their illness. The same was not seen with low T4, low TSH or when any of these were combined with low T3. Our study showed low T3 (56.7%) is the commonest abnormality followed by low TSH (46.2%) and low T4 (37.5%). Previous study from pediatric ICU patients from Mumbai, showed low T3 in 80%, low T4 in 50 % and low TSH in 6.7% [26]., conducted among 30 critically ill children and control of less than 12years age admitted in pediatric ICU. Two samples were collected from all patients, first during admission and second during at the time of discharge from ICU or death. This study showed that mean T3 and T4 levels were significantly lower in critically ill children than control. The combination of low T3 and T4 together increased the mortality risk by 30 times. Our study differs in the study population (adults), no. of study sample (single sample at admission only), and lack of control group from previous study explaining the discrepancy in observed data [26].

Our study did not establish any relation between RBS, Serum Insulin in predicting the mortality of ICU patients. The outcome in serum glucose level was variable amongst survivors and non survivors. This may be attributed to the small sample size of the study. Even though not statistically significant serum insulin level, we did find that out of 24 patients having high level of serum insulin (>9µIU/ml), 13 (54.2%) patients succumbed to their illness, hence pointing towards increased mortality rate in patient with high insulin

level. In a prospective randomized control trial study conducted on 1200 ICU patients in Belgium; it was found that although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapies. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (P=0.009) and morbidity was also reduced [27]. So it can be stated that intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU [28].

Our study also did establish the relationship between APACHE II scoring and outcome of the patient, as a score of > 14 was found to be a bad prognostic marker in 14(60.9%) patients out of 23 patients. This is in agreement with a recent study done on 5815 intensive care admission from 13 different hospitals showing an increasing score (range 0-71) was closely correlated with the subsequent risk of hospital death [29].We also studied the influence of addition of free T3 to APACHE II and found that if taken together they were more accurate in prediction of the outcome [30].

The limitations in our study were firstly the small sample size. It was calculated based on the admission frequency in ICU of the hospital and considering the time frequency of the study (2months). Although the results obtained were statistically significant in parameters like free T3 and APACHE II scoring but outcomes related to other parameters could have been significant in a larger study sample because in our study those parameters were variable amongst survivors and non-survivors. This study can be a reference to future studies based on similar hypothesis, with a larger sample size where a universal dictum can be made based on the hormonal correlation of the ICU patients. Secondly we could not relate other hormones like cortisol, which also plays an important part in deciding the outcomes of ICU patients because of the cost restrain.

6. Conclusions

To conclude, our study points that in critical illness hormones plays a very important role in outcome of ICU patients. This study suggested that low serum free T3 is an important marker to correlate with the outcome of patients admitted in ICU. A scoring of >14 on APACHE II grading scale also is an indication of poorer outcome in ICU patients. Addition of APACHE II scoring to serum free T3 increases the prediction capacity of APACHE II scoring. This study also concludes that free serum T3 is a better prognostic marker than glycemic status of the patient (RBS, and serum insulin).

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