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Indranil Sen
MD, General Medicine, Assistant Professor, Department of General Medicine, Calcutta National Medical College, Kolkata, West Bengal, India

Swayang Prakash Chowdury
DM, Endocrinology, Professor Department of General Medicine, Calcutta National Medical College, Kolkata, West Bengal, India

Sumit Ranjan
MBBS, Junior Resident in General Medicine, Department of General Medicine, Calcutta National Medical College, Kolkata, West Bengal, India

Correspondence Author:
Indranil Sen
MD, General Medicine, Assistant Professor, Department of General Medicine, Calcutta National Medical College, Kolkata, West Bengal, India

A study on thyroid profile, serum prolactin and glycosylated haemoglobin in critically ill patients and their corelation with mortality

Indranil Sen, Swayang Prakash Chowdury and Sumit Ranjan

Abstract
Background: In a host of critical illness there is a gross alteration of different endocrine parameters due to changes required to maintain internal homeostasis. Sick euthyroid syndrome characterized by low serum levels of free and total triiodothyronine (T3) and high levels of reverse T3 (rT3) accompanied by normal or low levels of thyroxine (T4) and thyroid-stimulating hormone (TSH) seen in patients with or without previous thyroid dysfunction is a common finding in the ICU setup. Hyperglycemia is also a common cause for increased mortality and morbidity. Prolactin is also one of the relatively new markers for sepsis. In this study these endocrine markers were studied in critically ill patients and their correlation with mortality was carried out.
Aims & Objectives: To correlate mortality with serum levels of Prolactin, HbA1c, and thyroid profile
Materials & Methods: In this single centre, prospective, observational study, 100 consecutive patients admitted to ICU irrespective of diagnosis were included. Patients with previous thyroid disorders were excluded. All participants underwent complete physical examination and laboratory parameters like free triiodothyronine (T3), freel thyroxine (T4), thyroid stimulating hormone (TSH), HbA1c, and prolactin were measured. The patients were divided into two groups: Group 1 – survivors (discharged from the hospital) and Group 2 – non survivors (patients succumbed to their illness inside the hospital). The data were analyzed by appropriate statistical methods and a *P*-value of <0.05 was considered significant.
Results: In all 100 patients were analysed among them 38 people survived and 62 succumbed to their illness. The mean free T3 among survivors was 1.61 and among non survivors was 1.13 with a p value <0.001 but there was no significant association between free T4 and TSH among the two groups. The mean HBA1C value among survivors was 6.21 and non survivors was 8.23 and P value was <0.001. The mean prolactin among survivors was 6.32 and among non survivors was 8.33 and P value was 0.03.
Conclusion: Serum free T3, HBA1C and prolactin levels was associated with poor prognosis in critically ill patients and should be measured in all patients admitted to ICU irrespective of diabetes and thyroid status.

Keywords: sick euthyroid syndrome, HBA1C, prolactin, mortality in critically ill

Introduction
Stress of critical illness brings about several and serious changes in hormonal concentrations and metabolism that become difficult to interpret and manage. Some of the changes are adaptive to accommodate stress and protect tissues from catabolic breakdown. Others are the consequence of factors such as toxins and cytokines released during stress. The endocrine and autonomic nervous systems provide mechanisms to provide rapid adaptation thus maintaining homeostasis of body. The commonest endocrine modification pertains to the thyroid gland which is known as sick euthyroid syndrome (SES). It is described as abnormalities in circulating thyroid hormone levels without pre-existing hypothalamic pituitary or thyroid gland dysfunction in the setting of a Non-Thyroidal Illness (NTI). It reverts back to normal after recovery from the NTI. ESS is characterized by low triiodothyronine (T3), low or normal thyroxine (T4) and normal Thyroid Stimulating Hormone (TSH). Three patterns are described in ESS; Type 1or low T3 syndrome (Seen in moderately sick patients), type 2 or low T4 syndrome (low T3 and T4, seen in very sick

patients and associated with poor prognosis) and type 3 or low TSH syndrome. These probably reflect different stages on a continuum and severity of illness [1]. Among these type 1 is commonest. In normal individuals whole of thyroxine T4 and only 10-20% of tri-iodothyronine T3 is secreted by thyroid gland but the later is responsible for all its actions. This apparent anomaly is solved by the peripheral conversion of T4 to T3 and inactive fragment reverse T3 by 5'deiodinase by a process called monoiodination. In sick euthyroid syndrome this peripheral conversion is hampered leading to reduced T3 and an excess of useless rT3. There are a number of factors preventing these conversion-like drugs like glucocorticoids, cytokines, free (non-esterified) fatty acids which are part of critical illness and sepsis in particular. Apart from thyroid hormones there is release of number of inflammatory mediators which cause metabolic derangements commonest among which is hyperglycaemia arising from muscle glycolysis and lipolysis, and subsequent gluconeogenesis and glycolysis in the liver. But too tight glycaemic control can be detrimental because there is increased propensity for hypoglycaemic episodes due to the altered metabolic milieu in sepsis. In view of these hormonal perturbations this study was carried out to study the thyroid profile, glycosylated haemoglobin and prolactin levels in critically ill patients in the ICU set up and an attempt to determine any correlation of these factors with mortality was carried out.

Materials and Methods

This study was carried out in medical ICU of a tertiary care hospital in eastern India. A total of 100 consecutive patients irrespective of the underlying diagnosis and diabetic status were included in this prospective, observational study. Admission into ICU was based on the grave presentation of the patient and underlying clinical conditions unrelated to the study objectives. Patients with a known history of thyroid disease, intake of drugs altering thyroid function, were excluded from the study. All the patients had a detailed clinical examination and were managed appropriate to their primary condition according to established hospital protocol. The patients were divided into two groups for comparison: Group 1 – survivors (discharged from the hospital) and Group 2 – non-survivors (patients succumbed to their illness inside the hospital). An informed consent, to participate in the study, was obtained from the patients or relatives where appropriate, and the study protocol was approved by the institutional ethical committee.

Fasting venous blood samples were collected immediately on admission to ICU from all patients and were subjected for hormone analyses. Samples were tested for free T3, free T4.

TSH, prolactin, and glycosylated haemoglobin in addition to the standard ICU protocol tests. The normal reference range for thyroid hormones in our laboratory is given below: TSH (0.3–4.6 mIU/L), T3 (67–156 ng/ dL), T4 (4.5–11.6 µg/dL), prolactin (0–15 ng/mL males, 0–25 females). Any deviation of the hormone results from the normal ranges is considered to be abnormal (low or elevated). Thyroid and prolactin hormones were estimated by solid phase competitive chemiluminescence and HbA1c using the high performance liquid chromatography method using immunometric kit which works on Goldstein Wildmayer method.

Statistical analysis: Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were presented on (Mean ± SD (Min Max) and results on categorical measurements was presented in number (%). Significance is assessed at 5% level of significance. Summary data was presented as mean values ± SD and comparison between groups was done by Mann–Whitney *U*-test. Fisher's exact test and Chi-square test were used to compare frequency of variables among two groups. *P* values were reported for all statistical tests and a value of <0.05 was considered to be significant. Standard statistical method was used for the analysis of the data.

Results

100 patients were included in the study and analysed among which 70 were males and 30 females. The distribution of patients according to age is shown in figure 1. Sepsis contributed to a significant proportion of ICU admissions with 25 among the 100. In all 38 patients survived and were discharged from the hospital and 62 patients succumbed to their illness. The comparison of metabolic parameters between the two groups of survivors and non survivors is shown in table 1.

Table 1: Comparison of parameters among survivors and non survivors

	Outcome							
	Survivor			Non-Survivor				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	p Value	Significance
AGE	47.34	46.00	15.24	46.77	47.00	11.97	0.823	Not Significant
FREE T3	1.61	2.00	0.59	1.13	1.00	0.59	<0.001	Significant
FREE T4	1.46	1.39	0.71	1.32	1.36	0.53	0.544	Not Significant
TSH	4.12	3.66	2.61	4.50	3.73	3.86	0.870	Not Significant
SERUM PROLACTIN	6.32	5.85	3.34	8.33	8.04	4.48	0.030	Significant
HBA1C	6.21	5.92	0.89	8.23	7.63	2.57	<0.001	Significant
FBS	169.74	116.00	97.01	171.08	145.00	87.51	0.699	Not Significant
TLC	10776.66	10540.00	5668.12	12988.58	12595.00	6848.04	0.065	Not Significant
PPBS	238.53	160.50	146.40	239.77	185.00	120.55	0.354	Not Significant
Duration of ICU stay	7.45	8.00	3.24	4.97	5.00	2.78	<0.001	Significant
Duration of Hospital Stay	13.50	13.50	4.61	5.77	5.00	3.70	<0.001	Significant

The serum freeT3 was significantly less in non survivors compared to survivors with a lower mean (1.13) and median value. There was no statistically significant difference in the values of free T4 and TSH. The serum prolactin mean value of 8.33 was also more in the non survivors with a value of 6.32. The serum HBA1C mean, median and standard deviation values was also significantly more among non survivors compared to survivors but there was no statistically significant difference in fasting and post prandial blood sugar levels among the two groups. 45

patients were diabetic and 55 were non-diabetic. The diabetics were a significantly older population with a mean age of 54.53 compared to 40.82 among non-diabetics. A large number of diabetics were simultaneously hypothyroid with a higher mean value of TSH. The HBA1C, fasting blood sugar, postprandial blood sugar mean values were expectedly more among diabetics. The diabetics being more prone to infections had a higher total leucocyte values. The other parameters like free T3, free T4, prolactin, duration of stay in hospital and duration of stay in ICU were similar between the two groups. The value of different parameters among the 2 groups of diabetics and non-diabetics was shown in table 2.

Table 2: Comparison of different parameters among diabetics and non-diabetics

	H/O of Diabetes							
	NO			YES				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	p Value	Significance
AGE	40.82	40.00	11.62	54.53	56.00	11.07	<0.001	Significant
FREE T3	1.35	1.00	0.62	1.27	1.00	0.65	0.529	Not Significant
FREE T4	1.31	1.33	0.51	1.45	1.47	0.70	0.390	Not Significant
TSH	3.20	3.18	1.96	5.76	4.84	4.25	<0.001	Significant
SERUM PROLACTIN	7.40	6.22	3.91	7.77	7.47	4.54	0.688	Not Significant
HBA1C	6.09	5.91	0.78	9.15	9.36	2.45	<0.001	Significant
FBS	109.35	107.00	21.18	245.40	245.00	87.00	<0.001	Significant
TLC	10817.31	11000.00	5351.62	13774.51	13600.00	7387.99	0.038	Significant
PPBS	148.76	147.00	28.92	349.96	365.00	119.91	<0.001	Significant
Duration of ICU stay	5.91	5.00	3.43	5.91	5.00	2.90	0.941	Not Significant
Duration of Hospital Stay	8.87	7.00	6.03	8.51	7.00	4.90	0.981	Not Significant

Since sepsis constituted a significant proportion of patients the different parameters were studied among these patients compared to patients with other diagnosis. The patients with sepsis had lower free T3 levels but the free T4, TSH was not significantly different which was conformed to sick euthyroid syndrome type 1. The HBA1C level was also higher in patients with sepsis with a mean value of 8.89 compared to 7.20 in those with other diseases. The total leucocyte count was expectedly significantly raised in patients with sepsis. There was no significant difference among other parameters like age, free T4, TSH, prolactin, fasting, postprandial sugar, duration of hospital stay and duration of ICU stay. All these parameters are depicted in table 3.

Table 3: Comparison of different parameters among patients with sepsis and those with other diagnosis Hence free T3, HBA1c; prolactin has statistical significance with respect to mortality in ICU.

	SEPSIS							
	NO			YES				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	p Value	Significance
AGE	46.60	46.00	13.43	48.16	48.00	12.80	0.638	Not Significant
FREE T3	1.40	1.00	0.66	1.04	1.00	0.45	0.009	Significant
FREE T4	1.40	1.40	0.62	1.28	1.06	0.55	0.426	Not Significant
TSH	4.32	3.71	3.60	4.45	3.65	2.91	0.679	Not Significant
SERUM PROLACTIN	7.21	6.22	4.06	8.63	8.84	4.46	0.173	Not Significant
HBA1C	7.20	6.30	2.32	8.27	8.89	2.14	0.005	Significant
FBS	171.93	123.00	94.36	166.48	145.00	80.62	0.889	Not Significant
TLC	10010.07	9680.00	4176.88	18562.00	17000.00	7911.75	<0.001	Significant
PPBS	242.07	180.00	133.51	231.00	176.00	122.18	0.596	Not Significant
Duration of ICU stay	5.88	5.00	3.15	6.00	5.00	3.34	0.965	Not Significant
Duration of Hospital Stay	8.92	8.00	5.59	8.08	6.00	5.38	0.391	Not Significant

Discussion

In the study serum low free T3 was associated with poor prognosis but there was no significant difference when all the 3 parameters of thyroid profile were compared between survivor group and non survivors. Data from a previous study in paediatric ICU patients from Mumbai showed low T3 in 80%, low T4 in 50%, and low TSH in 6.7% patients [2] and it was conducted in 30 critically ill children and controls of less than 12 years age admitted in paediatric ICU. Two samples were collected from all patients, first at admission and second sample 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 controls. The combination of low T3 and T4 together increased the mortality risk by 30 times. Our study differs in the age of the study population (adults), number of study samples (single sample at admission only), and lack of the control group from the previous study explaining the discrepancy in observed data [2]. Another study from India in adult population showed low T3 (61%) as the commonest abnormality followed by low T4 (14%) and low TSH (7%). [3]. Elsewhere in a single centre but a large study with 480 unselected ICU patients found FT3 was found to be the most powerful predictor of ICU mortality among the complete thyroid indicators (FT3, TT3, FT4, TT4, TSH, rT3 and T3/rT3) by calculation of AUC, standardized β values [4]. In another study thyroid function was measured in 86 patients hospitalized in an intensive care unit. Two patients were found to have primary hypothyroidism and were excluded from the study. Hypothyroxinemia with normal thyroid-stimulating hormone (TSH) levels was found in 22% of the patients and was associated with a high mortality (thyroxine

[T4] levels less than 3.0 micrograms/dL, 84% mortality; T4 levels of 30 to 5.0 micrograms/dL, 50% mortality; and T4 levels greater than 5.0 micrograms/dL, 15% mortality). So there was a high correlation between low T4 levels and mortality [5]. Some reports are also given that addition of thyroid hormones to the APACHE II score improves the prediction of mortality for ICU patients [6, 7]. Mangas-Rojas *et al*., in a prospective cohort study of 37 adult patients with sepsis observed a decrease in serum T3 levels in nonsurvivors and survivors ($P< 0.001$) [8]. Nonsurvivors had lower T3 and T4 compared with survivors. The T3 (ng/dl) in nonsurvivors versus survivors was (30.40 ± 13.4 vs. 52. 5 ± 19.6, $P< 0.001$. The T4 (µg/dl), in nonsurvivors was 5.50 ± 1.70, whereas in survivors it was 7.20 ± 2.80, $P< 0.05$). They had taken a $P< 0.001$ as statistically significant, if $P< 0.05$ would have been considered T4 would come into perspective. The greatest discriminative efficacy of thyroid hormones study with an unfavorable sepsis evolution corresponded to a T3 value below 35 ng/dl. Similar to this study, in our study, nonsurvivors had lower T3 and greater decrease in T3 was associated with unfavorable outcome.

Prolactin is an immunomodulatory hormone involved in the endocrine response to the stress, and hyperprolactinemia is a common finding in initial phases. Blunted prolactin response during chronic stress is speculated to lead to increased susceptibility to infection [9]. Prolonged hypoprolactinemia (i.e., >7 days) has been shown to be a risk factor for lymphopenia and lymphoid depletion in patients with nosocomial sepsis and multiple organ failure [10]. However, in our study, baseline hypoprolactinemia was not associated with low lymphocyte counts within 72 hours of ICU admission. These findings might suggest that the association between hypoprolactinemia and lymphopenia during critical illness develops over time. The study showed significant difference in prolactin levels between survivors compared to non-survivors. prolactin rises in the acute phase of critical illness; this rise has been attributed to the actions of vasoactive intestinal polypeptide, oxytocin or cytokines. Higher prolactin was noted in trauma patients compared to other ICU patients. This was contrary to previous studies like by K.V.S Harikumar *et al* where there was no significant difference of admission prolactin levels between survivors and non survivors. It may be noted that these high values may be due to confounding factors like intake of common drugs like H2 blockers and domperidone.

The mean HBA1C among survivors was 6.21 and among non survivors were 8.23. So patients with higher HBA1C had lesser chance of survival and poorer prognosis. These results were similar to other studies like by Gornik *et al* where 286 patients admitted to medical wards or the medical ICU was evaluated. Hospital mortality for all patients with sepsis was 21.7% with a median LOS of 6 days (95% CI 6–7 days). Patients who survived had significantly ($P< 0.001$) lower HbA1c (median 8.2%; 95% CI 7.8–8.6%) than patients who died (median 9.75%; 95% CI 8.7–10.6%) [11]

The importance of HBA1C as a predictor of mortality was also evaluated in a study in Greece by Kompati M *et al* where admission HBA1C was seen in 555 consecutive patients irrespective of glycaemic status and a cut-off of 6.5 predicted more severe disease (as described by Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores at admission) and higher ICU mortality (adjusted odds ratio, 2.33; 95% confidence interval, 1.04-5.25) [12]. In another study conducted in Iran without considering the history of diabetes, non survivors had significantly higher HbA1c values compared to survivors (7.25 ± 1.87 vs. 6.05 ± 1.22, respectively, $P< 0.001$). Blood glucose levels in ICU admission also showed a significant correlation with risk of death ($P< 0.006$, confidence interval [CI]: 1.004-1.02, relative risk [RR]: 1.01). Logistic regression analysis revealed that HbA1c increased the risk of death; with each increase in HbA1c level, the risk of death doubled [12].

The mechanism behind low serum T3 and fT3 and its correlation with severity of clinical illness are multifactorial. Cytokines play a major role in the pathogenesis of sepsis. Cytokine such as tumor necrosis factor, interferon-alpha (INF alpha), and interleukin-6 (IL-6) levels are elevated in patients with sepsis [13] Corssmit *et al*. assessed the acute effects of INF alpha, administration on thyroid hormone metabolism in healthy men. They found no decrease in serum T4 and fT4 levels; however, there was a significant decrease in serum TSH, T3, and fT3. The INF alpha-induced a moderate increase in IL-6 but not that of IL-1 and tumor necrosis factor. The acute effects of INF-alpha mimics the NTIS possibly mediated in part by IL-6 [14]. Stouthard *et al*. assessed the effects of IL-6 on thyroid hormone metabolism in humans. In the acute phase, they found no effects of IL-6 on T4 and fT4 but a decrease in TSH, T3, and fT3 [15]. Inhibition of the enzyme 5 ′-deiodinase that catalyzes the conversion of T4 to T3 is known to occur in NTIS [16]. Cytokines also contribute to the inhibition of 5 ′-deiodinase leading to low serum T3 and fT3 in NTIS in sepsis [17]. These studies not only show that cytokine are pathogenic factors in NTIS but also that the pattern of alteration in thyroid hormones is quiet similar to our present study on patients with sepsis. Alteration in cytokines levels may be the predominant mechanism behind NTIS in sepsis. Tanycytes are specialized ependymal cells lining the floor and inferolateral borders of the third ventricle in the mediobasal hypothalamus (MBH). Recent animal studies have shown that bacterial lipopolysaccharide (LPS) induces type 2 iodothyronine deiodinase (D2) activation in tanycytes independently of circulating thyroid hormone and leads to the central hypothyroidism associated with infection [18]. Further Sánchez *et al*., in their studies on Sprague Dawley rats have shown that the LPS-induced increase in D2 gene expression in the tanycytes of MBH is generally not mediated by the associated increase in glucocorticoids, and other mechanisms, such as an increase in proinflammatory cytokines, may be of primary importance in the D2 response to prolactin [19]. As plasma selenium levels are often low in sick patients, especially those with severe illness and sepsis, it has been suggested that the expression of the selenoenzymes D1, D2, and D3 may be limited by the low selenium supply in these patients, and that this represents a mechanism for the pathogenesis of the low T3 in NTS [20].

The current evidence thus suggests that down-regulation of thyroid hormone transporters does not occur in the NTIS, and other mechanisms must be responsible for the impaired uptake of thyroid hormone that is manifest in illness. Such mechanisms may include depletion of hepatic ATP or the presence in plasma of substances that impair hepatic uptake of thyroid hormone. NEFA and numerous substances that accumulate in the plasma of patients with renal or liver

dysfunction inhibit cellular transport of T4 into cultured hepatocytes [21].

The demographic profile of the study patients did not differ significantly between the survivors and non-survivor. The mean age among diabetics was 54.53 years and that among non-diabetics was 40.82 years. 70 were male and 30 patients were female. TSH showed a linear correlation with age in our study population. This was explained earlier by many investigators that the age-related elevation in TSH could be due to increasing autoimmunity, environmental, and genetic factors. Although insulin resistance and diabetes are also related to the age, our data did not show any correlation between HbA1c and age. This could be explained because of the selection bias of critically ill patients in the study which does not represent the general population.

It is postulated that the abnormal elevation in HbA1c indicates that the control of blood glucose was not satisfactory, but studies have confirmed that abnormal elevation in blood glucose is an independent risk factor for the poor prognosis of critically ill patients, [23, 25] and strict control of blood glucose is one of the target treatments for these patients. [26, 28]

There were some limitations in the study like the measurements were taken at a point of time when patient presented to ICU not when the disease started so the hormonal levels may have altered due to secondary adaptive response by the body to maintain homeostasis. Measurements of random blood sugar may have been a better option than fasting and post prandial glucose for many patients in ICU were either nil orally or on special diet which might alter the results. The measurements may have been confounded due to common drugs used in ICU like heparin, amiodarone, corticosteroids, dopamine etc. Both medical and surgical patients were analysed but a comparable single cohort could have been better as there is wide range of difference of adaptive changes between medical and surgical cases like blunt trauma.

Conclusion

Serum free T3 was raised in the patients but there was no significant difference among other thyroid hormone parameters among survivors and non-survivors' in spite of all previously known euthyroid sample being selected. This lent further evidence to presence of sick euthyroid syndrome in the critically ill ICU patients. Patients with low free T3 had poorer prognosis than euthyroid patients. Serum prolactin was also raised in especially in the sepsis patients. This is due to the rise of prolactin in acute phase of sepsis. As regarding glycaemic status people with higher HBA1c were less likely to survive but there was no relation between mortality and fasting or postprandial blood glucose. So these markers should be evaluated in all patients admitted to ICU for prognostication. However since the metabolic and endocrinal alterations due to stress in critical illness is a complex interplay of various factors in an attempt to maintain body homeostasis a combination of these parameters has a higher predictive value than a single entity. Larger and more extensive studies should be carried out by combining the parameters in this study with established scales like APACHE II, SOFA to find a more reliable scale for prognosis in the critically ill.

References

1. Vasa FR, Molitch ME. Endocrine problems in the chronically ill patient. Clin Chest Med. 2001; 22:193-208.
2. Suvarna JC, Fande CN. Serum thyroid hormone profile in critically Ill children. Indian J Pediatr. 2009; 76:1217-21.
3. Kumar KV, Kapoor U, Kalia R, Chandra NS, Singh P, Nangia R *et al*. Low triiodothyronine predicts mortality in critically ill patients. Indian J Endocrinol Metab. 2013; 17:285-8.
4. Wang F, Pan W, Wang H, Wang S, Pan S. Relationship between thyroid function and ICU mortality: A prospective observation study. Critical Care. 2012; 16:11.
5. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB *et al*. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA. 1981; 245:43-5.
6. Chinga-Alayo E, Villena J, Evans AT, Zimic M. Thyroid hormone levels improve the prediction of mortality among patients admitted to the intensive care unit. Intensive Care Med. 2005; 31(10):1356-61.
7. Suresh M, Srivastava NK, Jain AK, Nandy P. Thyroid dysfunction in critically ill patients in a tertiary care hospital in Sikkim, India. Thyroid Res Pract. 2017; 14:58-62.
8. Mangas-Rojas A, García-Rojas JF, Barba Chacón A, Millán Núñez-Cortés J, Zamora-Madaria E. Changes in the hypophyseal-thyroid axis and their prognostic value in sepsis. Rev Clin Esp. 1990; 187:395-8.
9. Russell DH, Kibler R, Matrisian L, Larson DF, Poulos B, Magun BE *et al*. Prolactin receptors on human T- and Blymphocytes: Antagonism of prolactin-binding by cyclosporin. J Immunol. 1985; 134:3027-31.
10. Bernton EW, Meltzer MS, Holaday JW. Suppression of macrophage activation and T lymphocyte function in hypoprolactinemic mice. Science. 1988; 239:401-4.
11. Gornik I, Gornik O, Gasparovic V. Hemoglobin A1c predicts outcome of sepsis in patients with diabetes. Crit Care. 2006; 10(1):P.251.
12. Kompoti M, Michalia M, Salma V, Diogou E, Lakoumenta A, Clouva-Molyvdas PM *et al*. Glycated hemoglobin at admission in the intensive care unit: clinical implications and prognostic relevance. J Crit Care. 2015; 30(1):150-5.
13. Mohammad Afkhami-Ardekani, Maryam Rashidi, Ahmad Shojaoddiny. Effect of Thyroid Dysfunction on Metabolic Response in Type 2 Diabetic Patients; iranian journal of 20 diabetes and obesity, 2010, 2(1).
14. Hack CE, Aarden LA, Thijs LG. Role of cytokines in sepsis. Adv Immunol. 1997; 66:101-95.
15. Corssmit EP, Heyligenberg R, Endert E, Sauerwein HP, Romijn JA. Acute effects of interferon-alpha administration on thyroid hormone metabolism in healthy men. J Clin Endocrinol Metab. 1995; 80:3140-4.
16. Stouthard JM, van der Poll T, Endert E, Bakker PJ, Veenhof CH, Sauerwein HP, *et al.* Effects of acute and chronic interleukin-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab. 1994; 79:1342-6.
17. Chopra IJ. Nonthyroidal illness syndrome or euthyroid sick syndrome? Endocr Pract. 1996; 2:45-52.
18. Fekete C, Gereben B, Doleschall M, Harney JW, Dora JM, Bianco AC *et al*. Lipopolysaccharide induces type

2 iodothyronine deiodinase in the mediobasal hypothalamus: Implications for the nonthyroidal illness syndrome. Endocrinology. 2004; 145:1649-55.
19. Fekete C, Sarkar S, Christoffolete MA, Emerson CH, Bianco AC, Lechan RM *et al*. Bacterial lipopolysaccharide (LPS)-induced type 2 iodothyronine deiodinase (D2) activation in the mediobasal hypothalamus (MBH) is independent of the LPS-induced fall in serum thyroid hormone levels. Brain Res. 2005; 1056:97-9.
20. Sánchez E, Singru PS, Fekete C, Lechan RM. Induction of type 2 iodothyronine deiodinase in the mediobasal hypothalamus by bacterial lipopolysaccharide: Role of corticosterone. Endocrinology. 2008; 149:2484-93.
21. Maehira F, Luyo GA, Miyagi I, Oshiro M, Yamane N, Kuba M *et al*. Alterations of serum selenium concentrations in the acute phase of pathological conditions. Clin Chim Acta. 2002; 316:137-46.
22. Hennemann G, Docter R, Friesema EC, de Jong M, Krenning EP, Visser TJ *et al*. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev. 2001; 22:451-76.
23. Kenneth E. Laboratory diagnosis and monitoring of diabetes mellitus. Am J Clin Pathol. 1999; 112:665-674.
24. Kang H, Jiang ZL, Zhang XL. Clinical significance for glycosylated hemoglobin detection. J Pract Med Techni. 2006; 13:2561-2562.
25. Gerstein HC. Glyculation hernoglobin: finally ready for prime tima as a cardiovascular risk factor. Ann Inter Med. 2004; 141:475-476.
26. He W, Zhang TY, Zhou H, Li T, Zhao JY, Zhao D *et al*. Impact of intensive insulin therapy on surgical critically ill patients. Zhonghua Wai Ke Za Zhi. 2007; 45:1052-1054.
27. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I *et al*. Intensive insulin therapy in the medical ICU. N Eng J Med. 2006; 345:449-461.
28. Umpierrez GE, Hellman R, Korytkowski MT *et al*. Management of hyperglycemia in hospitalized patients in non-critical care setting: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2012; 97:16-38.