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Symposium Article

Sick Euthyroid Syndrome: A Myth or Reality

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ABSTRCT:

Altered thyroid function in non-thyroidal illness(NTI) is a well-recognized finding. The term euthyroid sick syndrome (ESS) identifies abnormalities in thyroid function observed in patients with systemic nonthyroidal illnesses (NTIs). ESS being most common endocrine change seen in critically ill patients, is characterized by low triiodothyronine (T3), low or normal thyroxine (T4) and normal thyroid stimulating hormone (TSH). The extent of SES is associated with prognosis, but no proof exists for causality of this association. T3 levels reflect the patient's clinical status, T4 levels can predict survival. Initially, SES is a consequence of the acute phase response to systemic illness and macronutrient restriction, which might be beneficial. Pathogenesis of SES in long term critical illness is more complex and includes suppression of hypothalamic thyrotropin-releasing hormone, accounting for persistently reduced secretion of thyroid-stimulating hormone despite low plasma thyroid hormone. Distinguishing between SES and other primary thyroid disorders, can be difficult in ICU setting. Clinical benefits of supplementing thyroid hormone in SES has not been answered adequately. No evidence-based consensus or guideline advocates thyroid hormone treatment of SES at present.

Key words:

Sick Euthyroid Syndrome, Non-Thyroidal illness, Thyroid hormone, Critical illness

Introduction:

Thyroid hormone is essential for the regulation of energy metabolism, and for the physiological function of virtually all tissues.[1,2] The production of thyroxine (T4) by the thyroid gland is regulated by the classic hypothalamus- pituitary-thyroid(HPT) axis, which is controlled by a classic endocrine feedback loop. Thyrotropin- releasing hormone (TRH) is

released at the level of the hypothalamus, which stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). In turn, TSH drives the thyroid gland to release thyroid hormones. The biological activity of thyroid hormone (i.e., the availability of the active hormone 3,5,3V-triiodothyronine [T3]), is largely regulated by the iodothyronine deiodinases D1, D2, and D3.[3,4]which convert T4 to either T3 or to the inactive metabolite reverse T3 (rT3). Both T4 and T3 have an inhibitory effect on TRH and TSH secretion by way of a negative feedback loop. Thus, the HPT axis was assumed to have a fixed setpoint, aiming at individually determined serum concentrations of thyroid hormones.[5] However, studies have shown that these serum concentrations can be variable and adaptive in response to environmental factors, including nutrient availability and inflammatory stimuli. [6]

Substantial changes in plasma concentrations of thyroid hormones have been noted in a range of diseases, characterised by clearly decreased plasma T3, low plasma T4, and increased plasma reverse T3 (rT3) concentrations. Despite low T3 and T4, TSH is typically maintained within its normal range or is slightly decreased. This ensemble of changes in thyroid function tests is collectively known as the non-thyroidal illness syndrome (NTIS)[7,8] or Sick Euthyroid Syndrome (SES). Other terminologies used are 'Low T3 syndrome', 'thyroid allostasis in critical illness, tumours, uremia and starvation' (TACITUS). In this review, we will use the term SES.

It is an ongoing debate that these changes are physiological responses during critical illness or maladaptive response to underlying illness. In this review, we focus on the presentation, pathogenesis, metabolic consequences, and clinical management of thyroid dysfunction in critically ill patients. The distinction between SES and primary thyroid disorders also has been discussed.

Whether SES in response to critical illnesses should be an adaptive mechanism, such as in starvation, or rather a maladaptive mechanism is unknown. On the one hand, a seemingly logical assumption is that a reduction in serum T3 would decrease thyroid hormone action in important T3 target organs, such as the liver and muscles, thereby affecting metabolism that might be beneficial in critically ill patients. On the other hand, patients with extended critical illness show clear symptoms and signs that resemble those noted in patients with hypothyroidism including impaired consciousness, myocardial dysfunction, hypothermia, neuropathy, muscle weakness, atrophy of the skin, and hair loss, which together might impede recovery.[9,10] Although the hypothesis that SES in patients in the ICU could be maladaptive has been extensively discussed,[11] surprisingly few clinical studies (some being randomised controlled trials [RCTs]) aimed at modulating SES to improve clinical outcome have been reported. With some clinical intervention studies, irrespective of their design, the risk–benefit ratio might seem favourable with most patients showing a benefit and only a few showing harms, but this ratio has not been formally analysed when only RCTs with clinically relevant outcome measures, such as mortality or morbidity, are considered.[12]

Acute Vs chronic critical illness

Within a few hours after the onset of disease, plasma T3 decreases and plasma rT3 increases, and the magnitude of these changes is related to the severity of the disease. In severely ill patients, T4 decreases as well and both low T4 and low T3 are associated with a poor prognosis.[13,14] Although serum TSH levels may increase briefly after the onset of disease, circulating TSH usually remains within the normal range, despite the decreased levels of serum T3, and in severe illness also of serum T4. The nocturnal surge of TSH that occurs in

the normal physiological state is absent in the acute phase of critical illness.[15]

The thyrotropic profile in chronic critical illness differs from the acute phase. Patients who have been receiving intensive care for several days have even lower levels of T3 and a low T4.In addition, levels of TSH are low to normal and there is hardly any pulsatility in the nocturnal TSH secretory pattern compared with healthy individuals.[16-18] Hypothalamic expression of the TRH gene is low in patients who died after chronic severe illness compared with patients who died from an acute event.[19] Obviously, not only the duration, but also the severity of illness is an important factor determining the changes in serum thyroid hormone levels.

Pathogenesis of SES

HPT axis feedback dysregulation

Severe illness induces large changes in thyroid hormone economy, resulting in a downregulation of the HPT axis both at the hypothalamic and pituitary levels with an associated decrease in circulating thyroid hormone concentrations.[7] This finding points to substantial changes to the negative feedback regulation in the HPT axis during SES.[2] Central downregulation of the HPT axis during SES was supported by the observation in autopsy samples of decreased TRH gene expression in the hypothalamic paraventricular nucleus. TRH mRNA expression in the paraventricular nucleus showed a positive correlation with antemortem concentrations of plasma TSH and T3.[13] Additionally, simultaneous changes in liver metabolism of thyroid hormone contribute to the characteristic changes in thyroid hormone plasma concentrations: low plasma T3 and high plasma rT3, normal or low to normal plasma TSH, and low plasma T4 during severe illness.[7]

Although the mechanisms associated with these seemingly paradoxical HPT axis changes are not completely understood, findings from animal studies using various SES models have elucidated some aspects of SES pathogenesis. SES induces specific changes in enzymes associated with thyroid hormone metabolism (deiodinases type 1 [D1], 2 [D2], and 3 [D3]), thyroid hormone transporters, and thyroid hormone receptors (TRα and TRβ).[7] Induction of acute inflammation in rodents by a single peripheral injection of bacterial endotoxin or lipopolysaccharide stimulates D2 mRNA expression in tanycytes lining the third ventricle in the hypothalamus.[20] This D2 upregulation is followed by an increased local conversion of T4 to T3, which subsequently lowers TRH mRNA expression in the paraventricular nucleus, as noted in people (figure 1).[21] Although an increase in D2 activity has not yet been proven, experiments in an in-vitro co-culture system showed that glial D2 modulates T3 concentrations and gene expression in neighbouring neurons.[22] Thus, inflammation inhibits hypophysiotropic TRH neurons probably via increased D2 activity, thereby accounting for hypothalamic downregulation of the HPT axis during SES.

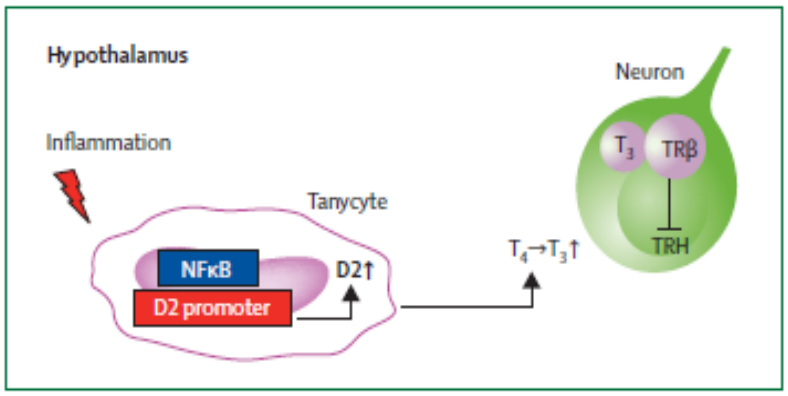

Figure 1: Schematic representation of hypothalamic thyroid hormone signaling during inflammation. [T3=tri-iodothyronine. TRβ=thyroid hormone receptor β. TRH=thyrotropin-releasing hormone. NFκB=nuclear factor kappa-light-chain-enhancer of activated B cells. D2=deiodinase type 2. T4=thyroxine.]

The liver is one of the key metabolising organs of thyroid hormone. It expresses the thyroid hormone transporters mono carboxylate transporter 8 (MCT8) and MCT10, both D1 and D3 (although D3 is expressed at very low concentrations in a healthy liver), TRβ1, and TRα1. Although liver-expressed D1 contributes about only 20% of the circulating T3, this enzyme's involvement in SES pathogenesis has been extensively studied. Investigations showed reduced liver D1 mRNA expression and enzyme activity in people during illness, suggesting a role for liver-expressed D1 in the pathogenesis of illness-induced changes in plasma T3 and rT3.[23] Induction of D3 during SES in tissues that do not normally express, or express only very little, D3 is likely to greatly contribute to the abnormalities in thyroid economy reported during ischaemic injury.[24]

Role of inflammatory response

Clear association between the changes in thyroid hormone metabolism and the activation of various proinflammatory cytokines has been proved. Cytokines are important mediators of the acute phase response affecting fever, leucocytosis, the release of stress hormones and the production of acute phase proteins. Cytokines are also able to affect the expression of many proteins connected with thyroid hormone metabolism and are causally involved in the pathogenesis of SES.[25,26] Lipopolysaccharide stimulation of a range of cells results in a strong inflammatory response characterised by the production of various cytokines, including tumour necrosis factor α (TNFα), interleukin 1, and interleukin 6. For the induction of cytokines, the activation of inflammatory signalling pathways, including nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) and activator protein 1, is mandatory.[27] Activation of NFκB was shown to play an important part in the up regulation of D2 in hypothalamic tanycytes during inflammation.[27,28] D1 is also sensitive to cytokines; D1 expression in a liver cell line decreases upon interleukin 1β stimulation and this response can be abolished by simultaneous inhibition of NFκB and activator protein 1.[28] In summary, cytokines that are activated as a result of the inflammatory response are causally associated with the pathogenesis of SES, making SES part of the acute phase response.

Role of nutrition

Critical illness is associated with loss of appetite and poor oral and enteral nutritional intake.[29] Fasting induces a decrease in serum thyroid hormones through a multifactorial mechanism and includes a decrease in serum leptin, and downregulation of hypothalamic, hypophysiotropic TRH neurons, contributing to persistently low concentrations of serum TSH. Decreased caloric intake during critical illness is associated with pronounced SES. At the organ level, activity of D1, the enzyme driving the conversion of T4 into the biologically active T3 and clearing the biologically inactive rT3, is decreased. Increased activity of D3, the T3 inactivating enzyme, has also been reported.[30,31] The sub analysis of the EPaNIC trial [32] suggested that the inactivation of T3 to rT3, as part of the fasting response, might be a beneficial adaptation during acute illness. Targeting of fasting blood glucose concentrations with intensive insulin treatment in children with critical illness to 2.8–4.4 mmol/L (50 -80 mg/dl) in infants and 3.9–5.6 mmol/L(70-100mg/dl) in children, thereby mimicking a fasting response, resulted in improved outcomes,[33] but at the same time aggravated peripheral SES. Use of a multivariate, Cox proportional hazard analysis showed that the further reduction of T3 and rT3 accounted for part of the therapy improving patient mortality rates.Together, these findings suggest that thyroid economy is affected by decreased nutritional intake during acute critical illness and that the inactivation of T4 to rT3 and T3 to T2, as part of the fasting response, might be a beneficial adaptation during acute illness.[32]

Diagnosis

Substantial changes in thyroid function occurs during different phases of critical illness. (Figure.2)[33] In the acute phase of illness, the following are observed: reduction in circulating T_3, increase in serum rT_3, and no change in serum FT_4, total T_4, or TSH. In stage 2: modest increase in FT_4 and further decrease in T_3 and increase in rT_3. In phase 3: a loss of pulsatile secretion of TSH; decrease in T_4, T_3, and FT_4; and an increase—followed by a decrease—in serum rT_3. In the recovery phase: a gradual normalization of parameters; TSH can be elevated in this stage.

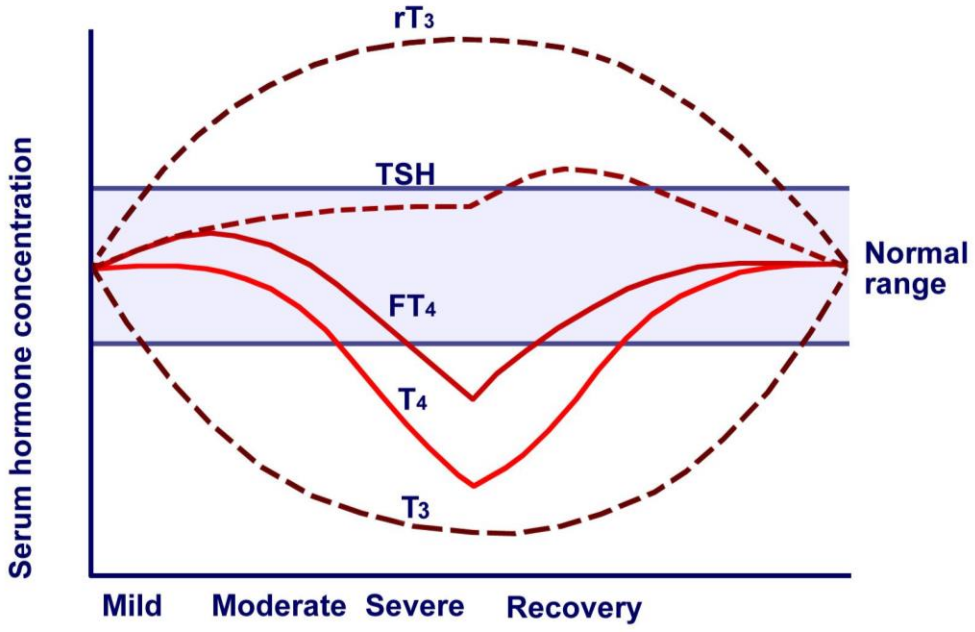

Figure 2. Changes in thyroid function during different phases critical illness[33]

T3, T4 and TSH as predictor of outcome

At any given point T3 level reflects clinical status of patient and persistent low serum T3 levels with non-improvement would predict bad prognosis. Low T3 & T4 values at admission are associated with very high risk of mortality. T4 levels independently can predict mortality PRISMII score. Children with combined low T3 and T4 levels need more close observation and aggressive therapeutic intervention.[34-36]
Many drugs used commonly in ICUs can alter the thyroid hormone levels as shown in Table.1. Hence interpretation of Thyroid function test should be done with great caution in critical care settings.

Table 1: Effects of Various Drugs used in ICUs on Thyroid Hormone Metabolism

Drug	Effect
Dopamine	Blunts TSH response to TRH
Corticosteroids	Suppresses basal and TRH-stimulated TSH release
Iodinated contrast agents	Decreases hepatic conversion of T4 to T3
Amiodarone	Decreases hepatic conversion of T4 to T3 and decreases servo feedback T3 binding at the pituitary
Phenytoin	Enhances T4 to T3 conversion (low free T4 and low total T4)

TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone.

SES: Differentiation from primary Thyroid Disorders

Diagnosis of primary hypothyroidism can be difficult in patients who are severely ill and not known to have hypothyroidism before admission to the ICU because serum thyroid hormones, especially T3, are decreased in most patients in the ICU due to SES. In patients clinically suspected to have severe hypothyroidism, the most useful test for diagnosis is measurement of plasma TSH, because a normal plasma TSH excludes primary hypothyroidism. In patients with a combination of primary hypothyroidism and SES, serum TSH concentration is still high and responsive to levothyroxine treatment. However, of note is that in patients who have hypothyroidism the high serum TSH concentration might decrease during the acute phase of illness especially if dopamine or high doses of glucocorticoids are given. Thus, high serum

TSH in combination with low serum T4 is indicative of hypothyroidism; although, this combination can also be seen in patients recovering from SES. A high serum T3 to T4 ratio and a low serum rT3 favour the presence of hypothyroidism, since these ratios are reversed in SES, but the diagnostic accuracy of these measurements is poor.[8] Table 2 elaborates differentiation of primary Thyroid Disorders from SES in details.

A low serum TSH could suggest thyrotoxicosis, especially if serum free T4 is also high. The extent of TSH suppression is associated with the likelihood of thyrotoxicosis. Combination of suppressed TSH, high concentrations of free T4, and normal T3 concentrations might point to the combination of thyrotoxicosis and SES, and has been referred to as T4 thyrotoxicosis.[8]

Table 2. Changes in thyroid function tests in hypothyroidism and during critical illness

	TSH	**T_4**	**F T_4**	**T_3**	**r T_3**
Primary hypothyroidism	↑↑	↓	↓	↓ or =	↓
Central hypothyroidism	= or ↓	↓ or =	↓ or =	=	↓
SES, acute phase	=	= or ↑	= or ↑	↓	↑
NTS, Chronic phase	↓	↓	↓	↓↓	↑ or =
NTIs, recovery phase	= or ↑	↓ or =	↓ or =	↓ or =	V

V, variable; ↑, increased; ↓, decreased; =, normal range

Management of SES

Treatment with T3 or T4

Treatment of euthyroid sick syndrome is more controversial. Although the basis for the observation is not clear, adult investigators have previously demonstrated that low serum T3 levels represent the single most significant predictor of cardiovascular and all-cause mortality among adults with heart disease.[34] Interventions aimed at normalising thyroid hormone concentrations in patients with extended critical illness has so far not been proved beneficial satisfactorily. Triiodothyronine replacement in adults with impaired left ventricular function resulted in improved left ventricular function, as well as restored cardiomyocyte gene expression to euthyroid levels.[37] Among adult patients with heart failure, infusion of T3 for 72 hours

resulted in normalization of serum T3 levels with concomitant improvement in stroke volume, as well as left ventricular end-diastolic volume.[38] Similarly smaller studies, involving thyroid treatment during coronary bypass,[39,40] valvular heart surgeries[41] and for treating left ventricular dysfunction[42] have shown positive results in adult patients.

Such findings have stimulated interest in thyroid hormone pathophysiology among children with cardiovascular disease. Thyroid function and clinical outcomes were assessed serially among children undergoing cardiac bypass surgery. All subjects demonstrated euthyroid sick syndrome characterized by reduced TSH, total T3, free T3 index, and T3 uptake. These changes were correlated with prolonged need for mechanical ventilation, degree of organ dysfunction, and vasoactive-inotropic scores.[43] Replacement dosing of T3 following cardiopulmonary bypass resulted in increases in plasma T3 concomitant with measures of improved myocardial performance, particularly among those children exhibiting low postoperative cardiac output.[44]

Small RTCs have assessed the effects of treatment with thyroid hormones in patients with SES other than cardiac surgeries like in patients with burn injury,[45] acute renal failure[46] and those in the ICU with low T4 concentrations.[47] Furthermore, the age of the study population varies greatly in these studies,[42-47] ranging from premature newborns to children and adults. Disease severity is another variable, ranging from critical illness at the medical ICU to healthy participants. Surprisingly little consistency is present in the choice of the active study drug, since both T3 (given orally and intravenously) and levothyroxine have been used. In the context of studies with T4 or T3, of note is that normalising thyroid hormone concentrations in serum does not necessarily result in normal tissue concentrations of thyroid hormone.

Selenium and N-acetylcysteine

In addition to treatment with thyroid hormones, the effect of selenium on SES per se and on clinical outcomes has been studied.[48,49] A small RCT[50] investigated the effect of N-acetylcysteine, an antioxidant that restores intracellular glutathione (a cofactor required for D1 catalytic activity), on SES. N-acetylcysteine administration seemed to prevent the derangement in thyroid hormone concentrations that commonly happens in the acute phase of acute myocardial infarction, suggesting that oxidative stress is part of the pathogenesis of SES in acute myocardial infarction.

Future therapies

First possibility, use of hypothalamic neuropeptides, especially TRH, to stimulate the HPT axis to treat SES could be promising. Given in combination with growth hormone releasing peptide 2, can restore circulating concentrations of thyroid hormone and TSH pulsatility to a remarkable extent.[51] Another possibility will be to investigate treatment with recombinant human TSH, because this is a physiological stimulus—like TRH—for thyroid hormone release from the thyroid. TSH treatment in patients with central hypothyroidism was sufficient not only to increase plasma TSH concentrations to the normal range but to improve patient's quality of life and sleep behaviour in small pilot study.[52] Again, these investigations should be done in adequately powered, randomised, placebo-controlled studies.

Conclusion

Alteration of Thyroid function in critical illness is a complex process. SES has been a well-established entity during critical illnesses with unclear resulting effects. In critically ill patients, changes at the level of the HPT axis, and at the thyroid level, are beneficial or harmful in terms of outcome probably depends on disease stage and severity. Whether SES is beneficial adaptation that protects against hyper catabolism, or it is a maladaptation that contributes to a worsening of the disease is controversial. Interventions aimed at normalising thyroid hormone concentrations in patients with extended critical illness are beneficial has so far not been satisfactorily answered. No evidence-based consensus or guideline advocates thyroid hormone treatment of SES at present. Adequately powered RCTs need to be undertaken to explore the management of SES to improve clinical outcome in critically ill children.

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References:

1. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev 2001; 81(3):1097 –142.
2. Larsen PR, Davies TF, Hay ID. The Thyroid Gland. In: Wilson JD, Foster DW, Kronenberg HM, et al, editors. Williams Textbook of Endocrinology. 9th edition. Philadelphia7 WB Saunders; 1998. p. 389 – 515
3. Leonard JL, Koehrle J. Intracellular pathways of iodothyronine metabolism. Philadelphia7 Lippincott Williams & Wilkins; 2000.
4. Bianco AC, Salvatore D, Gereben B. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002;23(1):38 – 89.
5. Alkemade A, Friesema EC, Unmehopa UA. Neuroanatomical pathways for thyroid hormone feedback in the human hypothalamus. J Clin Endocrinol Metab 2005; **90:** 4322–34.
6. Fekete C, Lechan RM. Negative feedback regulation of hypophysiotropic thyrotropin-releasing hormone (TRH) synthesizing neurons: role of neuronal afferents and type 2 deiodinase. Front Neuroendocrinol 2007; 28**:** 97–114.
7. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev 2011; **32:** 670–93.
8. Wiersinga WM, van den Berghe G. Nonthyroidal illness syndrome. In: Braverman LE, Cooper DS, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text, 10th edn. Philadelphia: Lippincott Williams and Wilkins, 2013: 203–17.
9. Arem R, Wiener GJ, Kaplan SG, Kim HS, Reichlin S, Kaplan MM. Reduced tissue thyroid hormone levels in fatal illness. Metabolism 1993; 42**:** 1102–08.
10. Bello G, Pennisi MA, Montini L. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. Chest 2009; 135**:** 1448–54.
11. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 2014; 24: 1456–65.
12. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol 2015;3: 816–25
13. Docter R, Krenning EP, de Jong M. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993;39(5): 499–518.
14. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995;23(1):78- 83.
15. Bartalena L, Pacchiarotti A, Palla R. Lack of nocturnal serum thyrotropin (TSH) surge
16. McIver B, Gorman CA. Euthyroid sick syndrome: an overview. Thyroid 1997;7(1):125 – 32.
17. Peeters RP, Wouters PJ, van Toor H. Serum rT3 and T3/rT3 are prognostic markers in critically ill patients and are associated with post-mortem tissue deiodinase activities. J Clin Endocrinol Metab

2005;90(8):4559 – 65.
18. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 1997;82: 4032–36
19. Van den Berghe G, de Zegher F, Veldhuis JD. Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone- secretagogues. Clin Endocrinol (Oxf) 1997;47(5):599 – 612.
20. Fekete C, Gereben B, Doleschall M. Lipopolysaccharide induces type 2 iodothyronine deiodinase in the mediobasal hypothalamus: implications for the nonthyroidal illness syndrome.Endocrinology 2004; 145: 1649–55.
21. Lechan RM, Fekete C. Feedback regulation of thyrotropin-releasing hormone (TRH): mechanisms for the non-thyroidal illness syndrome. J Endocrinol Invest 2004; 27 (suppl): 105–19.
22. Freitas BC, Gereben B, Castillo M. Paracrine signaling by glial cell-derived triiodothyronine activates neuronal gene expression in the rodent brain and human cells. J Clin Invest 2010; 120: 2206–17.
23. Peeters RP, van der Geyten S, Wouters PJ. Tissue thyroid hormone levels in critical illness. J Clin Endocrinol Metab 2005;90: 6498–507.
24. Huang SA, Bianco AC. Reawakened interest in type III iodothyronine deiodinase in critical illness and injury. Nat Clin Pract Endocrinol Metab 2008; 4: 148–55.
25. Chopra IJ, Sakane S, Teco GN. A study of the serum concentration of tumor necrosis factor-alpha in thyroidal and nonthyroidal illnesses. J Clin Endocrinol Metab 1991; 72: 1113–16.
26. Pålsson-McDermott EM, O'Neill LA. Signal transduction by the lipopolysaccharide receptor, Toll-like receptor-4. Immunology 2004;113: 153–62.
27. de Vries EM, Kwakkel J, Eggels L. NFκB signaling is essential for the lipopolysaccharide-induced increase of type 2 deiodinase in tanycytes. Endocrinology 2014; 155: 2000–08.
28. Kwakkel J, Wiersinga WM, Boelen A. Differential involvement on nuclear factor-kappaB and activator protein-1 pathways in the interleukin-1beta-mediated decrease of deiodinase type 1 and thyroid hormone receptor beta1 mRNA. J Endocrinol 2006; 189: 37–44.
29. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014; 370: 2450–51.
30. Richmand DA, Molitch ME, O'Donnell TF. Altered thyroid hormone levels in bacterial sepsis: the role of nutritional adequacy. Metabolism 1980; 29: 936–42.
31. Casaer MP, Mesotten D, Hermans G. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365: 506–17.
32. Langouche L, Vander Perre S, Marques M. Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its relation with outcome: a randomized, controlled clinical study. J Clin Endocrinol Metab 2013; 98: 1006–13.
33. Brent GA, Hershman JM. Effects of nonthyroidal illness on thyroid function tests. In: Van Middlesworth L. ed. The Thyroid Gland: A Practical Clinical Treatise. Chicago: Year Book Medical, 1986;83–110.
34. Iervasi G, Pingitore A, Landi P.Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation 2003; 107:708-713.
35. SuvarnaJC, FandeCN. Serum thyroid hormone profile in critically ill children. Indian J Pediatr 2009; 76(12): 1217-21.
36. Patki VK, Antin JV. Alterations of thyroid Function in Critically Ill Children. J Pediatr Crit Care 2014;1(4):229-35.
37. Ladenson PW, Sherman SI, Baughman KL. Reversible alterations in myocardial gene expression in a young man with dilated cardiomyopathy and hypothyroidism. Proc Natl Acad Sci USA 1992; 89:5251-55.
38. Pingitore A, Galli E, Barison A. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 93:1351-1358 2008 18171701
39. Güden M, Akpinar B, Sagğbaş E, Sanisoğlu I, Cakali E,Bayindir O. Effects of intravenous triiodothyronine during coronary artery bypass surgery. Asian Cardiovasc Thorac Ann 2002;10: 219–22
40. Choi YS, Shim JK, Song JW, Song Y, Yang SY, Kwak YL. Efficacy of perioperative oral triiodothyronine replacement therapy in patients undergoing off -pump coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2013; 27: 1218–23.

41. Choi YS, Kwak YL, Kim JC, Chun DH, Hong SW, Shim JK. Peri-operative oral triiodothyronine replacement therapy to prevent postoperative low triiodothyronine state following valvular heart surgery. Anaesthesia 2009; 64: 871–77.
42. Sirlak M, Yazicioglu L, Inan MB. Oral thyroid hormone pretreatment in left ventricular dysfunction. Eur J Cardiothorac Surg 2004; 26: 720–25.
43. Marks SD, Haines C, Rebeyka IM, Couch RM. Hypothalamic-pituitary-thyroid axis changes in children after cardiac surgery. J Clin Endocrinol Metab 2009; 94:2781-6.
44. Bettendorf M, Schmidt KG, Grulich-Henn J. Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. Lancet 2000; 356:529-34.
45. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxin concentration. J Clin Endocrinol Metab 1986; 63:1–8.
46. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyroxine in acute renal failure. Kidney Int 2000; 57: 293–98.
47. Becker RA, Vaughan GM, Ziegler MG. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med 1982;10: 870–75.
48. Berger MM, Reymond MJ, Shenkin A. Effect of selenium supplements on the low T3 syndrome after trauma: a randomized trial. Intensive Care Med 1996; 22: 575–81.
49. Mishra V, Baines M, Perry SE. Effect of selenium supplementation on biochemical markers and outcome in critically ill patients. Clin Nutr 2007; 26: 41–50.
50. Vidart J, Wajner SM, Leite RS. N-acetylcysteine administration prevents nonthyroidal illness syndrome in patients with acute myocardial infarction: a randomized clinical trial. J Clin Endocrinol Metab 2014; 99: 4537–45.
51. Van den Berghe G, Wouters P, Weekers F. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab 1999; 84: 1311–23.
52. Dixit K, Iwen A, Lehmphul I, Hoefi g C, Köhrle J, Brabant G. Treatment of central hypothyroidism with recombinant human TSH- a pilot study. Eur Thyroid J 2013; 2 (suppl 1): 75–194. P153.