Symposium Article

Sick Euthyroid Syndrome: A Myth or Reality

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ABSTRACT:

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 3,5,3'-triiodothyronine [T3]), is largely regulated by the iodothyronine deiodinases D1, D2, and D3, 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. However, studies have shown that these serum concentrations can be variable and adaptive in response to environmental factors, including nutrient availability and inflammatory stimuli.

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) 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.

Although the hypothesis that SES in patients in the ICU could be maladaptive has been extensively discussed, 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.

**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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} This finding points to substantial changes to the negative feedback regulation in the HPT axis during SES.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (TR\textalpha and TR\textbeta).\textsuperscript{7} Induction of acute inflammation in rodents by a single peripheral injection of bacterial endotoxin or lipopolysaccharide stimulates D2 mRNA expression in tanyctyes lining the third ventricle in the hypothalamus.\textsuperscript{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).\textsuperscript{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.\textsuperscript{22} Thus, inflammation inhibits hypophysiotropic TRH neurons probably via increased D2 activity, thereby accounting for hypothalamic downregulation of the HPT axis during SES.
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. 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.

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. 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. Activation of NFκB was shown to play an important part in the up regulation of D2 in hypothalamic tanycytes during inflammation. 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. 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. 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. The sub analysis of the EPaNIC trial 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 (70–100 mg/dl) in children, thereby mimicking a fasting response, resulted in improved outcomes, 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.

Diagnosis

Substantial changes in thyroid function occurs during different phases of critical illness. In the acute phase of illness, the following are observed: reduction in circulating T3, increase in serum rT3, and no change in serum FT4, total T4, or TSH. In stage 2: modest increase in FT4 and further decrease in T3 and increase in rT3. In phase 3: a loss of pulsatile secretion of TSH; decrease in T4, T3, and FT4; and an increase—followed by a decrease—in serum rT3. In the recovery phase: a gradual normalization of parameters; TSH can be elevated in this stage.
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 PRISMI score. Children with combined low T3 and T4 levels need more close observation and aggressive therapeutic intervention. 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>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Blunts TSH response to TRH</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Suppresses basal and TRH-stimulated TSH release</td>
</tr>
<tr>
<td>Iodinated contrast</td>
<td>Decreases hepatic conversion of T4 to T3</td>
</tr>
<tr>
<td>agents</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Decreases hepatic conversion of T4 to T3 and decreases servo feedback T3 binding at the pituitary</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Enhances T4 to T3 conversion (low free T4 and low total T4)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>TSH</th>
<th>T4</th>
<th>F T4</th>
<th>T3</th>
<th>r T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td>↑↑</td>
<td>↓</td>
<td>↓</td>
<td>↓ or =</td>
<td>↓</td>
</tr>
<tr>
<td>Central hypothyroidism</td>
<td>= or ↓</td>
<td>↓ or =</td>
<td>↓ or =</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>SES, acute phase</td>
<td>=</td>
<td>= or ↑</td>
<td>= or ↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>NTS, Chronic phase</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
<td>↑ or =</td>
</tr>
<tr>
<td>NTIs, recovery phase</td>
<td>= or ↑</td>
<td>↓ or =</td>
<td>↓ or =</td>
<td>↓ or =</td>
<td>V</td>
</tr>
</tbody>
</table>

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.\textsuperscript{38} Similarly smaller studies, involving thyroid treatment during coronary bypass,\textsuperscript{39,40} valvular heart surgeries\textsuperscript{41} and for treating left ventricular dysfunction\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{45} acute renal failure\textsuperscript{46} and those in the ICU with low T4 concentrations.\textsuperscript{47} Furthermore, the age of the study population varies greatly in these studies,\textsuperscript{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.\textsuperscript{48,49} A small RCT\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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Source of Funding: None

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