Endocrine and metabolic considerations in critically ill patients 4:

Thyroid function in critically ill patients

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Abstract

Patients in the intensive care unit (ICU) typically present with decreased concentrations of plasma tri-iodothyronine, low thyroxine, and normal range or slightly decreased concentration of thyroid-stimulating hormone. This ensemble of changes is collectively known as non-thyroidal illness syndrome (NTIS). The extent of NTIS is associated with prognosis, but no proof exists for causality of this association. Initially, NTIS is a consequence of the acute phase response to systemic illness and macronutrient restriction, which might be beneficial. Pathogenesis of NTIS 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. In some cases distinguishing between NTIS and severe hypothyroidism, which is a rare primary cause for admission to the ICU, can be difficult. Infusion of hypothalamic-releasing factors can reactivate the thyroid axis in patients with NTIS, inducing an anabolic response. Whether this approach has a clinical benefit in terms of outcome is unknown. In this Series paper, we discuss diagnostic aspects, pathogenesis, and implications of NTIS as well as its distinction from severe, primary thyroid disorders in patients in the ICU.

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Introduction

The hypothalamic–pituitary–thyroid (HPT) axis 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 prohormone thyroxine (T_4) is converted in peripheral tissues to the active hormone tri-iodothyronine (T_3). Hypothalamic TRH neurons were identified as determinants of thyroid hormone setpoint regulation more than three decades ago, and this discovery was followed by thyroid hormone receptor (TR) β being shown to have a key role in thyroid hormone negative feedback at the level of both the hypothalamus and anterior pituitary. Thus, the HPT axis was assumed to have a fixed setpoint, aiming at individually determined serum concentrations of thyroid hormones.[1] However, studies[2] 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 T_3, low plasma T_4, and increased plasma reverse T_3 (rT_3) concentrations. Despite low T_3 and T_4, 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).[3] In this Series paper we focus on the presentation, pathogenesis, metabolic consequences, and clinical management of thyroid dysfunction in critically ill patients. The distinction between NTIS and primary thyroid disorders in patients in the intensive care unit (ICU) can sometimes be difficult, which will also be briefly discussed.

Non-thyroidal illness

In both human beings and rodents, illness decreases serum concentrations of thyroid hormones without a concomitant rise in serum TSH. This effect represents a deviation from normal negative feedback regulation in the HPT axis. If a similar drop in serum T_3 and T_4 happened in the context of primary hypothyroidism, serum TSH would be substantially increased and the patient would need thyroid hormone replacement therapy. The combination of low serum T_3 and serum TSH within the reference range in the context of illness is called NTIS.[3,4] Several different names have been used to refer to NTIS, including sick euthyroid syndrome and low T_3 syndrome[5] (suggesting low plasma T_3 as the most consistent and striking change); in this Series paper we will use the term NTIS.

Very rapidly after the onset of acute stress, such as from myocardial infarction or surgery, serum T_3 concentrations decrease. In patients undergoing abdominal surgery, a fall in serum T_3 was noted within 2 h after the start of surgery.[6] NTIS has been reported in patients with acute and chronic illnesses including infectious diseases, cardiovascular and gastrointestinal diseases, cancer, burns, and trauma.[4] Serum T_3 further decreases as the severity of disease progresses. This change is shown in the reported correlations between the fall in serum T_3 concentrations and the size of a myocardial infarction, the increase in serum creatinine in renal insufficiency, and also burn severity.[4] Therefore, the scale of the decrease in plasma

concentrations of thyroid hormone generally represents the severity of the disorder and as a result, is associated with prognosis. In a study[7] with patients in the ICU, the sensitivity and specificity in predicting mortality were 75% and 80%, respectively, for serum T_4 less than 40 nmol/L. For combined low serum T_4 and high serum cortisol these numbers were even higher—ie, 100% and 81%. Likewise, low T_3 was shown to be a strong predictor of mortality in patients with heart disease.[8]

NTIS is present in most, if not all, critically ill patients—ie, patients with any life-threatening disorder that requires support of vital organ function and without which death would be imminent.[9] Thus, critically ill patients who need long-term treatment in the ICU typically show decreased plasma T_3 and T_4 concentrations. An absent TSH response in this context points to profoundly altered feedback regulation of the HPT axis.[10] Although the normal TSH concentration in the presence of low plasma T_3 has been interpreted as suggesting a euthyroid status, this assumption has not been sub stantiated by data. Common changes in plasma thyroid hormone ranges that can be easily assessed in the clinical setting are the result of changes in the central regulation of the thyroid axis, including decreased TSH pulsatility.[10] Moreover, several changes take place in the peripheral components of the thyroid axis that vary according to the tissue and the severity of illness.[11] Peripheral changes include, but are not limited to, changes in the concentrations of thyroid hormone binding proteins and transporters, in expression and activity of thyroid hormone deiodinases, and in expression of thyroid hormone receptors.[3] Changes in thyroid characteristics that are similar but not identical to those reported during NTIS, occur in response to fasting in healthy individuals.[12] NTIS in response to fasting in healthy people is regarded as adaptive and beneficial because it reduces energy expenditure to restrict catabolism via decreased thyroid hormone action.

Whether NTIS in response to critical illnesses should be seen as an adaptive mechanism, such as in starvation, or rather as a maladaptive mechanism is unknown. On the one hand, a seemingly logical assumption is that a reduction in serum T_3 would decrease thyroid hormone action in important T_3 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 con sciousness, myocardial function, hypothermia, neuropathy, muscle weakness, atrophy of the skin, and hair loss, which together might impede recovery.[13,14] Although the hypothesis that NTIS in patients in the ICU could be maladaptive has been extensively discussed,[9] surprisingly few clinical studies (some being randomised controlled trials [RCTs]) aimed at modulating NTIS 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 harm (table), but this ratio has not been formally analysed when only RCTs with clinically relevant outcome measures, such as mortality or morbidity, are taken into account.

Pathogenesis of NTIS

HPT axis feedback regulation and local thyroid hormone metabolism

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.[3] This finding points to substantial changes to the negative feedback regulation in the HPT axis during NTIS.[2] In people, central downregulation of the HPT axis during NTIS 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 T_3.[33] Additionally, simultaneous changes in liver metabolism of thyroid hormone contribute to the characteristic changes in thyroid hormone plasma concentrations: low plasma T_3 and high plasma rT_3, normal or low to normal plasma TSH, and low plasma T_4 during severe illness.[3]

Although the mechanisms associated with these seemingly paradoxical HPT axis changes are not completely understood, findings from animal studies using various NTIS models have elucidated some aspects of NTIS pathogenesis. NTIS 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).[3] For example, 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.[34,35] This D2 upregulation is followed by an increased local conversion of T_4 to T_3, which subsequently lowers TRH mRNA expression in the paraventricular nucleus, as noted in people (figure 1).[33,36,37] Although an increase in D2 activity has not yet been proven, experiments in an in-vitro co-culture system showed that glial D2 modulates T_3 concentrations and gene expression in neighbouring neurons.[38] Thus, inflammation inhibits hypophysiotropic TRH neurons probably via increased D2 activity, thereby accounting for hypothalamic downregulation of the HPT axis during NTIS.

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. Figure 2 shows a detailed overview of cellular thyroid hormone metabolism. Although liver-expressed D1 contributes about only 20% of the circulating T_3 in man,[47] this enzyme's involvement in NTIS pathogenesis has been extensively studied.[48] 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 T_3 and rT_3.[48]

Critical illnesses that include a substantial hypoxia or ischaemia component show a large increase in thyroid hormone catabolism via induction of D3. This effect was shown originally in post-mortem tissues of patients from the ICU[49] and later in a series of animal models, including in models for myocardial[50] and brain infarction.[38] Thus, induction of D3 during NTIS 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.[51]

NTIS: part of the acute phase response

Several clinical studies done more than 20 years ago showed a clear association between the changes in thyroid hormone metabolism and the activation of various proinflammatory cytokines.[52,53] Cytokines are import ant 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 NTIS.[54] 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.[55] Activation of NFκB was shown to play an important part in the up regulation of D2 in hypothalamic tanycytes during inflammation.[56,57] 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.[58] In summary, cytokines that are activated as a result of the inflammatory response are causally associated with the pathogenesis of NTIS, making NTIS part of the acute phase response.

Differential effects of illness on thyroid hormone action in metabolic organs

Energy homeostasis changes dramatically during illness, since activation of the immune system induces energy expenditure at the same time as food intake is decreased. Although the common view is that NTIS results in overall downregulation of metabolism in the organism to save energy, investigations have shown great variability between various key metabolic organs and tissues in the expression of genes encoding proteins involved in thyroid hormone metabolism.[3] These tissues include cells that are now known to be thyroid hormone responsive, such as granulocytes,[59] macrophages,[60] and lung epithelial cells (figure 3).[61]

Thyroid hormones are important for skeletal muscle function because a range of genes expressed in the muscles are regulated by T_3. Thyroid hormone signalling was shown to be different in skeletal muscle tissue during illness depending on the type (eg, acute inflammation or bacterial sepsis) and stage (ie, acute or long-term) of illness.[62–64] Whether the differential changes in thyroid hormone metabolism in muscles during illness are clinically relevant is unknown; however, muscle dysfunction has been associated with changes in muscle metabolism of thyroid hormones during extended critical illness.[65–68]

Thyroid hormones are now known to target cells and organs that respond to inflammation by increasing D2 or D3 expression, thereby affecting cellular function. For example, stimulation of macrophages with bacterial endotoxin increases D2 expression, which is essential for cytokine production and phagocytosis.[60] Moreover, granulocytes show increased D3 expression when infiltrating an infected organ.[69] A functional role for this

event was suggested by the finding that the absence of D3 in mice severely impaired the bacterial clearance capacity of the host.[70] Induction of D3 in activated granulocytes not only inactivates thyroid hormone, but also yields substantial amounts of iodide that can be used by the cell for bactericidal and tissue-toxic systems.[71] To summarise, the presence of D3 in activated granulocytes suggests a novel and protective role for the deiodinating enzymes in the defence against acute bacterial infection.

Role of nutrition

Critical illness is associated with loss of appetite and poor oral and enteral nutritional intake.[72] Because fasting in healthy individuals induces a similar NTIS response as that reported in patients who are critically ill,[12] decreased caloric intake during illness might greatly contribute to the development of NTIS. 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 (figure 4).[74] At the organ level, activity of D1, the enzyme driving the conversion of T_4 into the biologically active T_3 and clearing the biologically inactive rT_3, is decreased. Increased activity of D3, the T_3 inactivating enzyme, has also been reported.[75] Findings from three clinical studies that compared patients on different nutritional strategies suggested that decreased caloric intake during critical illness is associated with pronounced NTIS.[76–78]

In 2011, the large randomised controlled EPaNIC trial[79] reported comparisons between two nutritional regimens in 4640 adult patients in the ICU who were at risk of malnutrition: the early parenteral nutrition group received parenteral nutrition within 48 h of admission to the ICU (to supplement insufficient enteral nutrition), whereas the late parenteral nutrition group did not start this feeding regimen to supplement enteral nutrition before day 8 in the ICU. Findings from this study[79] showed that toleration of a nutritional deficit during the first week of critical illness resulted in fewer complications and accelerated recovery than with the early administration of supplemental parenteral nutrition. Ability to tolerate a fasting response thus seems to be beneficial for the patient. Of note, a subanalysis of the EPaNIC trial[80] (280 participants) showed that late feeding reduced complications and accelerated recovery of patients with NTIS, but also aggravated the changes in circulating concentrations of plasma TSH, total T_4, T_3, and the ratio of T_3 to rT_3. By contrast, the opposite was reported with patients given early feeding.[80]

Thus, the peripheral metabolism of T_3 is affected by decreased nutritional intake during acute critical illness. The subanalysis of the EPaNIC trial[80] suggested that the inactivation of T_3 to rT_3, 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 in infants and 3·9–5·6 mmol/L in children, thereby mimicking a fasting response, resulted in improved outcomes,[81] but at the same time aggravated peripheral NTIS. Use of a multivariate, Cox proportional hazard analysis showed that the further reduction of T_3 and rT_3 accounted for part of the therapy improving patient mortality rates.[82]

Together, these findings suggest that thyroid economy is affected by decreased nutritional intake during acute critical illness and that the inactivation of T_4 to rT_3 and T_3 to T_2, as part of the fasting response, might be a beneficial adaptation during acute illness.[80] Particularly, the acute peripheral inactivation of thyroid hormones by inner-ring deiodination during critical illness is probably a beneficial adaptation. Indeed, the reduced amount of circulating active T_3 could be interpreted as an attempt by the body to decrease the metabolic rate, reduce expenditure of scarce energy, and prevent protein breakdown, thereby, promoting survival. By contrast, the central lowering of T_4 could be harmful. Consistent with this interpretation is the finding that especially patients who are severely ill have a decrease in circulating T_4 concentrations, whereas virtually all patients who are ill have low T_3 and high rT_3 concentrations already on admission to the ICU.[62]

Diagnosis and management of severe primary thyroid disorders in patients in the ICU

The high prevalence of NTIS in patients in the ICU and the extent of HPT axis changes in these patients can make it difficult to distinguish NTIS from untreated primary hypothyroidism. Levothyroxine treatment should be continued during a patient's stay in the ICU in those who are known to have hypothyroidism. Although this practice seems trivial, prescription and continuation of chronic treatment is not always a main focus of care in the ICU setting. Findings from a retrospective chart review study[83] in a tertiary referral ICU, including 133 patients, showed that thyroid replacement therapy was not prescribed for more than 7 days in 23 (17·3%) patients and omitted in three (2·2%). 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 T_3, are decreased in most patients in the ICU due to NTIS. 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 NTIS, 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 T_4 is indicative of hypothyroidism; although, this combination can also be seen in patients recovering from NTIS. A high serum T_3 to T_4 ratio and a low serum rT_3 favour the presence of hypothyroidism, since these ratios are reversed in NTIS, but the diagnostic accuracy of these measurements is poor.[4] Especially in patients with long-standing and untreated hypothyroidism, cold exposure, infection, and vascular accidents might trigger the development of myxoedema coma. This disorder is a life-threatening condition with a high mortality of about 50%.[84] Key clinical features are hypothermia and altered consciousness, and features of laboratory findings include raised TSH with low or undetectable T_4 and T_3 concentrations. Of note, the presence of NTIS can reduce the extent of TSH increase. Active management is important for this disorder and depends on the recognition of the clinical features. Treatment of myxoedema coma aims to replace thyroid hormone, treat the underlying condition, and provide supportive care. Additionally, stress dose glucocorticoids should be given (eg, 100 mg hydrocortisone every

8 h) because con comitant autoimmune primary adrenal insufficiency might be present, especially in patients with hypo glycaemia.[85]

A low serum TSH could suggest thyrotoxicosis, especially if serum free T_4 is also high. The extent of TSH suppression is associated with the likelihood of thyrotoxicosis. Combination of suppressed TSH, high concentrations of free T_4, and normal T_3 concentrations might point to the combination of thyrotoxicosis and NTIS, and has been referred to as T_4 thyrotoxicosis.[4] Physical examination (eg, for a goitre or proptosis) and the presence of thyroid antibodies (antithyroid peroxidase and thyrotropin binding inhibiting immunoglobulins) might give further information about the probability of thyrotoxicosis. In the ICU setting, some patients can present with decompensated thyrotoxicosis, or thyroid storm, which is a life-threatening condition. Importantly, thyroid hormone concentrations do not distinguish between patients with thyroid storm from those with severe thyrotoxicosis because thyroid storm is a clinical diagnosis. Classic clinical characteristics of thyroid storm include fever, supra ventricular tachycardia, gastrointestinal symptoms, and an altered mental state including confusion, delirium, or even coma.[84] Precipitating factors include surgery, parturition, and infection. Treatment generally requires ICU monitoring and aims to restore thyroid gland function and at the same time diminish thyroid hormone effects on peripheral tissues with a combination of β blockers, thyrostatics, intravenous glucocorticoids, and eventually a high-dose of iodide compounds.[86] In a retrospective cohort study[87] of patients admitted to hospital with acute thyrotoxicosis, the presence of CNS dysfunction was the only significantly different clinical feature between patients with thyroid storm and those with compensated thyrotoxicosis. Thus, patients with thyrotoxicosis, possible thyroid storm, and altered mentation should be treated aggressively with supportive measures and antithyroid drugs.[87]

Treatment and management of NTIS

Whether interventions aimed at normalising thyroid hormone concentrations in patients with extended critical illness are beneficial has so far not been satisfactorily answered. The table contains clinical studies reporting interventions in patients with NTIS. Only a few, rather small, RTCs have assessed the effects of treatment with thyroid hormones in patients with NTIS. These trials report results obtained in a large range of patient groups—eg, patients with acute renal failure,[29] burn injury,[24] and cardiac surgery,[23,25–27] and those in the ICU with low T_4 concentrations.[28] Furthermore, the age of the study population varies greatly in these studies,[23–29] ranging from premature newborns to children and adults. Disease severity is another variable, ranging from critical illness at the medical ICU to heart surgery in quite healthy participants. Surprisingly little consistency is present in the choice of the active study drug, since both T_3 (given orally and intravenously) and levothyroxine have been used. In the context of studies with T_4 or T_3, of note is that normalising thyroid hormone concentrations in serum does not necessarily result in normal tissue concentrations of thyroid hormone. This finding was clearly shown in a study[48] of patients who were critically ill and received thyroid hormone treatment. In these patients, increases in liver T_3 concentrations after thyroid hormone treatment was disproportionally high compared with the increase in serum and muscle T_3 concentrations.[48] In addition to treatment with thyroid hormones, the effect of selenium on NTIS per se and on clinical outcomes has been

studied.[32,88] A small RCT[89] investigated the effect of N-acetylcysteine, an antioxidant that restores intracellular glutathione (a cofactor required for D1 catalytic activity), on NTIS. 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 NTIS in acute myocardial infarction.

An unresolved and somewhat controversial issue is whether there is a place for thyroid hormone treatment in patients with heart failure. Although a failing heart shows molecular changes partly overlapping with a hypothyroid heart, this does not necessarily imply that treatment of patients with heart failure and low serum T_3 in the setting of NTIS will improve their disorder.[8] Although the use of thyroid hormone treatment in patients with heart failure has not been adequately studied, some trials have reported encouraging findings. A small RCT[30] in patients with dilated cardiomyopathy showed beneficial effects of medium-term (3 months) levothyroxine treatment on cardiac performance, whereas another RCT[31] showed that the thyroid hormone analogue 3,5 di-iodothyropropionic acid improved some haemodynamic variables albeit without evidence for symptomatic benefit in heart failure.

Finally, hypothalamic neuropeptides (including combinations of growth hormone releasing hormone, growth hormone releasing peptide 2, gonadotropin releasing hormone, and TRH) have been used in patients with long-term critical illness in an attempt to stimulate the anterior pituitary gland and thereby restore endocrine function, in terms of plasma concentrations and hormone pulsatility.[10,19–22] Overall, the RCTs of T_3 or T_4 in critical illness have been largely negative in terms of clinical benefit (table). However, of note is that hypothalamic neuropeptides, especially TRH in combination with growth hormone releasing peptide 2 given intravenously, can restore circulating concentrations of thyroid hormone and TSH pulsatility to a remarkable extent. Additionally, this strategy improved overall metabolism, including bone markers and anabolic variables. Interpretation of these findings as representative of an insufficient hypothalamic drive of pituitary TSH release in protracted critical illness was supported by a study[33] reporting that deceased patients with NTIS seemed to have decreased hypothalamic TRH mRNA expression in the paraventricular nucleus, correlating with decreased antemortem plasma TSH and T_3 concentrations. However, the studies undertaken with hypothalamic neuropeptides consisted of only small numbers of patients. At present whether treatment with those neuropeptides offers clinical benefit in terms of morbidity and mortality is unclear. In summary, no definitive conclusion about the effectiveness of thyroid hormone treatment in patients in the ICU with NTIS can yet be made.[8]

Treatment with hypothalamic neuropeptides could possibly be harmful. The study by Acker and colleagues[29] in patients with acute renal failure raised some concern because of a tendency towards increased mortality after treatment with levothyroxine without any beneficial effect on outcome—eg, in terms of dialysis need (table). However, the reported mortality in the control group of this study[29] was lower than expected, which does not necessarily justify the interpretation that the intervention was harmful. Clearly, the reported studies were not adequately powered to detect clinically meaningful differences. Finally, most of these trials used rather high doses of either T_4 or T_3, probably inducing further

suppression of pituitary TSH release and altered tissue deiodinase activities. Use of neuropeptides, including TRH, to stimulate the HPT axis could be promising in this respect. Large RCTs in well defined patient groups will be needed to investigate possible positive effects of this approach in terms of outcome. High priority should be given to RCTs comparing the effect of hypothalamic neuropeptides including TRH with placebo, because this approach has already been shown to partly normalise concentrations of serum thyroid hormones and at the same time improve metabolic markers.[10] However, these effects have been shown only in small studies that were not powered to study clinically relevant outcome measures, such as mortality or morbidity. Another possibility will be to investigate treatment with recombinant human TSH, because this is a physiological stimulus—similar to TRH— for thyroid hormone release from the thyroid. A pilot study[90] showed that once a day low dose (30 μg) TSH treatment in patients with central hypothyroidism was sufficient to increase plasma TSH concentrations to the normal range. Furthermore, this treatment improved patients' quality of life and sleep behaviour.[90] Of interest will be to investigate whether this approach can be used in patients in the ICU with NTIS to normalise TSH and thyroid hormones, and, if possible, whether this approach can improve clinical outcomes. Again, these investigations should be done in adequately powered, randomised, placebo-controlled studies.

Conclusions

From a classic perspective, NTIS is a syndrome that occurs during various illnesses and is identified by decreased plasma concentrations of thyroid hormones with unclear resulting effects. Recent studies have shown that the changes in thyroid economy during NTIS suggest substantial and complex changes at the level of the HPT axis, in terms of setpoint regulation, and at the organ level, in terms of local metabolism of thyroid hormones (figure 5). Whether the noted changes in critically ill patients are beneficial or harmful in terms of outcome probably depends on disease stage and severity, the need for long-term vital support, and environmental factors (including parenteral nutrition). At present, no evidence-based consensus or guideline advocates thyroid hormone treatment of NTIS in patients who are critically ill. Adequately powered RCTs need to be undertaken to define whether active management of NTIS—eg, with hypothalamic neuropeptides including TRH—will yield clinical benefit in terms of patient outcome.

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Search strategy and selection criteria

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for articles published in English from inception to March 6, 2014, with the search terms "critically ill patients", "intensive care", or "sepsis" in combination with "thyroid dysfunction", "euthyroid sick syndrome", or "thyroid hormones". References chosen were selected on the basis of their title.
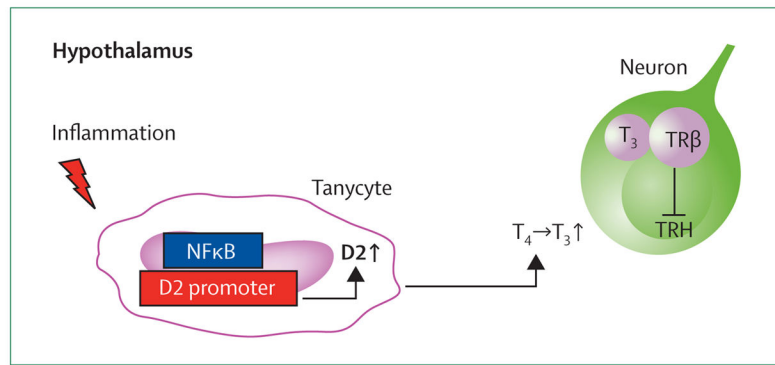
Figure 1. Schematic representation of hypothalamic thyroid hormone signalling during inflammation

Inflammation activates the NFκB pathway in tanycytes, specialised cells lining the third ventricle. Tanycytes express D2, the main T_3 producing enzyme in the brain, the promoter of which contains NFκB responsive elements. Binding of NFκB increases D2 expression and activity, and this stimulates the conversion of T_4 into T_3. T_3 will enter adjacent neurons and bind to neuronal TRβ thereby regulating transcriptional activity of TRH. T_3=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. T_4=thyroxine.
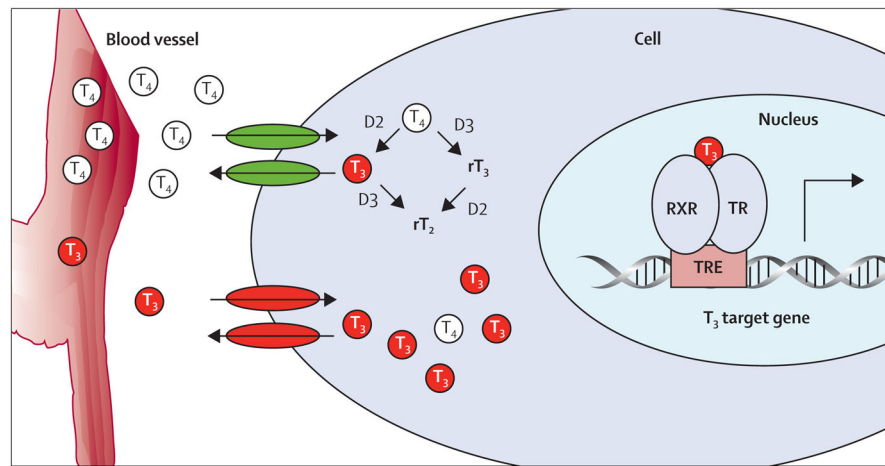
Figure 2. Schematic representation of cellular thyroid hormone metabolism
Cellular entry of thyroid hormones is necessary for intracellular conversion and for T_3 to exerts its actions in the nucleus. Two categories of thyroid hormone transporters have been noted: the organic anion transporters and the aminoacid transporters.[1,39–41] Once transported into the cell, thyroid hormones (T_4 and T_3) can be metabolised by outer or inner ring deiodination through the iodothyronine deiodinases. These enzymes belong to a selenocysteine containing enzyme family and comprise three types; type 1 (D1), 2 (D2), and type 3 (D3).[42] D1 is able to deiodinate the inner ring and outer rings of T4 as well as the outer ring of rT3. D1 is expressed in the liver, kidney, thyroid, and pituitary and localised in the plasma membrane.[43,44] D2 is localised in the endoplasmic reticulum and deiodinates T_4 into the biologically active T_3. D2 is the main enzyme involved in the production of tissue T_3 and therefore heavily involved in local thyroid hormone metabolism.[45,46] D3 is localised in the plasma membrane and can be viewed as the major thyroid hormone inactivating enzyme, as it catalyses inner-ring deiodination of both T_4 and T_3, exclusively resulting in the production of biologically inactive rT_3 and rT_2, respectively.[47] The balance between D2 and D3 determines the availability of cellular T_3, which enters the nucleus and binds to the nuclear receptor complex (RXR and TR). T_3 exerts its nuclear actions via the RXR and TR complex that binds to thyroid hormone response elements in target genes. TR complex regulates transcriptional activity of T_3-target genes. TR=thyroid hormone receptor. T_3=tri-iodothyronine. T_4=thyroxine. rT_3=reverse T_3. rT_4=reverse T_4. RXR=retinoid-X receptor. TRE=thyroid hormone response elements.
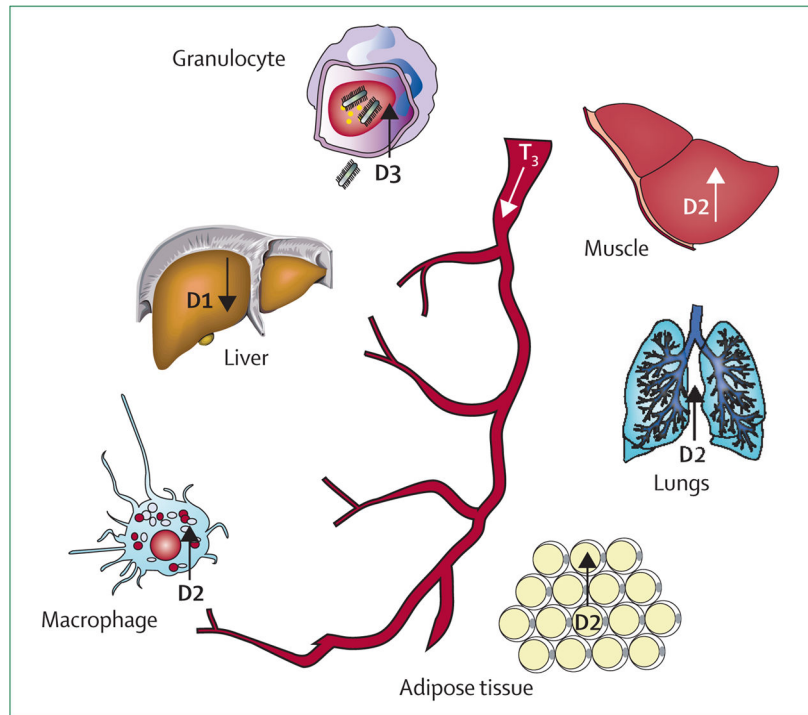
Figure 3. Simplified overview of various reported differential effects of NTIS on deiodinase activities in various tissues

Deiodinase effects probably induce interorgan differences in T_3 bioavailability in the presence of similarly decreased plasma concentrations of T_3. T_3=tri-iodothyronine.

D1=deiodinase type 1.

D2=deiodinase type 2. D3=deiodinase type 3.
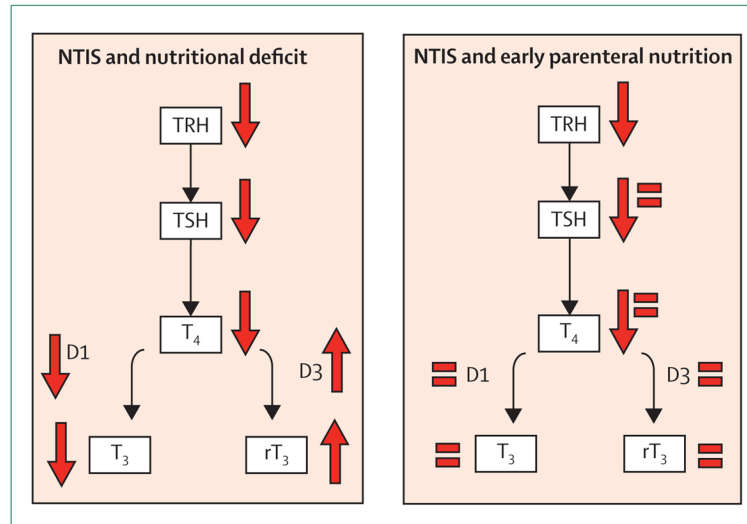
Figure 4. Schematic representation of the effect of parenteral nutrition during NTIS
Critical illness-induced NTIS is characterised by low circulating T_3 and raised concentration
of rT_3. Low hypothalamic TRH mRNA expression, low circulating TSH, and low T_4 are also
reported during NTIS. When early, full parenteral support is used to resolve the caloric
deficit, the peripheral changes in the thyroid axis partly normalise, but its central suppression
does not.[73] Solid arrows represent direction of change in concentration or activity. =
represents normalisation of concentrations. NTIS=non-thyroidal illness syndrome.
TRH=thyrotropin-releasing hormone. TSH=thyroid-stimulating hormone.
T_4=thyroxine. T_3=tri-iodothyronine. rT_3=reverse T_3.
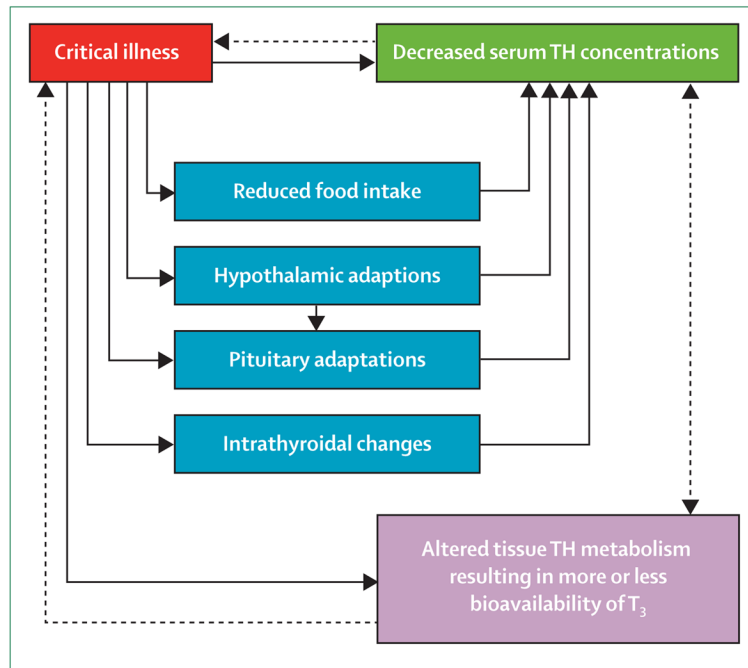
Figure 5. Schematic representation of the various changes during critical illness
The scheme is based on both experimental investigations and studies with people. The net result of altered tissue thyroid hormone metabolism could be beneficial or maladaptive, dependent on disease duration and severity. TH=thyroid hormone. T_3=tri-iodothyronine. Solid lines represent a causal association. Dashed lines represent a probable effect.

Table

Overview of clinical studies reporting interventions in patients with non-thyroidal illness syndrome

	RCT?	Participants	Intervention (duration)	Main outcomes	Beneficial or positive (endpoints)	Harmful?
Children after cardiopulmonary bypass surgery, age range from 2 days to 10·4 years (n=40)[15]	Yes	Children	2 μg/kg IV of T_3 given on day 1 after surgery and 1 μg/kg given on day 2 for 12 days	Cardiac function, ICU measures	Yes	No
Premature newborns, born after <37 days of gestation (n=100)[16]	No	Children	LT4 (25 μg/day) plus T_3 (5 μg/day) given orally	Mortality	Yes	No
Premature newborns, born after <32 weeks of gestation (n=49)[17]	Yes	Children	LT4, 10 μg/kg (IV) or 20 μg/kg (through nasogastric tube) for 21 days	Chronic lung disease, death, CNS damage, sepsis	No	No
Children <18 years with cessation of neurological function during assessment for organ recovery (n=171)[18]	No	Children	Weight-based LT4 bolus followed by infusion	Vasopressor score	Yes	No
Protracted critical illness (n=14)[10]	Yes	Adults	TRH (1 μg/kg per h) IV for 5 days plus GHRP-2 (1 μg/kg per h) IV for 5 days	GH and TSH secretion; biochemical anabolism and catabolism variables	Yes	No
Critical illness (n=76)[19]	Yes	Adults	GHRP-2 alone or in combination with TRH and GHRH (each peptide 1 μg/kg per h)	Synchrony among GH, TSH, and PRL release	Yes	No
Critical illness (n=40)[20]	Yes	Adults	Combinations of GHRH, GHRP-2 (both 1 μg/kg), TRH (200 μg) given as bolus, time interval 6 h	Serum GH, TSH, T_3, and T_4 concentrations	Yes	No
Protracted critical illness (n=20)[21]	Yes	Adults	Combinations of GHRH, GHRP-2, and TRH start with bolus (1 μg/kg) followed by 1 μg/kg per h (for two consecutive nights)	Serum hormone concentrations	Yes	No
Protracted critical illness (n=33)[22]	Yes	Adults	Combinations of GHRH, GHRP-2, and TRH (1 μg/kg per h of each), GnRH (0·1 μg/kg per 90 min) for 5 days	Serum hormone and metabolic marker concentrations	Yes	No
Elective coronary bypass surgery (n=80)[23]	Yes	Adults	T_3 (125 μg/day) orally (7 days pre-operative until discharge)	Haemodynamic data, morbidity, mortality	Yes (haemodynamic values); No (morbidity, mortality)	No
Burn injury (n=36)[24]	Yes	Adults	T_3 (200 μg/day) orally or via nasogastric tube in four divided doses until wounds healed	Mortality, resting metabolic rate	No	No
Coronary bypass surgery (n=60)[25]	Yes	Adults	T_3 (0·8 μg/kg) IV for 6 h	Operative outcome, morbidity, mortality	No	No

	RCT?	Participants	Intervention (duration)	Main outcomes	Beneficial or positive (endpoints)	Harmful?
Coronary bypass surgery (n=100)[26]	Yes	Adults	T_3 (20 µg/12 h) oral (48 h)	Serum T_3, haemodynamic variables, morbidity	No	No
High risk valvular heart surgery (n=50)[27]	Yes	Adults	T_3 (20 µg/12 h) orally (24 h)	Vasopressor need	Yes	No
Patients in the ICU with low T_4 concentrations (n=23)[28]	Yes	Adults	1·5 µg/kg bodyweight LT4 IV (2 weeks)	Mortality	No	No
Acute renal failure (n=59)[29]	Yes	Adults	LT4 infusion, 150 µg/20 mL every 12 h for 48 h	Percentage dialysis, percentage recovery, mortality	No	Possibly (increased mortality)
Idiopathic dilated cardiomyopathy (n=20)[30]	Yes	Adults	100 µg/day of LT4 for 3 months	Cardiac performance	Yes	No
Congestive heart failure (n=86)[31]	Yes	Adults	Thyroid hormone analogue DIPTA, two per day, maximum dose 360 mg/day	Composite congestive heart failure endpoints	No	Yes
Non-thyroidal illness syndrome after major trauma (n=31)[32]	Yes	Adults	Selenium (500 µg/day) with or without vitamin E and zinc supplement *vs* placebo (5 days)	Serum selenium levels, T_4 levels, duration of mechanical ventilation	Yes (T_4 and selenium plasma concentrations; uncertain (ventilation)	No
Patients with sepsis in the ICU (n=40)[17]	Yes	Adults	High dose selenium (158 µg/day for 3 days) followed by standard dose selenium-selenite (31·6 µg/day)	Serum selenium concentrations, oxidative damage values, need for renal replacement therapy	No	No

Whether trial showed overall beneficial and positive outcomes or harmful effects was defined by the authors on the basis of results reported. RCT=randomised controlled trial. IV=intravenous. T3=tri-iodothyronine. ICU=intensive care unit. LT4=levothyroxine. TRH=thyrotropin-releasing hormone. GHRP=growth hormone-releasing peptide. GH=growth hormone. TSH=thyroid-stimulating hormone. GHRH=growth hormone-releasing hormone. PRL=prolactin. T4=thyroxine. GnRH=gonadotropin-releasing hormone. DIPTA=di-iodothyropropionic acid.