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Review

Thyroid function during critical illness

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ABSTRACT

The metabolic support of the critically ill patient is a relatively new target of active research and little is as yet known about the effects of critical illness on metabolism. The nonthyroidal illness syndrome, also known as the low T_3 syndrome or euthyroid sick syndrome, describes a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses. The laboratory parameters of this syndrome include low serum levels of triiodothyronine (T_3) and high levels of reverse T_3, with normal or low levels of thyroxine (T_4) and normal or low levels of thyroid-stimulating hormone (TSH). This condition may affect 60 to 70% of critically ill patients. The changes in serum thyroid hormone levels in the critically ill patient seem to result from alterations in the peripheral metabolism of the thyroid hormones, in TSH regulation, in the binding of thyroid hormone to transport-protein and in receptor binding and intracellular uptake. Medications also have a very important role in these alterations. Hormonal changes can be seen within the first hours of critical illness and, interestingly, these changes correlate with final outcome. Data on the beneficial effect of thyroid hormone treatment on outcome in critically ill patients are so far controversial. Thyroid function generally returns to normal as the acute illness resolves.

Key words: Critical illness, Euthyroid sick syndrome, Low T_3 syndrome, Metabolic physiology, Thyroid gland function

INTRODUCTION

The metabolic responses to sepsis involve every organ and tissue of the body and yet, surprisingly, little is known about the underlying mechanisms. During sepsis and other critical illnesses, the state of stress results in hypermetabolism, increased energy expenditure, hyperglycemia and muscle loss.[1,2] It is anticipated that appropriate metabolic support could improve the outcome in these patients, but considerable controversy remains regarding the indicated therapeutic approach.

Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease.[3-5] Changes in parameters of thyroid function are very common but

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rarely isolated. They are often associated with alterations in other endocrine axes (reductions in serum gonadotropin and sex hormone concentrations and increases in serum adrenocorticotropic hormone and free cortisol levels).[6,7] Thus, the sick euthyroid syndrome should not be viewed as an isolated abnormal event but as part of a generalized systemic endocrine response to illness.

In this article, we will summarize the current knowledge on the status of thyroid hormones in the critically ill patient. In order to correctly interpret thyroid function tests (TFTs), the intensivist should be familiar with the changes that occur during critical illness in the function of the hypothalamic-pituitary-thyroid axis and in thyroid hormone metabolism as well as the effects of commonly used medications on thyroid physiology (Table 1).

THYROID HORMONES IN CRITICAL ILLNESS
(Tables 2,3)

Triiodothyronine (T3)

T3 is the biologically active thyroid hormone and its low serum levels in critical illness reflect altered thyroid homeostasis and a mechanism of adaptation. Normally most (80%-90%) of T3 is produced by monodeiodination of 40% of circulating T4, a reaction catalyzed by 5'-monodeiodinases in organs such as the liver and kidney (Figure 1). The remaining (10%-20%) is directly secreted by the thyroid gland.

Table 1. Drugs causing alterations in thyroid function and mechanisms involved

Hypothyroidism						
Drugs	thionamides, lithium, perchlorate, aminoglutethimide, thalidomide iodine and iodine-containing drugs • amiodarone, • radiographic agents, • expectorants • potassium iodine solutions • Betadine douches • topical antiseptics	cholestyramine colestipol, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole sevelamer lanthanum carbonate	interferon-alpha interleukin-2	dopamine	sunitinib	bexarotene
Mechanism	Inhibition of thyroid hormone synthesis and/or release	Decreased absorption of T4	Immuno-dysregulation	Suppression of TSH	Possible destructive thyroiditis	Increased T4 clearance and suppression of TSH
Hyperthyroidism						
Drugs	iodine amiodarone			interferon-alpha interleukin-2		
Mechanism	Stimulation of thyroid hormone synthesis and/or release			Immuno-dysregulation		
Drugs causing abnormal thyroid function tests without thyroid dysfunction						
Drugs	androgens, danazol, glucocorticoids, nicotinic acid l-asparaginase	estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane	salicylates salsalate furosemide heparin NSAIDs	phenytoin, carbamazepine, rifampin, phenobarbital	dobutamine, glucocorticoids, octreotide	amiodarone glucocorticoids, contrast agents (e.g., iopanoic acid), propylthiouracil, propanolol
Mechanism	Low serum TBG	High serum TBG	Decreased T4 binding to TBG	Increased T4 clearance	Suppression of TSH secretion	Impaired conversion of T4 to T3

Table 2. TSH values during critical illness and clinical outcome

	Serum TSH values (mU/L)	Diagnosis, outcome
Undetectable	<0.01	Hyperthyroidism or non- thyroidal illness (a)
Low but detectable	>0.05 and < 0.3	Euthyroidism when reassessed after recovery from their illness
High but	<20	Transient (recovery phase) or permanent hypothyroidism(uncommon)
High but	>20	Permanent hypothyroidism[x] (b)

a: Only 75% of patients with nonthyroidal illness and a TSH <0.01 will have hyperthyroidism when recovered from their illness.[40]
b: In patients with a TSH >20, only 50% will have true (permanent) hypothyroidism when recoverd from their illness.[52]

Table 3. Alterations in thyroid hormones during critical illness and their clinical correlation

Critical illness	T3	T4	TSH	Clinical correlation
Acute phase	Decreased	Increased	Normal	Severity of illness
Chronic phase	Decreased	Decreased	No change/decreased	May indicate recovery

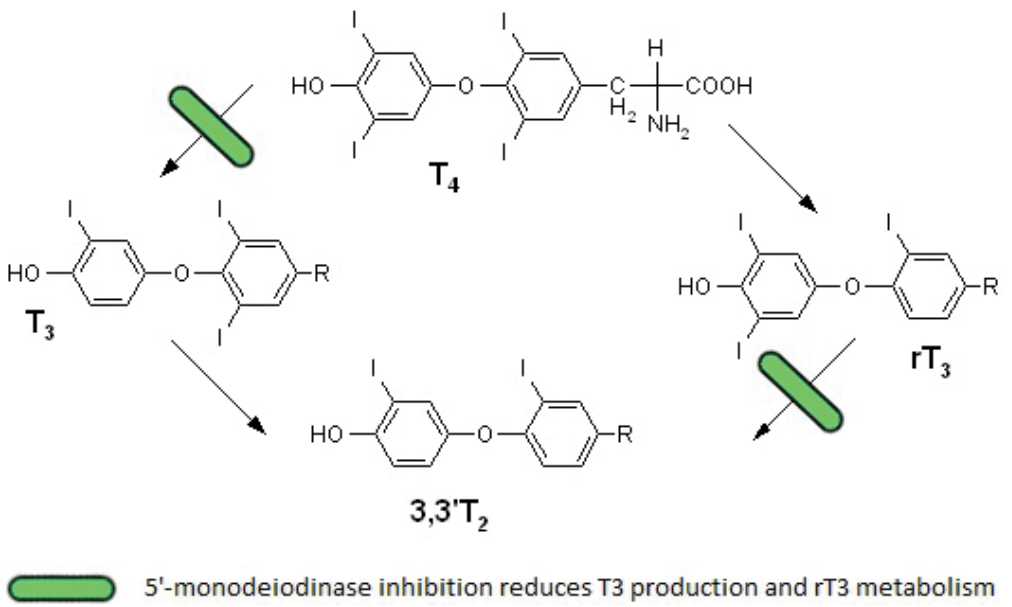

Figure 1. Thyroxine metabolism in nonthyroidal illness. The inhibition of 5'-monodeiodinase in nonthyroidal illness leads to decreased conversion of T4 to T3 and reduced metabolism of reverse T3.

Inhibition of the enzyme 5´-deiodinase that catalyzes the conversion of T4 to T3 has been considered a possible mechanism responsible for the sick euthyroid syndrome.[8,9] Additionally, many drugs that are commonly used in ICU, such as iodine, amiodarone and corticosteroids, also reduce the conversion of T4 to T3.

The majority of critically ill patients have low serum T3 concentrations, as do some outpatients during illness. Liver and skeletal muscle biopsies obtained within minutes after death from intensive care unit patients demonstrate reduced 5'-monodeiodinase activity and increased 5'-monodeiodinase activity (which converts T4 to rT3).[10,11] Moreover, patients with fatal illness have low tissue T4 and T3 concentrations.[12,13]

Several mechanisms can contribute to the inhibition of 5'-monodeiodination and therefore to the low serum T3 concentrations in critically ill patients with nonthyroidal illness:

A. Exogenous glucocorticoid therapy.[14]

B. Circulating inhibitors of deiodinase activity, such as free (non-esterified) fatty acids.[15]

C. Treatment with drugs that inhibit 5'-monodeiodinase activity, such as amiodarone and high doses of propranolol.

D. Cytokines (such as tumor necrosis factor, interferon-alpha, NF-kB and interleukin-6).[16-18]

Reverse triiodothyronine (rT3)

The initial and most common abnormality observed in any person who has a significant acute illness is a fall in total T3 concentrations accompanied by an increase in rT3 levels. T4 conversion to rT3 by 5'-deiodinase is called the "inactivating pathway".

The conversion of reverse T3 to diiodothyronine (T2) is reduced in nonthyroidal illness because of inhibition of the 5'-monodeiodinase activity.[19] This constitutes an additional mechanism of high serum rT3 values in patients with nonthyroidal illnesses, except in those with renal failure and some patients with AIDS.[20,21]

Thyroxine (T4)

Serum T4 in nonthyroid illness can be reduced within 24 to 48hrs.The initial decline is predominantly due to decreased binding to carrier proteins, such as thyroid hormone binding globulin (TBG), transthyretin (TTR), or thyroxine-binding prealbumin [TBPA]) and albumin.[22]

Many drugs (Table 1), including salicylates, phenyntoin, carbamazepine, furosemide, compete with thyroid hormone for binding to TBG, resulting in an acute increase in free T_4 and a decrease in total T_4 concentrations. The presence of circulating inhibitors of T_4 binding, such as high concentrations of fatty acid, disordered iodine uptake by the thyroid or abnormal peripheral metabolism, are also possibly implicated in the low total and/or free T_4 levels.[23-26] Some drugs including phenytoin, carbamazepine, rifampin, Phenobarbital, may also contribute to low total T_4 concentration by accelerating its clearance.

Free T4

Despite low total T_4 in critical illness, serum concentrations of free T_4 remain in the normal range in most patients unless the illness is severe and protracted.[27] However, hypothalamic-pituitary suppression, usually present in prolonged critically illness, leads to decreased secretion of TSH, decreased T_4 production by the thyroid gland and a subsequent decline of free T_4 levels in the circulation, a sign of severity of the disease and a predictor of poor outcome.[28]

Thyrotropin (TSH)

Under normal conditions, TSH synthesis is relatively stable and is controlled by thyroid hormones, neuropeptides and neurotransmitters. Hypothalamic thyrotropine-releasing hormone (TRH) is the main stimulating factor of TSH synthesis and its effect is enhanced by catecholamines. Somatostatin and dopamine are the main inhibitory factors of TSH synthesis. In euthyroid sick syndrome, TSH levels are commonly within the normal range and only in prolonged illness may be low. Serum TSH assays that have a detection limit of 0.01 mU/L should be used in assessing thyroid function in critically ill patients.[29] Some hospitalized patients have transient elevations in serum TSH concentrations (up to 20 mU/L) during recovery from nonthyroidal illness. Few of these patients prove to have hypothyroidism when re-evaluated after recovery from their illness. Patients with serum TSH concentrations over 20 mU/L usually have permanent hypothyroidism[8] (Table 2).

Most ICU patients suffer from sepsis. It is supposed that early alterations in the regulation of thyroid hormones economy during sepsis involve mainly peripheral mechanisms, such as impaired peripheral deiodination and reduced thyroid hormone secretion. The late phase of sepsis is associated with centrally induced hypothyroidism as suggested by restoration of T3 and T4 pulses by exogenous TRH infusion.[30] In addition, postmortem examination showed diminished thyroid gland weight and follicular size,[31] low expression of TRH messenger RNA in the hypothalamic paraventricular nuclei and low concentrations of tissue T3 in patients who died while in the late phase of sepsis.[32,33] Common late alteration in thyroid metabolism is a decrease in the pituitary secretion of TSH that typically occurs in parallel with the decline in serum T4 concentrations.[34] The causes are multifactorial and attributed to effects of the illness per se, malnutrition and the suppressive effects of

cytokines and medications such as corticosteroids and dopamine.[35,36] If the illness persists, reduced TSH secretion likely contributes to low total and eventually low free T4 concentrations. Clinically, low T3 and T4 levels, in association with normal, low-normal or decreased TSH, suggest the development of a variant of central hypothyroidism.[37] Such changes may be a self-protective adaptation to illness, as the body attempts to conserve energy. This state is usually transient, resolving once the patient shows signs of improvement. The recovery of the thyroidal axis begins with a rise in serum TSH and is eventually followed by normalization in T4 concentrations.[38] Because of the difference in half-lives of T4 (days) and TSH (hours), the normalization of T4 lags behind the increase in TSH. As a result, the picture during the resolution of euthyroid sick syndrome may suggest primary hypothyroidism (Table 3).

Assessment of thyroid function in ICU

The decreased 5'-monodeiodinase activity is often not recognized because measurement of serum T3 is rarely utilized as a screening test for thyroid function (nor should it be). It is, however, useful to measure serum T3 in hospitalized patients who have a low serum TSH concentration (Table 1) in whom the differential diagnosis is hyperthyroidism versus nonthyroidal illness. The serum T3 value should be high (or high-normal) in hyperthyroidism but low (or low-normal) in nonthyroidal illness. Rarely, a very sick patient with hyperthyroidism will have a low serum T3 concentration.[39]

In the differential diagnosis of low serum T_3 and T_4 in the critically ill patient, intensivists should include hypothyroidism. Measurements of rT_3 had been considered useful in differentiating nonthyroidal illness (high rT_3) from secondary hypothyroidism (low TSH), which should be associated with low rT_3. Subsequent studies however showed that rT_3 does not accurately distinguish the two states.[37]

In assessing thyroid function in ICU, two important general principles must be considered:[40]

- Thyroid function should not be assessed in seriously ill patients unless there is a strong suspicion of thyroid dysfunction.
- When thyroid dysfunction is suspected in critically ill patients, measurement of serum TSH alone is inadequate for the evaluation of thyroid function

THYROID HORMONE TREATMENT OF NONTHYROIDAL ILLNESS

It remains controversial whether development of the aforementioned changes in thyroid metabolism reflects a protective mechanism or a maladaptive process during illness.

If these changes constitute an adaptation mechanism, then treatment to restore thyroid hormone levels to the normal range could have deleterious effects. In contrast, if these changes are pathologic, treatment may improve an otherwise poor clinical outcome. Current literature data indicate that:

1. Starvation-induced decrease in serum T_3 concentrations most likely reflects a process of adaptation.
2. Treatment with dopamine and high-dose systemic corticosteroids, generally used in ICU patients, decreases serum TSH concentrations.
3. Alterations in deiodinase enzymes occur in tissues of humans who died in the setting of critical illness.[10,41]
4. Transport of thyroid hormones into target tissues of critically ill patients may also be reduced.[42]

However, clinical measurements of thyroid function with the use of parameters such as the Achilles tendon reflex time, cardiac QKD interval and metabolic rate indicate a euthyroid state.[5]

The presence of euthyroid sick syndrome is associated with increased mortality among critically ill patients.[43,44] Low serum T_4 or low T_3 levels seem to be a poor prognostic indicator in hospitalized cardiac patients[45,46] or in patients after bone marrow transplantation.[47] Whether this low hormone state could be related to recovery delay indicating therapeutic intervention has not been fully elucidated.

Only a few studies have examined the use of supplemental thyroid hormone therapy in critically ill general medical patients. Brent and Hershman[48] examined the effect of thyroid hormone therapy in medical intensive care unit patients. The patients included in the study had serum T_4 levels <5 μg/

dL with no evidence of intrinsic thyroid dysfunction and were given either T_4 or placebo intravenously on a daily basis. There was no significant difference in mortality between the two groups and the T_4 replacement was detrimental to the restoration of normal pituitary-thyroid regulation. In organ donors exogenous thyroid hormones stabilizes the function of the cardiovascular system. There have been other trials in patients who suffered acute renal failure or underwent renal transplantation that also failed to show any benefit.[49,50]

One could argue that levothyroxine therapy applied for the management of the euthyroid sick syndrome is not expected to have any effect because of the pronounced inhibition of conversion of T_4 to T_3 in these patients. It is interesting that hepatic deiodinase is a selenoprotein and selenium deficiency is commonly seen in septic ICU patients. Thus, one could conclude that supplementation with selenium may result in a quicker normalization of T_4 and rT_3. Becker et al examined the effect of treatment with T_3 in 36 patients with acute burn injuries.[51] Treatment with liothyronine (LT_3) normalized serum T_3 concentrations but resulted in no change in either mortality or basal metabolic rate. Since it is easier to diagnose sick euthyroid syndrome than to treat it properly, avoidance of thyroid hormone substitution seems a reasonable option at present.

Generally speaking, TFTs should not be carried out routinely in the intensive care setting unless there is a suspicion of thyroid dysfunction, based on past history or clinical evaluation. The goal of TFTs in the ICU should mainly be the identification of previously unrecognized thyroid dysfunction that would require therapeutic intervention. When hypothyroidism is suspected clinically in an ICU patient (e.g. hypothermia, bradycardia, respiratory acidosis, pleural effusions, failure to wean), and the evaluation suggests central hypothyroidism, one should consider, that the probability of euthyroid sick syndrome is much higher than the pituitary or hypothalamic disease. If hyperthyroidism is suspected (e.g. tachyarrhythmias, widened pulse pressure, respiratory alkalosis, high-output heart failure) and low TSH is detected, true hyperthyroidism, is unlikely unless the TSH is suppressed fully on a third-generation assay and the free T_4 is elevated or at least in the upper limits of the normal range. If the free T_4 is low or low-normal, the patient is probably not hyperthyroid. Because of inaccuracy of all free T_4 assays in this setting, however, repeating the free T_4 by another method is advised before firmly establishing the diagnosis, especially if clinical suspicion persists.

CONCLUSION

The evaluation of altered thyroid function parameters in systemic illness and stress remains a complex issue and presents many diagnostic problems because changes occur at all levels of the hypothalamic-pituitary-thyroid axis. Unique changes in thyroid function parameters are observed in various relevant clinical states, including starvation and fasting, cardiac disease, renal disease, hepatic disease and infection. Many pharmacologic agents also cause changes in thyroid economy that can complicate the interpretation of thyroid function parameters in systemic illness. Whether alterations in thyroid parameters during critical illness represent adaptive changes to conserve energy expenditure by reducing metabolic activity is still debatable. According to current data thyroid hormone replacement therapy has not been shown to be of benefit in the vast majority of these patients. LT_3, however, appears to slightly improve hemodynamic and neurohumoral variables in patients with congestive heart failure, these benefits possibly representing a pharmacologic effect of T_3 rather than a physiologic hormonal replacement effect.

Establishing thyroid dysfunction based on a single set of TFTs may be misleading. Careful clinical evaluation, knowledge of hospital course and of recent therapies are essential for the correct interpretation of such testing. Early pursuit of endocrine consultation may be helpful in difficult situations.

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