MINERVA MEDICA COPYRIGHT®

REVIEW

The role of thyroid dysfunction in the critically ill: a review of the literature

G. BELLO, I. CEAICHISCIUC, S. SILVA, M. ANTONELLI

Department of Anesthesiology and Intensive Care, Sacro Cuore Catholic University, A. Gemelli Hospital, Rome, Italy

ABSTRACT

During critical illness, patients with no known history of thyroid disorders may experience multiple alterations in their serum thyroid hormone levels. Such alterations have been termed sick euthyroid syndrome or, more recently, non-thyroidal illness syndrome (NTIS). The laboratory parameters of NTIS usually include low serum levels of triiodothyronine (T3), normal or low serum levels of thyroxine (T4) and normal or low serum levels of thyroid-stimulating hormone (TSH). The magnitude of the alteration in thyroid function correlates with the severity of the illness and its outcomes in critically ill patients with NTIS. The pathogenetic mechanisms involved in NTIS include a decreased conversion of T4 to T3 in extrathyroidal tissues and alterations in thyroid hormones' binding to serum proteins. In cases of protracted critical illness, a decrease in the pulsatile frequency of TSH secretion, resulting from reduced thyrotropin-re leasing hormone (TRH) release by the hypothalamus, may also occur. Several medications or clinical conditions that are commonly present in critically ill patients may be responsible for lowering serum concentrations of thyroid hormone. Among those who study the condition, the question of whether NTIS is a protective adaptation of the organism to illness or a maladaptive response to a stressful insult remains unanswered. In either case, thyroid hormone abnormalities are likely to play a role in the critically ill patient.However, there is currently no convincing evidence to suggest that restoring physiological thyroid hormone concentrations in unselected patients with NTIS would be beneficial. *(Minerva Anestesiol 2010;76:919-28)*

Key words: Critical illness - Thyroid gland - Triiodothyronine - Hypothalamic hormones - Intensive Care Units.

Critical illness can be defined as any life-threatening condition requiring the support of failing vital organ functions.[1] In patients with no previously diagnosed intrinsic thyroid disease, critical illness can cause profound changes in thyroid hormone metabolism. Such changes have been named "euthyroid sick syndrome"[2-4] or, more recently, "non-thyroidal illness syndrome (NTIS)".[5] The latter term will be used throughout this review.

The abnormalities observed in cases of NTIS include low serum levels of triiodothyronine (T3), normal or low levels of thyroxine (T4) and normal or low levels of thyroid-stimulating hormone (TSH).[1, 5] NTIS affects about 70% of patients hospitalized with diseases of various etiologies.[5-7] In this context, the magnitude of either the decrease in thyroid hormone or the blunted response of TSH to thyrotropin-releasing hormone (TRH) has been shown to reflect the severity of the patient's illness and outcome.[8-13]

Even though NTIS has been studied for several decades now, it is still unclear whether this condition represents a protective and appropriate adaptation to a stressful event or a maladaptive response to illness that needs correction.[14, 15]

The following sections deal with the pathophysiology of the thyroid function alterations that can occur during critical illness and the potential benefits and hazards of restoring normal serum concentrations of thyroid hormone in patients with different critical illnesses.

MINERVA MEDICA COPYRIGHT®

Pathophysiology of NTIS

The pathogenetic mechanisms involved in NTIS are shown in Figure 1. The thyroid hormone changes observed after an acute and stressful event show different features during the initial and chronic phases of a critical illness. The most common alteration to occur within the thyroid axis during the acute phase of a critical illness is the decreased conversion of T4 to T3 (the active form of thyroid hormone) in extrathyroidal tissues due to the acute inhibition of type I 5'-deiodinase. A second explanation of thyroid hormone abnormalities during acute critical illness suggests that the thyroid hormone-binding proteins – T4 binding protein, transthyretin, and albumin – become impaired in their production or in their affinity for the thyroid hormones.[16]

Within the hours immediately following the onset of the stressful event, T3 serum concentrations decrease, while T4 and TSH may slightly increase. Serum concentrations of reverse T3 – which is biologically inactive – may increase because T4's inner ring deiodination process (which produces reverse T3) is not inhibited by acute illness. At the same time, the normal degradation of reverse T3 by type I 5'-deiodinase is reduced. Later on, serum concentrations of TSH and T4 usually return to more normal values, whereas T3 concentrations remain low. At this stage, the normal nocturnal serum TSH surge seems to be decreased or even absent,[17] even though measured serum TSH concentrations may be normal.

In cases of protracted critical illness, thyroid hormone abnormalities may also be explained by a decreased TRH release by the hypothalamus, which results in a decrease in the pulsatile frequency of TSH secretion.[1] In this phase, thyroid function tests usually reveal low circulating levels of T3 and T4 and low or normal levels of TSH. Additionally, the pulsatile secretion of TSH significantly decreases because of reduced hypothalamic stimulation. Finally, during a patient's recovery from critical illness, a modest increase in serum TSH concentrations may occur.[18] Full restoration of the patient's normal physiological biochemical state may not occur until several months after hospital discharge.[19] In the critically ill patient, several medications and clinical conditions may induce or maintain NTIS by various mechanisms (Table I).

The abnormalities in thyroid hormone metabolism observed during critical illness are part of a systemic response to stress that involves other neuroendocrine systems. The first reaction, which occurs within hours of the onset of acute illness, is the activation of the anterior pituitary gland and the associated suppression of anabolic pathways in the periphery. This reaction has been consid-

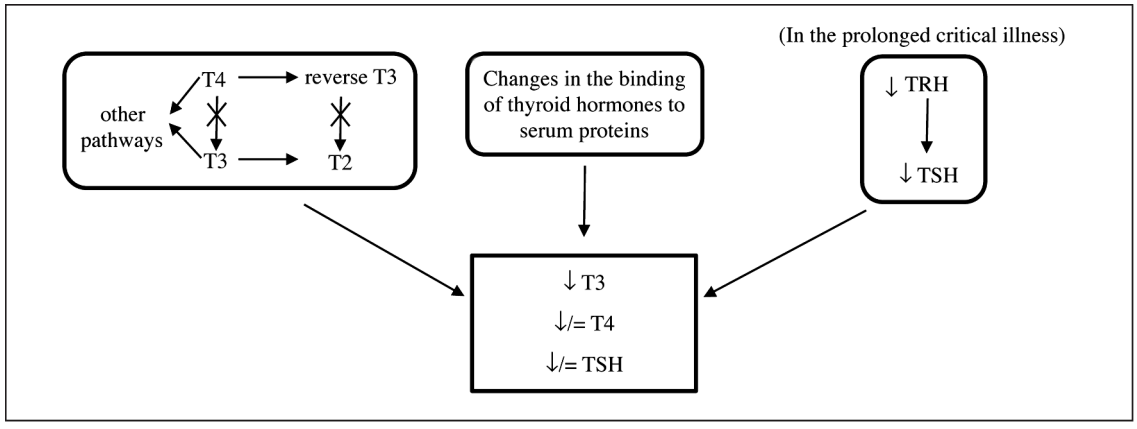

Figure 1.—Major changes within the thyroid axis during critical illness. The pathogenetic mechanisms proposed to explain serum thyroid hormone abnormalities during critical illness include the following: decreased conversion of T4 to T3 in extrathyroidal tissues; alterations in the binding of thyroid hormones to serum proteins; and, in the protracted phase of critical illness, a decreased pulsatile frequency of TSH secretion, resulting from a reduction in TRH release by the hypothalamus. T4: thyroxine; T3: triiodothyronine; T2: diiodothyronine; TSH: thyroid-stimulating hormone; TRH: thyrotropin-releasing hormone.

MINERVA MEDICA COPYRIGHT®

Table I.—*Factors that may cause alterations in the hypothalamic-pituitary axis during critical illness.*

Causes of inhibition of the type I 5'deiodinase enzyme activity
Critical illness
Starvation
Glucocorticoids
Beta blockers
Amiodarone
Selenium deficiency
Cytokines
Fatty acids
Causes of decreased secretion of thyroid-stimulating hormone
Critical illness
Starvation
Glucocorticoids
Catecholamines
Opioids
Causes of impaired binding of thyroid hormones to serum proteins
Critical illness
Glucocorticoids
Furosemide
Heparin
Nonesterified free fatty acids
Phenytoin
Carbamazepine
Salicylates

ered to be beneficial, as it should contribute to the patient's metabolic adaptation and thus be essential for survival. However, when patients are treated in the Intensive Care Unit (ICU) for weeks or even months, a different set of hormonal changes may occur, including the uniform suppression of the pulsatile secretion of growth hormone (GH), TSH, and prolactin, as well as the decrease in serum levels of thyroid hormones, insulin-like growth factor I, and leptin.[1]

Different critical illness conditions

The following sections will analyze the most common populations of subjects in whom NTIS has been described, as well as the available evidence on the effects of restoring normal serum concentrations of thyroid hormone in critically ill patients with NTIS.

Heart disease

Thyroid hormone exerts a variety of direct and indirect actions on the cardiovascular system, including the following: an increase in cardiac inotropy and chronotropy, resulting from either the binding of T3 to nuclear receptors in cardiac myocytes or non-nuclear T3 actions on the ion channels for sodium, potassium, and calcium; an increase in tissue oxygen and substrate requirements, which leads to a secondary increase in cardiac contractility; a decrease in systemic vascular resistance, resulting from the direct action of T3 on vascular smooth muscle cells; and an increase in blood volume caused by either the activation of the renin-angiotensin-aldosterone axis, resulting from vasodilation, or an increase in erythropoietin secretion, resulting from direct thyroid hormone stimulation.[20]

Changes have been observed in the thyroid hormone profiles of patients with cardiovascular disorders of various origins, such as acute myocardial infarction [21] and congestive heart failure,[22, 23] as well as in those undergoing cardiopulmonary bypass surgery.[24-26]

Pingitore *et al.*[23] showed that administering thyroid hormone to patients with dilated cardiomyopathy and NTIS significantly increased left ventricular end-diastolic volume and stroke volume while decreasing heart rate. Klemperer *et al.*[24] randomized 142 patients undergoing coronary artery bypass surgery to receive either intravenous T3 or a placebo immediately after aortic cross-clamp removal. Raising serum T3 concentrations in those patients increased their cardiac output and lowered systemic vascular resistance, but it could not change the patients' outcomes or alter their need for standard postoperative therapies. In the randomized controlled study conducted by Bennett-Guerrero *et al.*,[25] which looked at 211 patients at a high risk of requiring inotropic drug support after coronary artery bypass graft surgery, an intravenous infusion of T3 did not change patients' hemodynamic variables or inotropic drug requirements. Mullis-Jansson *et al.*[26] studied 170 patients undergoing elective coronary artery bypass grafting who were randomly given either intravenous T3 or a placebo after aortic cross-clamp removal. T3-treated patients had a higher cardiac index and lower inotropic requirements after the operation, and they showed a significantly lower incidence of postoperative myocardial ischemia as well as a

MINERVA MEDICA COPYRIGHT®

reduced need for pacemakers or mechanical cardiac support devices.

To date, the pathophysiological role of the thyroid hormone changes that occur in patients with heart disease has not yet been established. These changes could be mere biochemical markers of the severity of the disease, or they could actually contribute to the development and progression of cardiac dysfunction. Moreover, the existing data on the use of T3 in patients with heart disease remains contradictory, even though potential benefits of thyroid hormone supplementation have been widely reported in this setting. Thus, it must be borne in mind that giving thyroid hormone to cardiac patients may carry risks. Exogenous thyroid hormone administration may directly influence myocardial oxygen supply and demand, resulting in a myocardial ischemic event, even in the absence of coronary artery stenosis or spasms.[27] Therefore, further studies are required to clarify the potential value of thyroid hormone replacement and define specific treatment recommendations for patients with heart disease.

Brain-dead potential organ donors

Several studies have been published concerning the association between brain death and hypothalamic-pituitary-adrenal axis impairment.[28-30] Low levels of circulating thyroid hormone may alter mitochondrial function, thus impairing the use of metabolic substrate and hindering the production of ATP.[29]

Novitzky *et al.*[29] found that T3 supplementation after brain death increased pyruvate, glucose, and palmitate use, and also normalized plasma lactate and free fatty acid concentrations, suggesting an apparent reversal from an anaerobic to an aerobic metabolism in the tissue. On the basis of these data, the authors concluded that T3 should be administered to all brain-dead potential organ donors to correct and maintain a more physiologic metabolic status, thus improving organ function.[29]

Rosendale *et al.*[30] retrospectively analyzed more than 10,000 brain-dead donors recovered in the United States from January 1, 2000 to September 30, 2001. Their analysis showed that hormonal resuscitation of the donor, consisting of a methylprednisolone bolus, an infusion of vasopressin, and either T3 or T4, was associated with a significantly higher probability that an organ could be successfully harvested from the donor.[30]

Although the benefits of thyroid hormone treatment in brain-dead donors have been reported in several studies, most of these studies have included only a small number of subjects and have not been controlled. Moreover, other studies have disproved the hypotheses regarding the presence of hormonal depletion in brain-dead donors and the correlation between vasopressor requirements and levels of circulating lactate and thyroid hormone.[31, 32] Furthermore, the existing research does not unanimously report improved outcomes among patients receiving hormone administration.[33, 34]

Pérez-Blanco *et al.*[34] prospectively randomized 52 adult organ donors to receive T3 or a placebo. Hemodynamic measurements did not differ significantly between the two groups, and the inotrope dose could not be diminished after treatment. Additionally, T3 treatment did not affect the concentration of adenine nucleotides in any of the biopsied organs. Based on these observations, the authors suggested that brain death, per se, should not cause impairment in the hypothalamic-pituitary axis, as the thyroid hormone abnormalities they found in the study population could be explained by the pre-existing conditions that had led to brain death.[34]

All of these findings would invalidate the rationale for a routine replacement therapy of T3 or cortisol to maintain endocrine homeostasis prior to organ harvesting. In the absence of clear evidence, further research should be conducted to better define the efficacy and optimal timing of thyroid hormone administration in brain-dead donors.

Burn patients

Circulating thyroid hormone concentrations are generally suppressed in severe burn patients, and the low T3 state in these patients seems to be associated with a poor prognosis.[35]

MINERVA MEDICA COPYRIGHT®

Gangemi *et al*.[36] retrospectively analyzed the serum levels of free T3, free T4 and TSH in 295 burn patients, finding that free T3 and TSH serum concentrations were significantly lower in non-survivors compared to survivors, while no significant difference between the two groups was found in the serum levels of free T4. Additionally, serum concentrations of free T3 were significantly correlated with fatal outcomes.

In a prospective randomized study, Becker *et al*.[37] assigned 28 patients with 2nd and 3rd degree burns covering a total of 18-93% of the body's surface area to receive either a placebo or T3 at a rate of 200 μg/day (orally or via nasogastric tube) in four divided doses until their wounds were healed. In the survivors (N=20), T3 supplementation managed to restore free T3 serum levels but did not affect mortality, resting metabolic rate, or plasma catecholamine concentrations.

In the absence of strong evidence, no conclusions can be drawn regarding the possible effectiveness of thyroid hormone replacement in burn patients with NTIS.

Acute renal failure

Thyroid hormone supplementation has been demonstrated to ameliorate or reverse ischemic and toxic acute renal failure in a wide variety of animal models.[38-40] However, the positive effects seen in the experimental models have not been confirmed in humans. Acker *et al*.[41] randomized 59 patients with acute renal failure to receive intravenous T4 or a placebo. The protocol solution consisted of 150 μg of T4 in 20 mL of normal saline, administered over five minutes by intravenous infusion. Thyroid hormone administration resulted in a progressive and sustained suppression of TSH serum levels in the T4 group but had no effect on renal failure severity. Additionally, mortality was higher in the treated group than in the control group (43% vs. 13%; P=0.01) and correlated with TSH suppression. Thus, we conclude that thyroid hormone administration is not beneficial for the treatment of clinical acute renal failure in critically ill patients with NTIS.

Heterogeneous populations in the ICU

In the 1980s, Brent and Hershman[42] undertook a randomized prospective study to assess the responses to either T4 treatment (N=11) or a placebo (N=12) among patients admitted to a medical ICU with severe NTIS and total T4 serum levels of less than 5 μg/dL. These patients' diagnoses included sepsis, respiratory failure, gastrointestinal hemorrhage, aspiration pneumonia, and hepatic failure, and these conditions were similarly distributed in both groups. T4-treated patients received a daily intravenous injection of T4 in a dose of 1.5 μg per kilogram for two weeks. Interestingly, in this study, the authors used T4 rather than T3 to treat thyroid hormone alterations. In the treatment group, circulating T4 levels significantly increased from day 1 to day 3, and they were in the normal range on day 5. Despite treatment, serum T3 levels significantly increased only on the 10th day and failed to return to the normal range at any point in the study. Moreover, serum TSH levels in the treated patients decreased significantly, as did the TSH response to TRH. Mortality was similar in the two groups (75% control *versus* 73% treatment).

The authors of the study concluded that T4 treatment was not beneficial to critically ill patients with non-thyroidal illnesses admitted to the ICU. They also suggested that the suppressive effects of T4 treatment on TSH secretion may have dangerously compromised the physiological normalization of the hypothalamic-pituitary axis during recovery.

We cannot exclude the possibility that, due to the relatively small number studied, a treatment effect existed that was not immediately evident. Furthermore, there is a possibility that the failure to obtain a beneficial effect from T4 treatment might be due to the failure of serum T3 concentrations to be restored to the normal range. However, the data currently available are too limited to allow us to draw firm conclusions about the usefulness of thyroid hormone replacement in unselected patient populations with NTIS.

Starvation

The inhibition of type I 5'-deiodinase that occurs within 24 hours of the onset of caloric dep-

MINERVA MEDICA COPYRIGHT®

rivation results in a decrease in the serum levels of T3 and an increase in reverse T3 levels.[43] Also, it has been reported that fasting induces a drop in the basal metabolic rate.[43] These neuro-hormonal changes are thought to be "teleological," adaptive responses to starvation as a way of keeping metabolic demands to a minimum. Based on this interpretation, starving subjects should not receive endocrine correction.

Most of the existing data support the view that the decrease in thyroid hormone during times of starvation is an appropriate and protective response by the body to reduce energy expenditure. The general interpretation of NTIS as an adaptive response to spare energy has often been based on the changes in thyroid hormone metabolism that are observed during starvation. However, it is unclear whether the altered state of thyroid hormone during starvation is comparable to the thyroid hormone decrease induced by critical illness.

Respiratory failure

Respiratory function has been widely investigated in primary hypothyroidism.Conversely, only a few reports address the correlation between respiratory failure and NTIS.

Hypothyroidism has been found to be a cause of respiratory failure that may require prolonged mechanical ventilation.[44, 45] In addition, the respiratory failure associated with hypothyroidism responds well to thyroid hormone supplementation.[46-48] Several mechanisms have been suggested to explain the association between respiratory failure and hypothyroidism: a change in the normal ventilatory responses to hypercapnia and hypoxia,[46, 47, 49-51] diaphragmatic and skeletal muscle impairment,[46, 47, 50, 52-55] pleural effusions,[56] and obstructive sleep apnea.[57] In a one-year study conducted at a long-term weaning center, Pandya *et al.*[44] discovered four cases of hypothyroidism in a group of patients with ventilator-dependent respiratory failure. The correction of hypothyroidism allowed three of these patients to be weaned from mechanical ventilation. Datta and Scalise[45] reported similar results in an analogous patient population.

Data relating to the correlation between ventilator-dependent respiratory failure and a low T3 state are scarce. Plikat *et al.*[58] retrospectively analyzed 220 patients whose complete serum hormone levels had been determined within 24-48 hours of ICU admission. They found that patients with NTIS were more often mechanically ventilated than those with normal results on thyroid function tests (44% for euthyroid patients, 50% for patients with only low levels of free T3, and 83% for patients with low levels of free T3/free T4). More recently, in a retrospective study of 264 patients admitted to our ICU who underwent mechanical ventilation following respiratory failures of various etiologies, NTIS was found to be an independent risk factor for prolonged mechanical ventilation (OR, 2.25; 95% CI, 1.18-4.29; P=0.01).[59] The latter was defined as dependence on mechanical ventilation for >13 days, which was the median value of the duration of mechanical ventilation in the entire study population

Similar to other critical illness conditions, it remains unclear whether NTIS contributes to impaired respiratory function or only acts a negative prognostic marker of that condition. This question might be answered by evaluating whether respiratory function benefits from the administration of thyroid hormones or hypothalamic peptides to a selected group of NTIS patients in randomized controlled trials.

Role of the hypothalamus in NTIS

Hypothalamic changes seem to play a major role in the pathogenesis of the lowered activity of the thyrotropic and somatotropic axes in cases of prolonged critical illness. A number of findings are in line with this concept.

In a postmortem examination of human brain specimens in 10 subjects with varying degrees of NTIS, Fliers *et al.*[60] found that TRH gene expression in hypothalamic paraventricular nuclei is decreased when death occurs after a prolonged critical illness, whereas such a decrease is not observed when death is caused by acute events such as trauma. In this study, the reduction of TRH gene expression in the hypothalamus was significantly correlated with decreases in serum levels of both TSH and T3, but not T4.

MINERVA MEDICA COPYRIGHT®

In healthy subjects, GH, TSH and prolactin are released from the anterior pituitary gland in a pulsatile and synchronized fashion. During protracted critical illness, the nocturnal secretory patterns of GH, TSH and prolactin have been found to be reduced and desynchronized.[61] Under these conditions, it has been shown that GH, TSH and prolactin may still be released in response to a continuous infusion of GH secretagogues and TRH,[61] and a continuous infusion of GHPR-2 (but not TRH) may have a synchronizing effect on the serum concentrations of these hormones.[62] It remains unknown whether GHRP-2 exerts this coordinating action at the level of hypothalamus or at the level of uni- or pluri-hormonal pituitary cell types.

Additionally, patients suffering from a prolonged critical illness who were treated for five days with an intravenous co-infusion of TRH and GH-releasing peptide (GHRP-2) experienced not only a reactivation of blunted GH and TSH secretion and a partial restoration of circulating thyroid hormone levels (without affecting cortisol release) but also a return of peripheral tissue responsiveness, as documented by increased markers of anabolism and decreased markers of catabolism.[63]

Interestingly, the co-infusion of TRH and GHRP-2 seems to be more advantageous than the administration of TRH alone; the combination can increase the pulsatile fraction of TSH release and overcome the impaired peripheral conversion of T4 to T3 observed during critical illness. Additionally, the effects of co-infusing a GH secretagogue with TRH seem to be self-limited by intact feedback inhibition loops. In fact, the negative feedback exerted by thyroid hormone on the thyrotropes remains in place during TRH infusion, thus preventing overstimulation of the thyroid gland.[61]

To treat or not to treat: a persistent dilemma

There is no consensus in the literature about correcting serum concentrations of thyroid hormone in critically ill patients affected by NTIS. However, on one point most authors seem to agree: carefully controlled studies are needed to clarify the role of thyroid hormone changes during critical illness.[14, 15] In evaluating the effects of hormone replacement therapy in NTIS patients, a number of issues must be discussed before settling on an optimal method.

Establishing clinical endpoints is one major concern in developing and evaluating a treatment for NTIS. Obviously, the aim of such a treatment would not be to cure critically ill patients with NTIS but to contribute somehow to their recovery from critical illness. Theoretically, if NTIS patients were actually hypothyroid, the normalization of their circulating thyroid hormone levels might reverse at least some of the abnormalities that tend to accompany hypothyroidism and have no other evident explanation. Based on this assumption, a possible study of the treatment of NTIS might analyze a series of clinical disorders including mental obtundation, dry skin, hypothermia, bradycardia, hypotension, sluggish tendon reflexes, constipation, pleural or pericardial or peritoneal effusions, weight gain and hair loss, as well as laboratory disorders such as anemia and increased serum levels of triglycerides, creatinine phosphokinase, lactate dehydrogenase, and glutamic-oxaloacetic transaminase. Unfortunately, each of these disorders may result from a wide variety of factors commonly present in the ICU. Therefore, it would be difficult to show any correlation between the endocrine treatment and any correction of these disorders. Instead, clinical endpoints such as mortality and morbidity rates, physiological functions, or metabolic markers would seem to be more suited to evaluating the effects of thyroid hormone restoration (by giving thyroid hormone or releasing peptides) on critically ill patients in placebo-controlled, randomized trials.

Another important issue is to establish which thyroid hormone is best to use: T3, T4, or a combination of the two. In ICU patients with a low T3 state, the administration of T4 alone failed to normalize serum T3 concentrations,[42] probably because of the impaired peripheral conversion of T4 to T3 during critical illness. Therefore, treatment with T4 alone should be avoided.

Also, it will be important to define both the optimal dose of thyroid hormone and the optimal interval of time between one hormone determination and the next. Initial doses of thy-

MINERVA MEDICA COPYRIGHT®

roid hormone should rapidly restore the body's hormone reserves while preventing dangerously abnormal increases in serum hormone concentrations. At least during the first several days of treatment, serum thyroid hormone levels should be checked at frequent intervals, and hormone doses should be adjusted to maintain those levels within normal limits. Once serum hormone levels are steadily within the normal range, hormone determinations may be made less frequently. The interval between one hormone measurement and the next should be established on the basis of a series of factors such as the mode of hormone administration (oral dosage, intravenous boluses or intravenous infusion), the trend in serum hormone concentrations over time, the type of study, and the need to perform a pharmacokinetic evaluation of hormone replacement.

Once the treatment is started, an extremely prudent approach will be needed. Therefore, organ functions must be carefully monitored, and serum thyroid hormone concentrations should be kept stable throughout the whole endocrine treatment. In patients with NTIS, many tissues can be deficient in thyroid hormones, but the severity of these hormone deficits may vary from one organ to another.[64] Consequently, the same dose might be insufficient for one organ or tissue but excessive for another.

A further issue is to determine the cut-off values of serum thyroid hormone levels at which a treatment may be started, as well as how long that treatment should last.

The route of thyroid hormone administration, whether intravenous or oral, also requires consideration. Intestinal absorption of thyroid hormone can be affected by several factors, such as enteral nutrition, individual absorption kinetics,[65] and treatment with other medications.[66-68] Therefore, enterally nourished patients should take thyroid hormone either intravenously or on an empty stomach for optimal drug absorption. Patients with altered intestinal absorption should also receive thyroid hormones intravenously. For all of these reasons, intravenous administration would seem the preferred route for this prospective treatment.

Finally, it is possible that the eventual treatment of NTIS might move beyond the simple administration of T3 or T4. Abnormalities in hypothalamic function and interactions among the different anterior pituitary axes that can occur during critical illness should be taken into account if NTIS is to be treated. Administering hypothalamic releasing factors seems to improve metabolism and restore anterior pituitary pulsatile secretion in patients with chronic critical illnesses.[63] During the intravenous infusion of these neuropeptides, feedback-inhibition mechanisms seem to be maintained, thus allowing the introduction of appropriate amounts of thyroid hormone into the blood and preventing overtreatment.[61, 63] Based on these findings, the administration of hypothalamic peptides might be a safer strategy than thyroid hormone supplementation if treatment of NTIS is attempted.

Conclusions

There are, as yet, no definitive answers to the question of whether the metabolic changes in the hypothalamic-pituitary axis observed during critical illness represent an adaptive advantage or a maladaptive response to stress. Likewise, it is still not clear whether and when these changes may be corrected.

References

1. Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1-13.
2. Rubenfeld S. Euthyroid sick syndrome. N Engl J Med 1978;299:1414.
3. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev 1982;3:164-217.
4. Chopra IJ. Euthyroid sick syndrome: abnormalities in circulating thyroid hormones and thyroid hormone physiology in nonthyroid illness (NTI). Med Grand Rounds 1982;1:201-12.
5. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab 1997;82:329-34.
6. Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab 1975;41:27-40.
7. Kaplan MM, Larsen PR, Crantz FR, Dzau VJ, Rossing TH, Haddow JE. Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am J Med 1982;72:9-16.
8. Kaptein EM, Weiner JM, Robinson WJ, Wheeler WS, Nicoloff JT. Relationship of altered thyroid hormone indices to survival in nonthyroidal illnesses. Clin Endocrinol (Oxf) 1982;16:565-74.

MINERVA MEDICA COPYRIGHT®

9. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981;245:43-5.
10. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995;23:78-83.
11. Chinga-Alayo E, Villena J, Evans AT, Zimic M. Thyroid hormone levels improve the prediction of mortality among patients admitted to the intensive care unit. Intensive Care Med 2005;31:1356-61.
12. Rothwell PM, Udwadia ZF, Lawler PG. Thyrotropin concentration predicts outcome in critical illness. Anaesthesia 1993;48:373-6.
13. Sumita S, Ujike Y, Namiki A, Watanabe H, Kawamata M, Watanabe A *et al*. Suppression of the thyrotropin response to thyrotropin-releasing hormone and its association with severity of critical illness. Crit Care Med 1994;22:1603-9.
14. De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999;84:151-64.
15. Wartofsky L, Burman KD, Ringel MD. Trading one "dangerous dogma" for another? Thyroid hormone treatment of the "euthyroid sick syndrome". J Clin Endocrinol Metab 1999;84:1759-60.
16. Chopra IJ, Solomon DH, Teco GN, Eisenberg JB. An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. Science 1982;215:407-9.
17. Romijn JA, Wiersinga WM. Decreased nocturnal surge of thyrotropin in nonthyroidal illness. J Clin Endocrinol Metab 1990;70:35-42.
18. Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV *et al*. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab 1986;62:717-22.
19. Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S *et al*. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem 1987;33:1391-6.
20. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
21. Franklyn JA, Gammage MD, Ramsden DB, Sheppard MC. Thyroid status in patients after acute myocardial infarction. Clin Sci (Lond) 1984;67:585-90.
22. Hamilton MA, Stevenson LW, Luu M, Walden JA. Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol 1990;16:91-5.
23. Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D *et al*. 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 2008;93:1351-8.
24. Klemperer JD, Klein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ *et al*. Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med 1995;333:1522-7.
25. Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwinn DA. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. JAMA 1996;275:687-92.
26. Mullis-Jansson SL, Argenziano M, Corwin S, Homma S, Weinberg AD, Williams M *et al*. A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. J Thorac Cardiovasc Surg 1999;117:1128-34.
27. Bergeron GA, Goldsmith R, Schiller NB. Myocardial infarction, severe reversible ischemia, and shock following excess thyroid administration in a woman with normal coronary arteries. Arch Intern Med 1988;148:1450-3.
28. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB. Care of the potential organ donor. N Engl J Med 2004;351:2730-9.
29. Novitzky D, Cooper DK, Morrell D, Isaacs S. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy. Transplantation 1988;45:32-6.
30. Rosendale JD, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER *et al*. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003;75:482-7.
31. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. Crit Care Med 1990;18:702-8.
32. Gramm HJ, Meinhold H, Bickel U, Zimmermann J, von Hammerstein B, Keller F *et al*. Acute endocrine failure after brain death? Transplantation 1992;54:851-7.
33. Goarin JP, Cohen S, Riou B, Jacquens Y, Guesde R, Le Bret F *et al*. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. Anesth Analg 1996;83:41-7.
34. Pérez-Blanco A, Caturla-Such J, Cánovas-Robles J, Sanchez-Payá J. Efficiency of triiodothyronine treatment on organ donor hemodynamic management and adenine nucleotide concentration. Intensive Care Med 2005;31:943-8.
35. Becker RA, Wilmore DW, Goodwin CW Jr, Zitzka CA, Wartofsky L, Burman KD *et al*. Free T4, free T3, and reverse T3 in critically ill, thermally injured patients. J Trauma 1980;20:713-21.
36. Gangemi EN, Garino F, Berchialla P, Martinese M, Arecco F, Orlandi F *et al*. Low triiodothyronine serum levels as a predictor of poor prognosis in burn patients. Burns 2008;34:817-24.
37. Becker RA, Vaughan GM, Ziegler MG, Seraile LG, Goldfarb IW, Mansour EH *et al*. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med 1982;10:870-5.
38. Siegel NJ, Gaudio KM, Katz LA, Reilly HF, Ardito TA, Hendler FG *et al*. Beneficial effect of thyroxin on recovery from toxic acute renal failure. Kidney Int 1984;25:906-11.
39. Cronin RE, Brown DM, Simonsen R. Protection by thyroxine in nephrotoxic acute renal failure. Am J Physiol 1986;251:408-16.
40. Sutter PM, Thulin G, Stromski M, Ardito T, Gaudio KM, Kashgarian M *et al*. Beneficial effect of thyroxin in the treatment of ischemic acute renal failure. Pediatr Nephrol 1988;2:1-7.
41. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyroxine in acute renal failure. Kidney Int 2000;57:293-8.
42. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab 1986;63:1-8.
43. Gardner DF, Kaplan MM, Stanley CA, Utiger RD. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. N Engl J Med 1979;300:579-84.
44. Pandya K, Lal C, Scheinhorn D, Day IK, Sharma OP. Hypothyroidism and ventilator dependency. Arch Intern Med 1989;149:2115-6.
45. Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. Chest 2004;126:1307-12.
46. Ambrosino N, Pacini F, Paggiaro PL, Martino E, Contini V, Turini L et al. Impaired ventilatory drive in short-term primary hypothyroidism and its reversal by L-triiodothyronine. J Endocrinol Invest 1985;8:533-6.
47. Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. Am J Med 1988;84:877-83.
48. Gorini M, Spinelli A, Cangioli C, Gigliotti F, Duranti R,

MINERVA MEDICA COPYRIGHT®

Arcangeli P et al. Control of breathing in patients with short-term primary hypothyroidism. Lung 1989;167:43-53.
49. Nordqvist P, Dhuner KG, Stenberg K, Orndahl G. Myxoedema coma and carbon dioxide-retention. Acta Med Scand 1960;166:189-94.
50. Massumi RA, Winnacker JL. Severe depression of the respiratory center in myxedema. Am J Med 1964;36:876-82.
51. Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV. Ventilatory control in myxedema and hypothyroidism. N Engl J Med 1975;292:662-5.
52. Khaleeli AA, Edwards RH. Effect of treatment on skeletal muscle dysfunction in hypothyroidism. Clin Sci (Lond) 1984;66:63-8.
53. Laroche CM, Cairns T, Moxham J, Green M. Hypothyroidism presenting with respiratory muscle weakness. Am Rev Respir Dis 1988;138:472-4.
54. Martinez FJ, Bermudez-Gomez M, Celli BR. Hypothyroidism. A reversible cause of diaphragmatic dysfunction. Chest 1989;96:1059-63.
55. Siafakas NM, Salesiotou V, Filaditaki V, Tzanakis N, Thalassinos N, Bouros D. Respiratory muscle strength in hypothyroidism. Chest 1992;102:189-94.
56. Sachdev Y, Hall R. Effusions into body cavities in hypothyroidism. Lancet 1975;1:564-6.
57. Rajagopal KR, Abbrecht PH, Derderian SS, Pickett C, Hofeldt F, Tellis CJ *et al*. Obstructive sleep apnea in hypothyroidism. Ann Intern Med 1984;101:491-4.
58. Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Schölmerich J *et al*. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metabolism 2007;56:239-44.
59. Bello G, Pennisi MA, Montini L, Silva S, Maviglia R, Cavallaro F *et al*. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the intensive care unit. Chest 2009;135:1448-54.
60. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with non-thyroidal illness. J Clin Endocrinol Metab 1997;82:4032-6.
61. Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 1998;83:309-19.
62. Van den Berghe G, Wouters P, Bowers CY, de Zegher F, Bouillon R, Veldhuis JD. Growth hormone-releasing peptide-2 infusion synchronizes growth hormone, thyrotrophin and prolactin release in prolonged critical illness. Eur J Endocrinol 1999;140:17-22.
63. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD et al. 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.
64. Arem R, Wiener GJ, Kaplan SG, Kim HS, Reichlin S, Kaplan MM. Reduced tissue thyroid hormone levels in fatal illness. Metabolism 1993;42:1102-8.
65. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. Thyroid 1995;5:249-53.
66. Liel Y, Sperber AD, Shany S. Nonspecific intestinal adsorption of levothyroxine by aluminum hydroxide. Am J Med 1994;97:363-5.
67. Sherman SI, Malecha SE. Absorption and Malabsorption of Levothyroxine Sodium. Am J Ther 1995;2:814-8.
68. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. Thyroid 2001;11:967-71.

Conflicts of interest.—None.

Received on April 7, 2010 - Accepted for publication on July 22, 2010.

Corresponding author: G. Bello, MD, Istituto di Anestesiologia e Rianimazione, Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168, Rome, Italy. E-mail: gbello.gb@libero.it