Euthyroid Sick Syndrome

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ABSTRACT

In this review, we discuss the characteristics, pathophysiology, and therapeutic implications of the euthyroid sick syndrome. Multiple mechanisms have been identified to contribute to the development of euthyroid sick syndrome, including alterations in the iodothyronine deiodinases, thyroid-stimulating hormone secretion, thyroid hormone binding to plasma protein, transport of thyroid hormone in peripheral tissues, and thyroid hormone receptor activity. The euthyroid sick syndrome appears to be a complex mix of physiologic adaptation and pathologic response to acute illness. The underlying cause for these alterations has not yet been elucidated. Treatment of the euthyroid sick syndrome with thyroid hormone to restore normal serum thyroid hormone levels in an effort to improve disease prognosis and outcomes continues to be a focus of many clinical studies, although currently available data do not provide evidence of a clear benefit of treatment.
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Introduction

Abnormal serum thyroid hormone parameters have been well described in patients with acute illness but without prior history of thyroid disease since the 1970s (9, 14, 35, 46, 60, 86, 106). The most common alterations in thyroid hormone parameters seen in these cases include low triiodothyronine (T3) levels, normal thyroid stimulating hormone (TSH) levels, and increased reverse triiodothyronine (rT3) levels. These changes in serum thyroid function associated with acute illness have been termed "euthyroid sick syndrome," "nonthyroidal illness syndrome," or "low T3 syndrome."

The changes in the thyroid hormone parameters seen in the euthyroid sick syndrome are thought to be a response to systemic illness through a variety of different pathways. One theory postulates that euthyroid sick syndrome may be a compensatory mechanism in response to the oxidative stress of acute illness (95). In any event, the euthyroid sick syndrome includes alterations in: iodothyronine deiodinase activity, TSH secretion, thyroid hormone binding to plasma proteins, transport of thyroid hormone into peripheral tissues, nuclear thyroid hormone receptor activity and thyrotropin-releasing hormone (TRH) secretion. These alterations in thyroid hormone parameters represent a continuum of changes that depend on the severity of the illness and that follow a sequential progression of several distinct stages. The wide spectrum of changes observed often results from the differing points in the course of the illness when the thyroid function tests were obtained. Furthermore, the euthyroid sick syndrome can be seen with certain chronic illnesses in otherwise ambulatory patients. Importantly, these changes are rarely isolated and often associated with alterations of other endocrine systems, such as decreases in serum gonadotropin and sex hormone concentrations and increases in serum ACTH and cortisol levels (46). Thus, the euthyroid sick syndrome should not be viewed as an isolated pathologic event but as part of a coordinated systemic reaction to illness involving both the immune and endocrine systems.

Despite the abnormalities in thyroid hormone parameters seen in the euthyroid sick syndrome, their clinical significance has not been clear, with conflicting results in the literature of the effects of treatment with thyroid hormone on clinical outcome. If the changes are physiologic as an adaptive mechanism to decreased metabolism during periods of acute illness, treatment with thyroid hormone replacement to restore normal levels would not be beneficial and may even be harmful. However, if the changes are pathologic, especially in response to drug therapy in the acutely ill patient, thyroid hormone treatment may be indicated and beneficial. Current evidence suggests that the changes in thyroid hormone parameters seen in the euthyroid sick syndrome may be a combination of physiologic adaptation and pathologic alteration, with no unifying benefit of treatment with thyroid hormone.

In this review, we will discuss the pathways of thyroid hormone metabolism affected in the euthyroid sick syndrome, the stages of the syndrome and examine the evidence regarding therapy of the syndrome.

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Alterations in Thyroid Hormone Metabolism During Acute Illness in Euthyroid Sick Syndrome

The following alterations in thyroid hormone metabolism have been identified as potential underlying mechanisms for the thyroid hormone abnormalities seen in the euthyroid sick syndrome.

Alterations in iodothyronine deiodinases

Iodothyronine deiodinases are enzymes that catalyze the sequential monodeiodination of the iodothyronines. Their primary role is to either activate or deactivate the main product of the thyroid gland, thyroxine (T4). There are three iodothyronine deiodinases: type 1 (D1) and type 2 (D2) 5′-deiodinases that catalyze the activating reaction from T4 to 3,5,3′-triiodothyronine (T3) by removal of an outer ring iodine and type 3 (D3) 5-deiodinase catalyzing the deactivating reaction from T4 to 3,3′,5′-triiodothyronine (reverse T3 or rT3) by removal of an inner ring iodine (13). The acute decrease in T3 and increase in rT3 early in the euthyroid sick syndrome initially was thought to result solely from the acute inhibition of D1 in liver and kidneys by a variety of factors [Table 1 (13)]. However, increased D3 activity in liver and inflammatory cells has been reported in both animal models of tissue injury and hospitalized patients in acute illness (55). Studies on human tissues obtained from patients who died during acute illness showed a decrease in D1 activity and an increase in D3 activity, while there was no change or absent D2 activities in liver and skeletal muscles (50, 71, 88). In addition, increases in nondeiodinative pathways such as sulfoconjugation (21) and alanine side chain deamination/decarboxylation (46) have been reported to be increased in the euthyroid sick syndrome. Thus, it has become clear that there are many pathways that all serve to drive down T3 levels early in the euthyroid sick syndrome.

Table 1 Factors that Inhibit D1 Activity

Acute and chronic Illness
Caloric deprivation
Malnutrition
Glucocorticoids
β-Adrenergic blocking drugs (e.g., propranolol)
Oral cholecystographic agents (e.g., iopanoic acid, sodium ipodate)
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency
Hepatic disease

Table 2 Tissue-Specific Alterations in Iodothyronine Deiodinases in Illness (14)

Organ	Model	Alterations in deiodinases
Hypothalamus		
	Rodent—acute illness	Increased D2 mRNA expression and activity
	Mouse—acute inflammation	Decreased D3 activity
	Mouse—chronic inflammation	Increased D2 expression; decreased D3 activity
	Rabbit—critical illness	Increased D2 expression; unchanged D3 activity
Liver		
	Rodent—acute inflammation	Decreased D1 expression; decreased D3 expression
	Rodent—chronic inflammation	D1 mRNA expression unaffected; decreased D3 mRNA expression and activity
Muscle		
	Rodent—acute inflammation	Increased D2 expression; decreased D3 expression
	Mice—chronic inflammation	Increased D2 and D3 mRNA expression and activity
	Humans and mice—bacterial sepsis	Decreased D2 expression; unchanged or increased D3 expression
Adipose tissue		
	Humans—bacterial sepsis	No change in D1 or D3 activities

An extensive review of thyroid hormone metabolism in inflammation and infection by Boelen et al. (14) described different alterations in deiodinase activity in different tissues during acute illness, as summarized in Table 2. In a rodent model of acute inflammation, liver D1 expression is decreased, presumably as a result of regulation through thyroid hormone receptor β1 (TRβ1) (14). Changes in deiodinase expression have also seen in a pig model of septic shock induced by bacterial endotoxin, lipopolysaccharide (LPS), with decreases in liver and kidney D1 expression and activity and increases in hypothalamic, thyroidal, and liver D3 activity observed (19).

In the hypothalamus, D2 is thought to be the major contributor of hypothalamic T3 production. In the rodent model of acute illness, there is an increase in D2 mRNA expression and activity seen in hypothalamus (26), which is also seen in mouse model of chronic inflammation (14, 38) and rabbits with chronic illness (70). The mechanism of this increase in

D2 expression and activity is unclear at this time, but it appears to be independent of change in serum T3 levels, and the activation of nuclear factor-κB pathway may be involved (14). On the other hand, hypothalamic D3 activity is unaltered in rabbits with chronic illness (70) and decreased in mice models of both acute and chronic inflammation (14). The subsequent increase in local hypothalamic T3 levels may contribute to the decrease in hypothalamic TRH mRNA expression seen in acute illness.

Data from the deiodinase knockout mouse have raised questions regarding the clinical significance of the changes in deiodinase activity in the euthyroid sick syndrome. The illness-induced changes in serum T4 and T3 levels were not significantly different between wild-type and TRβ1 knockout mice, despite differences seen in liver D1 mRNA expression and activity (41). Similar findings were reported in alterations in liver D3 expression and activity in mouse models (14). The relative lack of effects of changes in deiodinase expression and activity on serum thyroid hormone levels have also been shown in various deiodinase knockout mice models, as serum T3 appears preserved even though rT3 levels are undetectable (41, 99, 106).

Alterations in thyroid-stimulating hormone secretion

Serum TSH levels usually remain normal during early phases of acute illness. However, with illness progression, TSH steadily decreases as a result of multiple factors (Table 3). These include several medications used for treatment of critical illness, such as dopamine and glucocorticoids, that have a direct inhibitory effect on TSH secretion (11, 16). In addition, D2 activity has been reported to be increased in the pituitary in the euthyroid sick syndrome, increasing local production of T3 and decreasing TSH synthesis (38, 39, 66). Further, increased production of thyroid hormone metabolites such as 3,5,3′-triiodothyroacetic acid (Triac) during acute illness also have a direct inhibitory effect on TSH synthesis.

There is ample evidence of decreased TRH production and secretion leading to a decrease in TSH in the euthyroid sick syndrome (14, 46). Leptin, a hormone encoded by the *ob* gene and secreted by adipocytes, plays a role in balancing the energy intake and expenditure. Leptin has been reported to directly regulate TRH production, and leptin and TSH levels are directly related to each other (15, 54, 75). Serum leptin levels decrease during fasting as well as in elderly patients with the euthyroid sick syndrome, leading to subsequent decrease in TSH levels (27). These changes likely serve as an adaptive mechanism to reduce catabolic process and energy expenditure in the setting of acute illness (9, 27, 106). Increased hypothalamic D2 activity as well as increased Triac production also have been reported to directly decrease TSH production, similar to what has been observed in the pituitary (14).

Some investigators have hypothesized a central role for decreased TRH production in the euthyroid sick syndrome (10). Further, TRH therapy has been postulated as a therapeutic intervention. Indeed, a trial of exogenous TRH administration in conjunction with growth hormone-releasing petide-2 in fourteen patients with prolonged critical illness has been shown to restore the alterations seen in serum thyroid hormone parameters, with subsequent improvement in some of the cardiometabolic parameters such as protein degradation (10).

Table 3 Factors that Alter TSH Secretion

Increase	Decrease
Chlorpromazine	Acute and chronic Illness
Cimetidine	Adrenergic agonists
Domperidone	Caloric restriction
Dopamine antagonists	Carbamazepine
Haloperidol	Clofibrate
Iodide	Cyproheptadine
Lithium	Dopamine and dopamine agonists
Metoclopramide	Endogenous depression
Sulfapyridine	Glucocorticoids
X-ray contrast agents	IGF-1
	Metergoline
	Methysergide
	Opiates
	Phenytoin
	Phentolamine
	Pimozide
	Somatostatin
	Serotonin
	Surgical stress
	Thyroid hormone metabolites

Alteration in serum thyroid hormone-binding proteins

The majority of thyroid hormone is bound to various binding proteins in plasma, primarily thyroxine-binding globulin (TBG) as well as transthyretin and albumin. Since both acute and prolonged illness are typically accompanied by malnutrition and high catabolic state, serum levels of binding protein are frequently reduced (8). A rapid decrease in TBG levels has also been seen in postcardiac bypass patients, which may also contribute to the decrease in serum T3 shortly after cardiac surgery (3).

In addition to decrease in the serum levels of binding proteins, binding of T4 to TBG is frequently decreased by a variety of factors in critical illness [Table 4 (46)]. Certain

Table 4 Factors that Alter Binding of T4 to TBG

Increase binding	Decrease binding
Drugs	
Estrogens	Glucocorticoids
Methadone	Androgens
Clofibrate	L-Asparaginase
5-Fluorouracil	Salicylates
Heroin	Mefenamic acid
Tamoxifen	Antiseizure medications (phenytoin, tegretol)
Raloxifene	Furosemide
	Heparin
Systemic factors	
Liver disease	Inherited
Porphyria	Acute illness
HIV infection	Nonesterified free fatty acids
Inherited	

medications (heparin, furosemide, antiseizure medication, and salicylates) have been implicated in this decrease in binding. In addition, a factor that has the characteristics of unsaturated nonesterified fatty acids (NEFAs) has been reported to interfere with TBG binding as well as inhibit T4 to T3 conversion (36) and block transport of T4 to tissue in the euthyroid sick syndrome (36, 67, 100).

Alterations in thyroid hormone transporters

Thyroid hormones are transported across the plasma membrane by specific thyroid hormone transporters, most notably those of the monocarboxylate transporter (MCT) and organic anion-transporting polypeptide (OATP) families (30, 104). Of these, MCT8, MCT10, and OATP1C1 have been extensively studied. OATP1C1 has been characterized in rat brain and found to have significant action in transporting T4 across the blood-brain barrier. It is also found to be regulated in part by thyroid hormone levels in the brain (101). MCT8 is found in cortical regions, striatum, cerebellum, and hypothalamus and transports both T4 and T3, whereas MCT10 preferentially transports T3 and is expressed in liver, kidney, and muscle (52, 104).

There is impaired transport of T4 into peripheral tissues such as liver and kidney seen in the euthyroid sick syndrome and in starvation, thereby decreasing the availability of substrate for T3 production in these tissues (51). Consistent with these observations, liver and muscle MCT8 mRNA expression is decreased in patients with acute illness or acute surgical stress, although MCT10 mRNA expression was not affected. However, there are conflicting data in animal studies showing increased OATP1C1 and MCT10 mRNA expression, while MCT8 mRNA expression did not change in a rabbit model of prolonged illness, contrary to what would be expected, given findings seen in the euthyroid sick syndrome and starvation (70). On the other hand, a more recent study using a pig model of septic shock showed decrease in pituitary, liver, and kidney MCT8 expression (19). Further studies are needed to better elucidate the underlying mechanisms of altered thyroid hormone transport in the euthyroid sick syndrome.

Alterations in nuclear thyroid hormone receptors

Thyroid hormone activity is mediated by binding to thyroid hormone receptors (TR), with two main isoforms: TRα and TRβ. TRs are ligand-bound transcription factors that regulate transcription of a variety of target genes in various tissues (84). Concentrations of the receptor isoforms vary by tissues, with TRα predominating in brain, TRβ in liver and both in cardiac muscles. Animal studies have shown conflicting data in change in TRs in the euthyroid sick syndrome. In a mouse model of acute illness induced by bacterial endotoxin, LPS, a rapid decrease in mRNA of both TRα and TRβ as well as coactivator expression was seen in cardiac tissue (37). This decrease in TRβ mRNA expression was also seen in heart, liver, and kidney in an LPS-induced pig model of acute septic shock (19). On the other hand, there were no significant changes in the levels of either TRα or TRβ in rabbits with prolonged illness model (70). Human studies in patients with liver and renal failure showed increased TRα and TRβ expression in mononuclear cells (108). These findings were different from what has been seen in humans with chronic liver disease, where no change in TR expression in hepatic tissues was seen (14). Meanwhile, adipose tissue of patients with septic shock showed decrease in transcription factors for TRβ1, with no significant change in TRα1 and other coactivators or corepressors (14). The mechanisms for these alterations in TRs remain unclear.

Stages of the Euthyroid Sick Syndrome

As noted earlier, the euthyroid sick syndrome represents a continuum of changes that progresses sequentially through several distinct stages.

Low T3 state

Common to all of the abnormalities in thyroid hormone concentrations seen in the euthyroid sick syndrome is a substantial depression of serum T3 levels, which can occur as early as 24 h after the onset of illness. Over half of patients admitted to the medical service will demonstrate depressed serum T3 concentrations (97, 98). As noted earlier, there are multiple pathways that are contributing to the development of the low T3 state. The low T3 state has been described as a predictor of both all-cause and cardiac mortalities in critical care patients

with acute decompensated heart failure (24). Low T3 levels are also found in peripheral tissues (88).

High T4 state

Serum T4 levels may actually be elevated early in acute illness due to either the acute inhibition of D1 or an increase in TBG levels. This is seen most often in the elderly and in patients with psychiatric disorders. As the duration of illness increases, nondeiodinative pathways of T4 degradation increase and serum T4 levels fall back into the normal range (97).

Low T4 state

As the severity and duration of the illness increases, serum total T4 levels decrease into the subnormal range. Contributors to this decrease in serum T4 levels are (1) a decrease in the binding of T4 to serum carrier proteins, (2) a decrease in serum TSH levels, leading to decreased thyroidal production of T4, and (3) an increase in nondeiodinative pathways of T4 metabolism. The decline in serum T4 levels correlates with prognosis in the ICU, with mortality increasing as serum T4 levels drop below 4 μg/dL and approaching 80% in patients with serum T4 levels below 2 μg/dL (61, 68, 96). Despite marked decreases in serum total T4 and T3 levels in the critically ill patient, free hormone levels have been reported to be normal or even elevated (20, 76), providing a possible explanation for why most patients appear eumetabolic despite thyroid hormone levels in the hypothyroid range. Thus, the low T4 state is unlikely to be a result of a hormone-deficient state and is probably more of a marker of multisystem failure in these critically ill patients.

Recovery state

As acute illness resolves, so do the alterations in thyroid hormone concentrations (33). This stage may be prolonged and is characterized by modest increases in serum TSH levels (47). Full recovery with restoration of thyroid hormone levels to the normal range may require several weeks (57) or months after hospital discharge (98).

Treatment of the Euthyroid Sick Syndrome

Whether the thyroid hormone abnormalities found in the euthyroid sick syndrome are a physiologic adaptation or a pathologic change is a topic that is still debated (35, 46, 60, 86, 87). Multiple studies have shown that there is a positive correlation between low serum T3 or high serum rT3 levels and poor prognosis. This is especially true in patients with renal disease, especially end-stage renal disease either on hemodialysis or peritoneal dialysis (32, 53) and cardiorenal syndrome (73). Increased mortality associated with low T3 levels is also correlated with increased cardiac risk factors, such as coronary calcification scores and arterial stiffness (72), lower left ventricular ejection fracture and higher mass index (63). Low free T3 and high rT3 levels have also been associated with increased risk for mortality in patients in the intensive care unit (ICU) (89, 105), hospitalized cardiac patients (82), patients with congestive heart failure (CHF) (40, 92) and patients with liver cirrhosis (34). Others have reported that the presence of nonthyroidal illness portends worsened overall prognosis in patients with enterocutaneous fistulas (49) and in burn patients (42). There is limited literature regarding nonthyroidal illness in children hospitalized in the ICU (69).

Therapies other than thyroid hormone have been suggested to be beneficial in treating the sick euthyroid syndrome. Because one of the suspected mechanism for deiodinase dysfunction seen in the euthyroid sick syndrome is generation of reactive oxygen species, Vidart and colleagues (103) investigated the use of *N*-acetylcysteine (NAC), a potent antioxidant, in prevention of the euthyroid sick syndrome in patients with acute myocardial infarction (MI). They found that treatment with NAC in acute MI increased serum T3 levels and decreased serum rT3 levels. However, the restoration of thyroid hormone abnormalities did not affect mortality or length of stay, although the authors state that the study was not designed to assess patient outcomes or effect of treatment on cardiac function (103). Changes in thyroid hormone parameters occurring postoperatively have been prevented by early institution of nutritional support (65). Finally, some investigators have suggested that patients with prolonged critical illness may represent a different disease entity than those with acute disease and treatment with hypothalamic releasing factors should be tested in future trials (9).

Although ascertaining causality between thyroid hormone abnormalities and poor outcome is difficult, treatment of acutely ill patients with thyroid hormone has been of great clinical interest (29, 35). Unfortunately, most of the studies on treatment of patients with the euthyroid sick syndrome have not found any significant positive effects on improvement of patient outcome despite restoration of thyroid hormone levels, although no clear deleterious effects have been found either. Consequently, there is no clear benefit on restoration of thyroid hormone levels in the euthyroid sick syndrome with thyroid hormone replacement at this time. The major clinical trials on treatment of the euthyroid sick syndrome with thyroid hormone are presented in Table 5.

Starvation and malnutrition

The changes in thyroid hormone levels in starvation or malnutrition appear to be an adaptive response to decrease catabolic process and preserve total body protein stores. Caloric restriction is known to be a potent inhibitory factor of D1, with decrease in serum T3 levels and increase in serum rT3 levels seen within 24 h of a fast (13). Decrease in D1 activity, coupled

Table 5 Summary of Clinical Trials on the Effects of Treatment of Euthyroid Sick Syndrome with Thyroid Hormone

Illness	Results of trial
Starvation/undernutrition	Treatment with T3 results in increased protein breakdown and increased nitrogen excretion in fasting normal and obese patients (18, 43, 64)
General intensive care unit patients	No benefit of LT4 on general medical patients (17), patients with acute renal failure (2), or those undergoing renal transplantation (1) No benefit of T3 in burn patients (6)
Premature infants	No benefit of LT4 on developmental indices of premature infants at 26 to 28 weeks of gestation (22) Possible beneficial effect of LT4 on infants of 25 to 26 weeks of gestation but possible deleterious effects on infants of 27 to 30 weeks of gestation (107) No benefit of T3 (5) Meta-analysis shows no significant effects of thyroid hormone treatment of premature infants (85)
Patients undergoing cardiac surgical procedures	Small studies suggest improved hemodynamic variables with T3 (77,78) Large trials show no benefit of T3 in patients undergoing cardiac bypass (7, 62, 102) Possible improvement in hemodynamic variables and hospital stay with T3 in children undergoing cardiac surgical procedures (12, 23)
Cardiac donors	Variable results—helpful (80,81), no benefit (45, 58)—of the effects of T3 in preserving function of normal hearts in brain-dead cardiac donors before transplantation Possible benefits of T3 in improving function of impaired hearts before transplantation, potentially increasing the pool of organs available for transplantation (58,59) Consensus conferences recommend the use of T3 as part of the hormonal resuscitation in donors whose cardiac ejection fraction is <45% (80)
Congestive heart failure	Small uncontrolled study suggested that short-term LT4 therapy increased cardiac output and functional capacity and decreased systemic vascular resistance (74) Improved hemodynamic variables and neurohumoral profiles with short-term intravenous T3 infusion, possibly necessitating supraphysiologic concentration (48, 91)

T3, triiodothyronine; LT4, levothyroxine.
Adapted from (35).

with increase in D3 activity and decrease in TSH secretion, in part from suppressed leptin secretion and reduction in thyroid hormone uptake, all appear to play a role in the thyroid hormone alterations seen in fasting or malnutrition (9). Studies have shown that early nutritional support in postoperative patients can prevent development of the euthyroid sick syndrome, suggesting again that acute fasting-induced euthyroid sick syndrome is an adaptive and potentially beneficial mechanism (65). On the other hand, early feeding within 24 h in hospitalized burn patients with evidence of the euthyroid sick syndrome, compared to delayed feeding after more than 48 h was associated with prevention of euthyroid sick syndrome development as well as decreased length of stay (90). As most acute illness is accompanied by decrease in caloric intake or malnutrition and/or a higher catabolic state, this aspect of the euthyroid sick syndrome appears to be physiologic and does not require treatment with thyroid hormone replacement.

General medical or intensive care unit patients

Only a few randomized controlled trials have been carried out in critically ill general medical patients. Despite poor prognosis seen in these critically ill patients with the euthyroid sick syndrome or increased short-term mortality risk in elderly hospitalized patients (4), treatment with thyroid hormone in patients in medical ICU showed no benefit on outcome (9, 86, 93).

Premature infants

The fetal thyroid gland forms by 12 to 13 weeks of gestation and starts taking up iodine into thyroid follicles at that time. However, the synthesis and secretion of fetal thyroid hormones are minimal until 18 to 20 weeks of gestation (83). Serum T4 levels in the fetus start increasing in the late second trimester, with most of the increase in 24 to 34 weeks of gestation. All premature infants have varying degrees of transient hypothyroxinemia, with a greater frequency of severe hypothyroxinemia in infants born less than 30 weeks of gestation. Premature infants also frequently experience complications such as respiratory distress syndrome, infections, or malnutrition, with increased frequency of the euthyroid sick syndrome.

In contrast to adults, in whom clinical manifestations of hypothyroxinemia can be reversed, untreated congenital hypothyroxinemia can have significant permanent detrimental effect on neurodevelopment in neonates (85, 94). However, trials of T4 in premature infants have not showed definitive benefit of treatment on developmental indices (35), neonatal mortality, neurodevelopmental outcome, or complications

such as respiratory distress syndrome (85). Therefore, there is no indication for thyroid hormone treatment in premature infants.

Patients undergoing cardiac surgery

There is a rapid fall in serum T4 and T3 levels with increase in serum rT3 levels seen within 15 to 30 min after initiation of cardiac bypass surgery (36). These changes in thyroid hormone levels may persist for several days. Animal studies have shown beneficial effects of T3 replacement after cardiopulmonary bypass, resulting in improvement in cardiac contractility and left ventricular function, and decrease in systemic vascular resistance. Human studies also showed promising results in the use of T3 in patients undergoing cardiac surgery, with less inotropic support requirement and improved hemodynamic parameters (79). However, randomized, controlled clinical trials in humans undergoing coronary artery bypass surgery failed to replicate clear benefits seen in animal studies or earlier smaller human studies (35).

Patients with congestive heart failure

As thyroid hormone is known to have inotropic effects on heart and interactions with the adrenergic system, the use of T3 and thyroid hormone analogues were investigated as adjuncts to the treatment of heart failure. Decreases in cardiac contractility and cardiac output have been observed in hypothyroidism and decreased serum T3 levels typical of the euthyroid sick syndrome are frequently observed in patients with CHF as well as in patients who suffered acute MI (44). Low T3 levels in the absence of TSH abnormalities, especially in conjunction with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with acute heart failure, has been associated with increased risk of mortality (24). Improvement of serum T3 levels along with cardiac function has also been seen in patients with CHF treated with short-term infusion of dobutamine (28). Low T3 levels have been strongly associated with increased mortality in patients with CHF (40, 56, 92). These findings have led to interest in the use of thyroid hormone as a treatment for CHF.

Small studies using T3 (48, 91) as treatment in CHF have reported improvement in cardiac output and decrease in systemic vascular resistance. However, a larger study is needed to determine if there is a role for thyroid hormone in the treatment of CHF.

Brain-dead potential organ donors

After brain death, there is a progressive reduction in cardiac contractility, a decrease in serum phosphates and accumulation of tissue lactate occurs, along with rapid decrease in serum T3 levels and increase in serum rT3 levels (36). Trial of intravenous infusion of T3, along with cortisol, and insulin in experimental brain-dead baboons showed restoration of hemodynamics, biochemical abnormalities mentioned earlier, and cardiac function (80). Similar findings were found in experimental brain-dead pigs treated with same intravenous hormonal therapy (80). Initial human studies were promising, showing improvement in hemodynamic stability, decrease in requirement for inotropic support, and preservation of cardiac function prior to transplantation (58, 80). However, other studies found no significant clinical benefits of T3 over placebo when there was no preceding cardiac dysfunction in the donor (25, 31, 45).

Consensus conferences in the United States and Canada have since recommended the use of four-drug hormonal resuscitation, including T3, vasopressin, methylprednisolone, and insulin, in donors with left ventricular ejection fraction of <45% and/or with unstable hemodynamics to increase the availability of suitable heart for transplant (25, 80, 109). Using the recommended protocol in cardiac donors as well as treating the recipients with T3 has shown improved outcome in one study (31), and use of T3 or T4 in potential donors showed increase in the number of organs successfully transplanted, with no detrimental effect on graft survival in a large retrospective cohort study of 63,593 donors over 10 years (82). However, several randomized clinical trials failed to substantiate these findings (31). While there is not quite concrete evidence to institute standardized protocol using T3 in cardiac donors, there is no evidence of deleterious effect of T3 in these situations.

Summary

The euthyroid sick syndrome and its typical thyroid hormone abnormalities are common in hospitalized patients or patients with critical illness. With the many aspects of thyroid hormone metabolism studied in relation to euthyroid sick syndrome, we can conclude that the mechanisms behind euthyroid sick syndrome are more complex than initially thought. Although we have learned much in the alterations in thyroid hormone metabolism since the description of the euthyroid sick syndrome in 1970s, the underlying cause for these changes remains elusive. With positive association between the euthyroid sick syndrome and poor prognosis in various illnesses, treatment of the euthyroid sick syndrome with thyroid hormone has been of interest as well. However, trials of treatment with T4 or T3 have not shown concrete benefit, and treatment of the euthyroid sick syndrome to restore normal serum thyroid hormone levels remains controversial.

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