Chapter 11
Thyroidal Changes During Critical Illness

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Abstract Patients suffering from a variety of critical illnesses present with uniform alterations within the thyroid axis with low plasma triiodothyronine (T3), but increased plasma reverse T3 (rT3). As these changes occur in the presence of low-normal thyroid stimulating hormone (TSH), this constellation is also referred to as Nonthyroidal Illness Syndrome (NTI). Both central and peripheral components of the thyroidal axis play a role in the development of NTI. Furthermore, nutritional intake can affect the extent and composition of NTI. The severity of NTI is associated with a poor prognosis, but it is still unclear whether this indicates a causal relationship, or in contrast, an adaptation to more severe illness.

11.1 The Thyroid Axis During Health

Thyroid hormones (TH) are essential for differentiation and growth, from fetal development throughout adult live [1]. They are important regulators of thermoregulation and energy metabolism and are involved in lipid and glucose metabolism [2]. The circulating concentrations of TH are tightly regulated by a classical hypothalamic-pituitary-thyroid feedback system. The hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to synthesize and release thyroid-stimulating hormone (TSH). TSH sequentially stimulates the thyroid gland to produce and release thyroxine (T4) [3]. The thyroid gland mainly generates T4, but the biological activity of TH is predominantly regulated by triiodothyronine (T3) [1]. Both T4 and T3 have inhibitory feedback control on both TRH and TSH secretion [4, 5].

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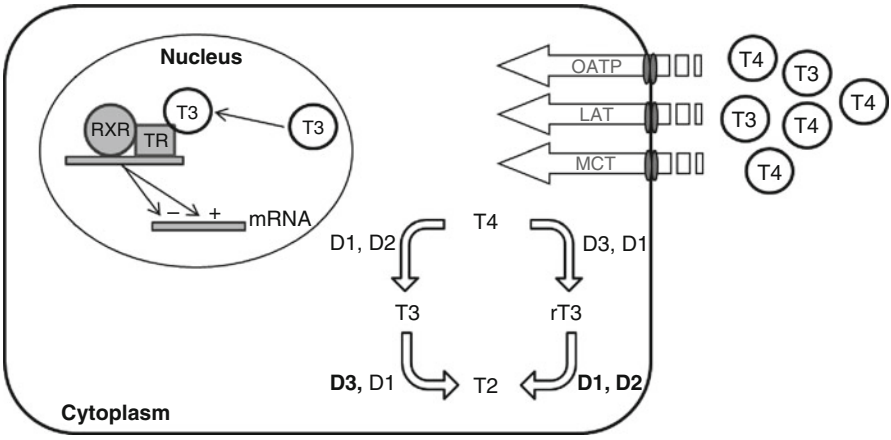

Fig. 11.1 Schematic outline of cellular uptake and metabolism of thyroid hormones

TH are transported in the blood by thyroxine-binding globulin (TBG), transthyretin, and albumin [6]. TBG is the dominant binding protein with the highest binding affinity for T4, around 50-fold higher than that of transthyretin and 7000-fold higher than that of albumin. Several transporters mediate the uptake of TH across the plasma membrane. The organic anion-transporting polypeptide-1C1, the monocarboxylate transporter (MCT) 8 and MCT10, and the L-type amino acid transporter (LAT) 1 and LAT2, and more recently LAT3 and LAT4 have been identified as relatively specific TH transporters [7, 8] (Fig. 11.1). The intracellular action of TH is further regulated by several subtypes of iodothyronine deiodinases. These enzymes are responsible for the deiodination of T4 to the active T3 or to the biologically inactive reverse T3 (rT3) [9, 10]. T3 mainly exerts its actions through interaction with its specific nuclear receptors TRα and TRβ to regulate gene transcription but can also induce nongenomic effects [11].

11.2 Alterations in the Thyroid Axis in Acute and Prolonged Critical Illness

Patients suffering from a variety of critical illnesses present with uniform alterations within the thyroid axis (Fig. 11.2). During acute and severe physical stress, caused by illness, surgery, or trauma, T3 plasma concentrations decline rapidly, whereas circulating rT3 concentrations increase. The concentration of T4 is only shortly elevated and subsequently returns to the normal physiological range, although in more severely ill patients, T4 concentration can also decrease [12]. In contrast with primary hypothyroidism, low plasma T3 concentration perseveres in the presence of normal TSH. This constellation, with low plasma T3 but normal TSH in the context of illness, has been described as "euthyroid sick syndrome," "low T3 syndrome," or "nonthyroidal illness (NTI)." The reduction in circulating T3 during the first hours after ICU admission reflects the severity of illness and correlates with outcome [13, 14].

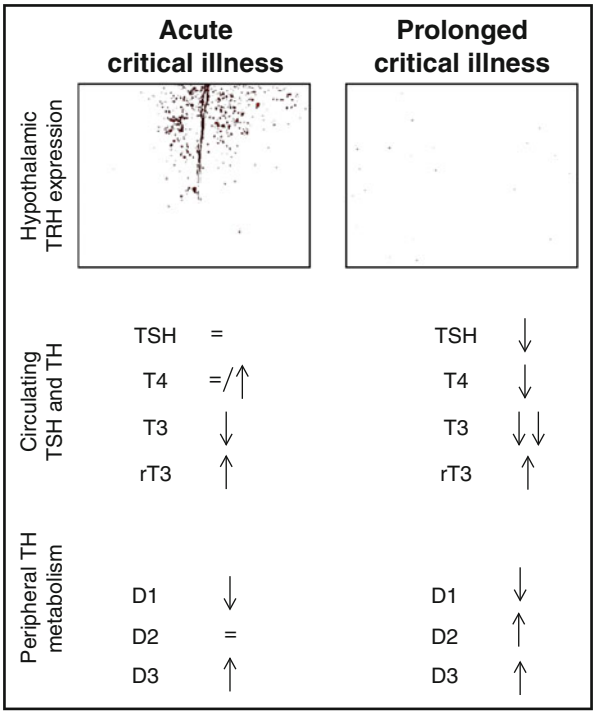

Fig. 11.2 Changes in the thyroid axis during acute and chronic critical illness. The upper panel displays reduced TRH gene expression in the hypothalamus of prolonged critically ill rabbits (Adapted from [28]). The middle panel illustrates schematically the observed adaptations in circulating TSH and TH of acute and prolonged critically ill patients. The bottom panel summarizes the findings in deiodinase tissue activity of acute and prolonged critically ill patients

The TSH profile is already affected in this acute phase of critical illness; while single-sample TSH levels are normal, the typical nocturnal TSH surge is no longer present [15]. When patients do not immediately recover and require prolonged intensive care, the pulsatile TSH release becomes substantially suppressed in addition to the absent nocturnal TSH surge [16]. Circulating T4 declines, with as a result much less elevated rT3, and circulating T3 can decrease even further. In this later phase of illness, reduced TSH, lowered T4 and T3, and elevated rT3 levels are associated with worse outcome [17].

11.3 Underlying Pathology of the Low T3 Syndrome

11.3.1 Binding Proteins and Peripheral Metabolism of Thyroid Hormones

In normal conditions, total plasma TH concentration is kept proportional to the concentration of TH-binding proteins, in order to maintain free hormone levels in

equilibrium [18]. In part, this is also observed during acute critical illnesses with reduced levels and reduced binding capacity of the TH-binding proteins TBG and albumin, whereby free TH levels are often increased [19]. However, TBG returns to normal reference values in prolonged critically ill patients [20].

The acute lowering of (total) T3 with the parallel increase in rT3 is predominantly due to an altered peripheral conversion of T4. Acute critical illness or inflammation reduces the activity of hepatic D1, the enzyme that converts T4 to T3 [21, 22]. At the same time, D3 activity is increased, the enzyme mediating the conversion of T4 to inactive rT3, as observed in muscle and liver tissue biopsies of critically ill patients [21, 23, 24].

In the prolonged phase of critical illness, peripheral tissues try to adapt to the sustained low availability of TH in the circulation. In both liver and muscle biopsies of prolonged critically ill patients, the TH transporter MCT8 expression was increased [25]. Also in a rabbit model of prolonged critical illness, MCT8 and MCT10 were upregulated in liver and kidney [25]. Also activity of type 2 deiodinase (D2), the second activating deiodinase, was increased in muscle tissue biopsies of prolonged ICU patients [26]. In animal studies, an increase in alveolar and in hypothalamic D2 expression was observed [22, 27–29]. Also at the level of the TH receptor, an upregulated TRα1/TRα2 appeared to be present in liver tissue biopsies of prolonged critically ill patients [30]. Although these changes could theoretically increase local tissue availability of TH, tissue or circulating T3 levels remained low [25, 26, 28].

11.3.2 The Impact of the Nutritional Status of the Patient

Loss of appetite and poor oral/enteral nutritional intake are very common in critical illness [31]. Of interest, the thyroidal alterations during the first days of critical illness are comparable to those observed for otherwise healthy subjects in the fasting state [32–34]. The contribution of restricted nutrition during human critical illnesses to the NTI has been documented in a few small clinical studies that indeed indicated that decreased caloric intake during critical illness is associated with more pronounced NTI changes [35–37]. More recently, the large randomized controlled EPaNIC trial compared two nutritional regimens in adult ICU patients [38]. This study demonstrated that tolerating a nutritional deficit during the first week of critical illness as compared with the early administration of supplemental parenteral nutrition resulted in fewer complications and accelerated recovery [38]. Furthermore, a subanalysis of this EPaNIC trial demonstrated that while not feeding early reduced complications and accelerated recovery of patients with NTI, it aggravated the decrease in circulating levels of TSH, total T4 and T3, and the T3 to rT3 ratio. The opposite was observed with early feeding that appeared to “improve” the NTI [39]. Similar findings were reported from an animal study which compared the effect of fasting versus feeding over 7 days of critical illness [40]. This study furthermore demonstrated that while early feeding diminished the lowering of T3, it also normalized peripheral D1 and D3 activity [40].

The instant drop in circulating T3 during nutrient restriction in otherwise healthy subjects has been explained as an attempt of the human body to avert protein breakdown by reducing energy expenditure [34]. Also in critically ill patients, tolerating a fasting response induced a more significant inactivation of T4 with lower T3 and higher rT3, which explained part of the outcome benefit of not feeding early [39]. Also targeting fasting blood glucose levels with insulin therapy in critically ill children, which mimics the blood glucose levels of a fasting response, resulted in improved outcome while further accentuating the NTI [41]. Together these findings indicate that at least a part of the immediate decrease in circulating T3 is induced by the reduced nutritional intake in critically ill patients rather than by the underlying illness and that this might be an adaptive response.

11.3.3 Central Regulation

The observation that despite the low circulating T3 and low-normal T4 single-sample TSH levels are low normal in the prolonged phase of critical illness, suggests a centrally suppressed thyroid axis [16]. This is further corroborated by the observed reduced hypothalamic TRH gene expression in brain sections of patients dying after chronic critical illness and in prolonged critically ill rabbits [28, 42]. In contrast, in the pituitaries of these prolonged critically ill rabbits, TSH gene and protein expression remained normal [43]. The substantial increase in TSH secretion and in peripheral TH concentrations, which is observed after TRH administration in prolonged critically ill patients and animals, supports this interpretation [44, 45]. Also the observation that the onset of recovery is preceded by a rise in TSH suggests that a suppressed hypothalamic stimulation of the pituitary plays a role in the prolonged phase of critical illness [46].

This central suppression of TRH could be the consequence of a changed set point for TH-induced feedback inhibition, due to a local upregulation of TH concentration. As stated above, in animal studies, an increase in hypothalamic D2 expression was observed after LPS injection [22, 29]. Also a rabbit study of prolonged critical illness demonstrated increased D2 levels as well as TH transporters in the hypothalamus [28]. However, as local hypothalamic T4 and T3 content were low normal in these rabbits, these findings could also suggest a compensatory response to a relative hypothyroid hypothalamic state rather than an altered set point. This attempt to compensate for sustained low thyroid levels also suggests that the hypothalamic suppression of the thyroid axis could be a deleterious consequence of prolonged or more severe critical illness. This was also suggested by the EPaNIC subanalysis, where the further lowering of T4 in nutrient-restricted patients was associated with worse outcome [39]. Also consistent with this interpretation is the observation that especially the more severely ill patients present a decline in circulating T4 levels, whereas all other critically ill patients reveal low T3 and high rT3 levels already from admission to the ICU [17]. Furthermore, ICU patients who received an infusion of TRH combined with a GH secretagogue displayed normalized TH levels coinciding with lowered markers of hypercatabolism [44].

11.3.4 Contributing Factors

Cytokines can mimic the acute changes of the thyroid axis and are assumed be involved in the pathogenesis of NTI [47, 48]. Especially TNF was clearly associated with the alterations in TH metabolism in human clinical samples [49, 50]. However, administration of cytokine antagonists did not restore normal thyroid function after endotoxemic challenge [51, 52].

Administered as well as endogenous dopamine or corticosteroids could also play a role as these can trigger or aggravate hypothyroidism in critical illness [53, 54]. The low selenium concentrations observed already from admission to the ICU is another potential interfering factor [55]. Indeed, deiodinases require selenium for their catalytic activity and defects in the synthesis of selenoproteins or nutritional selenium deficiency can lead to reduced deiodinase activity [2]. Furthermore, selenium supplementation in trauma patients was associated with modest changes in thyroid hormones, with an earlier normalization of T4, T3, and reverse T3 [56]. In patients with acute myocardial infarction, the administration of N-acetyl-cysteine, an antioxidant that can stimulate activity of the deiodinases by restoring intracellular cysteine and/or glutathione levels, prevented the T3 increase and lowered rT3 compared to placebo-treated patients [57].

11.4 TH Actions During Critical Illness

During the acute phase of critical illness, the peripheral alteration in deiodinase activity causes a reduction in circulating levels of the biologically active T3. As explained above, this acute part of the thyroidal response appears to be, at least in part, adaptive. Besides the overall downregulation of metabolism in the organism in order to save energy, also a direct effect of increased D3 could be beneficial, such as in granulocytes, where it could optimize bacterial killing capacity [58, 59].

In patients who require prolonged intensive care, the origin and impact of the thyroidal changes appear to differ. Several clinical symptoms observed during prolonged critical illness, such as muscle and skin atrophy and hair loss and also hypothermia, impaired consciousness, and hampered myocardial function, resemble those observed in hypothyroidism. Furthermore, during the prolonged phase of critical illness, peripheral tissues seem to adapt to the sustained low circulating TH levels with tissue-specific changes in TH transporters, deiodinases, and receptors. For example, endotoxin increased D2 expression in macrophages, which was shown to be essential for cytokine production and phagocytosis [60]. Also alveolar D2 upregulation during sepsis appeared to be adaptive during acute lung injury and sepsis [27].

11.5 Substitution Treatment?

Whether or not critically ill patients would benefit from TH treatment is yet unclear. The biphasic nature of the origin and consequences of low T3 during critical illness indicates that certainly in the early phase of critical illness, such benefit can be questioned. As the reduced nutritional intake that goes along with the acute response to illness is to a large extent responsible for the observed thyroidal alterations, these responses are likely selected by evolution and do not warrant interference. On the other hand, prolonged critically ill patients, who are fully fed, still suffer from sustained low T3 and T4 and display signs or symptoms of hypothyroidism and might benefit from a treatment that aims at normalizing thyroid hormones.

Unfortunately, only very limited clinical studies testing this hypothesis are available, often underpowered, with a high variability in patient selection (age, disease type, and timing) or treatment choice. Administration of T4 failed to demonstrate a clinical benefit, although this could be partly because of a compromised conversion of T4 to T3 [61]. Treatment with T3 substitution doses to children after cardiopulmonary bypass surgery was associated with improved postoperative cardiac function; however, the children received dopamine which induces iatrogenic hypothyroidism [62]. One also has to bear in mind that circulating TH levels do not necessarily reflect normalized tissue levels [24]. A continuous infusion of TRH combined with a growth hormone secretagogue not only normalized TH to physiological levels, but markers of hypercatabolism were also lowered [44]. Sufficiently powered randomized controlled trials in a well-selected patient population are required to test a potential beneficial effect on outcome.

11.6 Primary Thyroid Disorders in ICU Patients

Patients, who suffer from long-term primary hypothyroidism, depend physiologically on exogenous thyroid replacement, usually administered as oral levothyroxine. However, at admission to the ICU, the primary focus of care is the acute medical problem of the patient and not the prescription and continuation of chronic therapy. A retrospective chart review study in a tertiary referral university hospital demonstrated that thyroid replacement therapy was discontinued in up to 40 % of the patients for at least 7 days during their ICU stay. This was either due to lack of prescription or because the patient was intolerant to oral feeding and no parenteral preparation was prescribed [63]. Inadequate replacement or omission of therapy will lead to hypothyroidism in these patients, which can lead to adverse outcome including loss of consciousness and bradycardia [63].

The high prevalence of NTI and the extent of the thyroid axis changes in ICU patients can make it difficult to distinguish NTI from untreated primary

hypothyroidism. For the diagnosis of untreated primary hypothyroidism in ICU patients, the most useful parameter is elevated plasma TSH in the presence of low TH. In patients clinically suspected to have severe hypothyroidism and with demonstrated low plasma TH, a normal plasma TSH virtually excludes primary hypothyroidism. However, one should bear in mind that in hypothyroid patients, high serum TSH concentration may decrease during critical illness especially if the patient receives dopamine or high doses of glucocorticoids [53, 54]. On the other hand, although high plasma TSH in combination with low plasma T4 is indicative of hypothyroidism, this constellation can also be found in patients recovering from NTI [46]. A more clear distinction between primary hypothyroidism and NTI would be presence of a high plasma T3/T4 ratio in combination with low plasma rT3, as these changes are opposite to those of NTI, but these measurements only have limited diagnostic accuracy.

A very dangerous complication of untreated hypothyroidism is the development of myxedema coma. A secondary insult such as hypothermia, vascular accidents, or infection may trigger this life-threatening condition [64]. Diagnosis is based on elevated plasma TSH with low or undetectable T4 and T3 and the presence of clinical features such as changes in mental status (lethargy, stupor, delirium, or coma) and hypothermia. Again, the presence of NTI may reduce the degree of TSH elevation. Myxedema coma is potentially fatal (mortality up to 50 %), thus immediate treatment is required and depends on the recognition of the clinical features. Treatment should aim at TH replacement therapy, combined with ventilatory and hemodynamic support. In addition, stress dose glucocorticoids are advised as concomitant autoimmune primary adrenal insufficiency may be present, especially in patients with hypoglycemia [65].

Patients suffering from thyrotoxicosis, or hyperthyroidism, may present with high free T4 in combination with low serum TSH. The combination of suppressed TSH, high FT4, and normal T3 may point to the combination of thyrotoxicosis and NTI. Clinical features (thyroid enlargement, proptosis) and the presence of thyroid antibodies (anti-TPO, TBII) can give further confirmation.

Decompensated hyperthyroidism (or thyroid storm) is characterized by the acute onset of enhanced symptoms of hyperthyroidism. It is important to recognize that this condition is a clinical diagnosis; laboratory measurements cannot distinguish severe thyrotoxicosis from thyroid storm. The classic clinical features include fever, supraventricular tachycardia, gastrointestinal symptoms, and confusion, delirium, or sometimes coma [64]. Of note, altered mentation was the only clinical feature which was significantly different between patients with thyroid storm and patients with compensated thyrotoxicosis [66]. Precipitating factors include surgery, parturition, infection, iodinated contrast materials, stroke, diabetic ketoacidosis, and withdrawal or discontinuation of antithyroid medications. Treatment includes ICU monitoring and aims at restoring thyroid gland function while diminishing TH effects on peripheral tissues using a combination of beta-blockers, glucocorticoids, antithyroid drugs, and eventually high dose of iodide compounds [67].

11.7 Conclusion

Critically ill patients display low plasma T3 with increased plasma rT3, in the presence of low or normal TSH and low or normal T4. This constellation is referred to as nonthyroidal illness or NTI. Although the severity of illness strongly correlates with the severity of the changes in thyroidal hormone concentrations, the causality of this association is not fully elucidated. In the acute phase of illness, NTI is predominantly induced by the reduced nutritional intake and seems to be a beneficial adaptation in times of high metabolic demand. On the other hand, in prolonged critically ill patients also a central hypothalamic suppression seems to occur which appears to be related to worse outcome.

Sufficiently powered randomized controlled trials in a well-selected patient population, targeting especially prolonged critically ill patients, are required to test a potential beneficial effect on outcome. Treatment with hypothalamic-releasing factors might be the optimal choice to normalize circulating T4 and T3 levels in these patients.

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