

Nonthyroidal Illness Syndrome Across the Ages

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In conditions of acute illness, patients present with reduced plasma T3 concentrations without a concomitant rise in TSH. In contrast, plasma concentrations of the inactive hormone rT3 increase, whereas plasma concentrations of T4 remain low-normal. This constellation of changes, referred to as nonthyroidal illness syndrome (NTIS), is present across all ages, from preterm neonates and over-term critically ill infants and children to critically ill adults. Although the severity of illness strongly correlates with the severity of the NTIS phenotype, the causality of this association remains debated, and pathophysiological mechanisms remain incompletely understood. In the acute phase of illness, NTIS appears to be caused predominantly by an increased peripheral inactivation of thyroid hormones, in which reduced nutritional intake plays a role. Current evidence suggests that these acute peripheral changes are part of a beneficial adaptation of the body to reduce expenditure of energy and to activate the innate immune response, which is important for survival. In contrast, in more severely ill and prolonged critically ill patients, an additional central suppression of the thyroid hormone axis alters and further aggravates the NTIS phenotype. Recent studies suggest that this central suppression may not be adaptive. Whether treatment of this central component of NTIS in prolonged critically ill patients, with the use of hypothalamic releasing factors, improves outcome remains to be investigated in large randomized control trials.

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1. Thyroid Axis Alterations in Response to Critical Illness

Thyroid hormones are important regulators of thermoregulation, energy expenditure, and cellular metabolism, but they also directly affect the cardiovascular and immune systems [1, 2]. In healthy circumstances, the release of thyroid hormones by the thyroid gland is regulated by a classic neuroendocrine feedback loop. Whenever thyroid hormone levels are low, the hypothalamus releases TRH, which stimulates the anterior pituitary to synthesize and release TSH. TSH stimulates the thyroid gland to produce and release T4 and to a lesser extent T3. The source of the active thyroid hormone T3 is predominantly peripheral deiodination of T4. Negative feedback of T4 and T3 on TRH and TSH secretion further controls homeostasis of thyroid hormone activity. In conditions of acute illness, patients present with reduced plasma T3 concentrations without a concomitant rise in TSH. In contrast, plasma concentrations of the inactive hormone rT3 increase, whereas plasma concentrations of T4 remain low-normal [3–5]. This constellation of changes is referred to as nonthyroidal illness syndrome (NTIS) (Fig. 1).

The aim of this review is to provide an update on the current knowledge of NTIS across the ages. The review discusses NTIS in the most extensively studied population of adult critically

Abbreviations: ICU, intensive care unit; NTIS, nonthyroidal illness syndrome; PICU, pediatric intensive care unit; RCT, randomized control trial; THOP, transient hypothyroxinemia of prematurity.

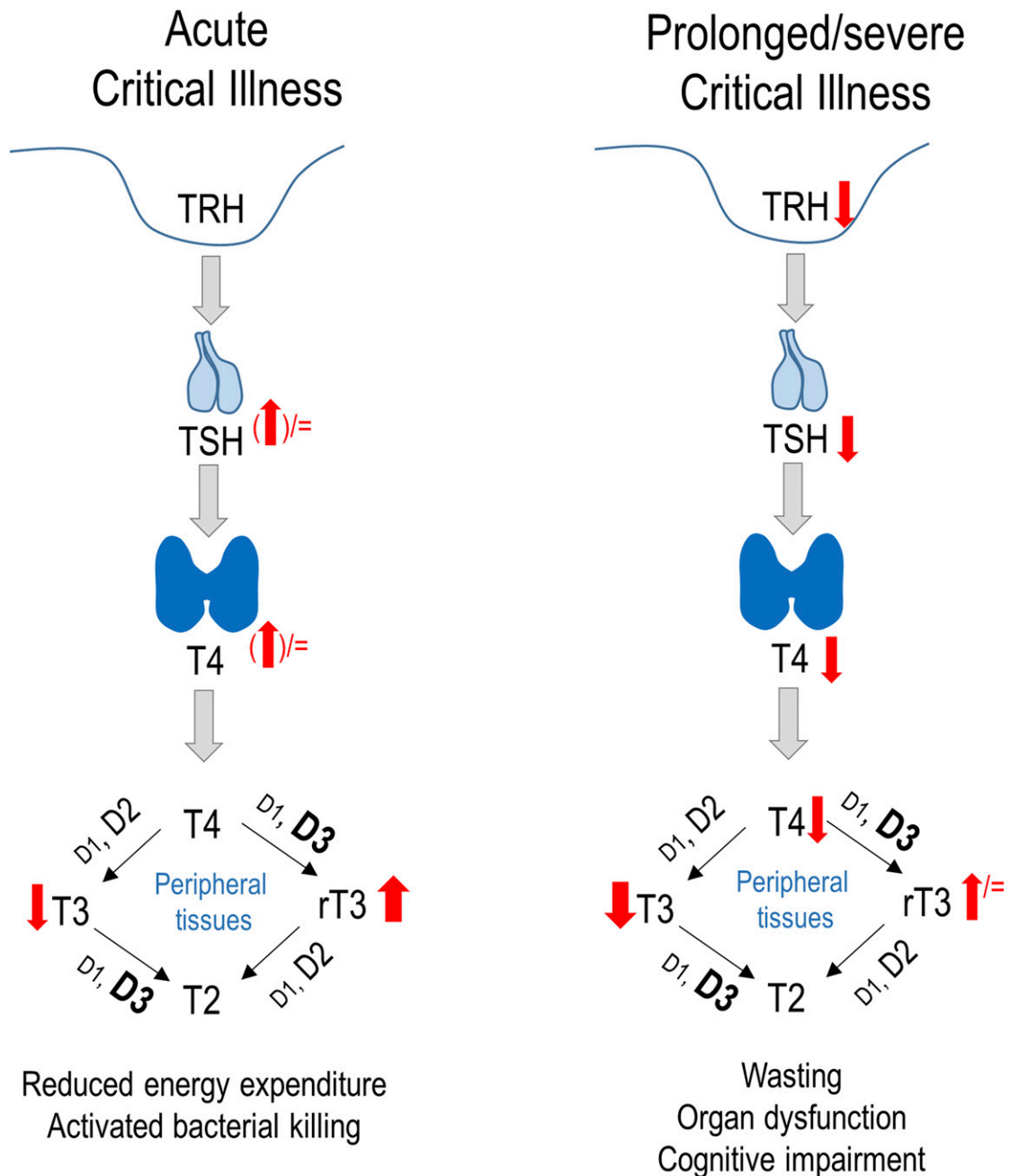


Figure 1. Schematic diagram of the biphasic changes observed in NTIS present in response to critical illness. Changes in the hypothalamus–pituitary–thyroid axis and in peripheral thyroid hormone metabolism. D1, D2, and D3 are iodothyronine deiodinase type 1, type 2, and type 3, respectively.

ill patients and summarizes insights into NTIS in critically ill infants and children and in premature newborns.

2. NTIS in Critically Ill Adults Treated in the Intensive Care Unit

Low plasma T3 and high rT3 concentrations are found in adults suffering from acute illnesses (e.g., infectious diseases, metabolic disorders, cardiovascular, pulmonary diseases, or gastrointestinal diseases) and in adults suffering from burns, trauma, and major surgery [6–10].

The severity of the illness is reflected by the magnitude of the changes in serum T3 and rT3 [4, 8, 11]. Patients with mild to moderate NTIS usually have normal plasma T4 and TSH concentrations, whereas patients with more severe and prolonged illness also display low serum T4 and TSH, both of which are indicative of a poor prognosis [12].

Plasma TSH transiently rises only in the first hours of critical illness, followed by a transient increase in plasma T4, whereas plasma T3 concentrations may already be low and rT3 concentrations high due to acute changes in peripheral thyroid hormone metabolism (Fig. 1) [9]. The expression of the inactivating outer-ring deiodinase D3, which is responsible for conversion of T4 to inactive rT3, was found to be upregulated in liver and skeletal muscle biopsies harvested from nonsurviving critically ill adults [13]. Also, within granulocytes, critical illness upregulates D3 activity, which may contribute to the bacterial killing capacity of these cells [14, 15]. However, increased D2 expression has also been reported in activated macrophages. Activated macrophages can locally increase T3, which could activate phagocytosis and the release of cytokines [16]. In contrast, hepatic activity of the activating inner-ring deiodinase D1 is suppressed by critical illness, which results in decreased deiodination of T4 into T3 [13, 17]. Cytokines and hypoxia are among the possible drivers of such peripherally altered thyroid hormone metabolism [18, 19]. In addition, lowered levels of thyroid hormone-binding globulin and albumin contribute to altered peripheral thyroid hormone availability at target tissues [20, 21].

When patients require prolonged intensive care, plasma T3 concentrations remain suppressed and accompanied by low plasma T4 and TSH concentrations (Fig. 2) [22]. This can be explained by reduced hypothalamic TRH expression, as was observed in postmortem biopsies harvested from prolonged critically ill patients [23]. Indeed, the low TRH mRNA correlated with low plasma TSH and T3 concentrations [23]. At the onset of recovery from illness, a rise in TSH and in total and free T4 has been observed, followed by normalization of circulating T4 and T3 levels [24, 25]. Such a rise in TSH preceding recovery suggests reversal of reduced TRH stimulation of the thyrotropes during prolonged critical illness. In prolonged critical illness, peripheral tissues appear to activate compensatory mechanisms to restore T3 availability, for example by upregulating D2 activity, as has been shown in skeletal muscle biopsies [26]. Also, the thyroid hormone transporter monocarboxylate transporter 8 was found to be upregulated in muscle and liver of prolonged critically ill patients [27].

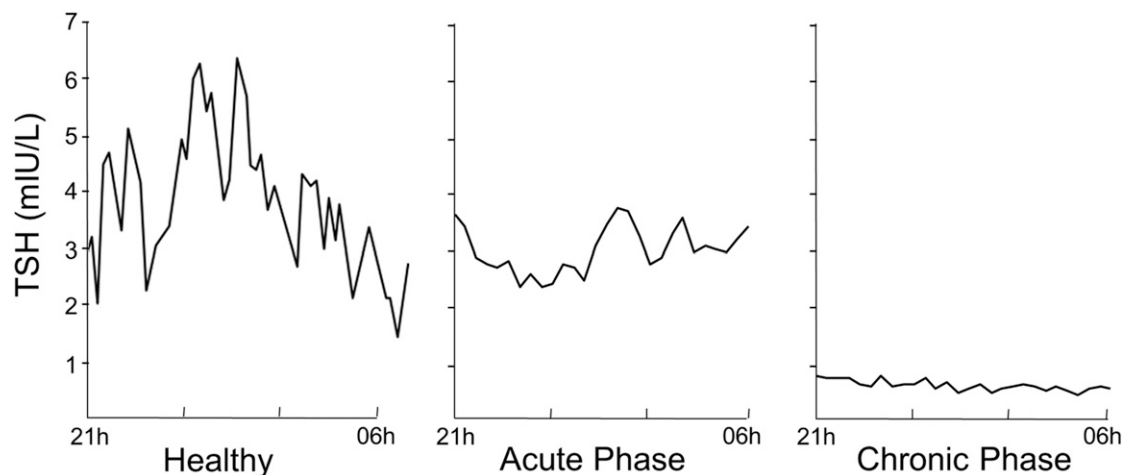


Figure 2. Illustration of the biphasic response of TSH to critical illness. Representative nocturnal TSH serum concentration profiles of a healthy volunteer and of two critically ill patients are shown to illustrate the differences between the acute and chronic phases of critical illness. [Adapted with permission from Van den Berghe G, de Zegher F, Bouillon R: Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab.* 1998;83(6):1827-1834.]

The changes within the thyroid axis are part of a broader neuroendocrine response to illness that encompasses all major endocrine axes, which together alter the balance between anabolism and catabolism [28]. Whereas the changes that occur acutely in response to critical illness are considered beneficial, reflecting an attempt to provide energy and limit unnecessary energy expenditure to promote survival, the changes that occur in prolonged critical illness may be harmful, with potentially detrimental consequences such as wasting, organ dysfunction, and impaired cognition. Such differences may explain the ongoing controversy about whether patients with NTIS should be treated to improve the outcome of critical illness. In patients undergoing cardiac surgery, treatment with T3 either did or did not improve postoperative cardiac function [29–31], but patient-centered clinical outcomes were never affected [31–34]. Furthermore, T3 treatment did not affect mortality in patients suffering from acute burn injury [35]. T3 infusion in mechanically ventilated patients with NTIS also did not affect respiratory muscle function [36]. In acutely ill patients with low serum T4 levels, T4 treatment did not affect mortality [37] or even increased it [38]. However, increasing circulating thyroid hormone levels in the acute phase of illness does not necessarily normalize tissue levels [39]. Furthermore, the often supraphysiological doses of T3 or T4 that were tested further suppressed circulating TSH levels, which could hamper the recovery of the pituitary TSH secretion [37–39]. Interestingly, a small proof-of-concept study of prolonged critically ill patients investigated the impact of a continuous infusion of TRH combined with a growth hormone secretagogue and found not only normalized thyroid hormone levels but also reduced catabolism and increased anabolism [40]. Larger studies investigating clinical outcome are currently lacking.

Hypothyroidism during critical illness can be very difficult to diagnose due to the superimposed NTIS. High plasma TSH and low plasma T4 are indicative of hypothyroidism, but the absence of elevated TSH does not exclude hypothyroidism in the context of critical illness [11]. It is generally accepted that patients with premonitory hypothyroidism, which is present in ~7% of the elderly population, should continue to receive thyroxine replacement while in the intensive care unit (ICU) [41]. Hyperthyroidism is characterized by suppressed plasma TSH in the face of high plasma free T4 and T3, but this constellation can be altered by superimposed NTIS during critical illness [42, 43]. Physical examination for goiter and proptosis and screening for thyroid antibodies can provide further information and help distinguish hyperthyroidism from NTIS. Thyroid storm can be lethal when untreated; however, its symptoms and signs, such as fever, supraventricular tachycardia, gastrointestinal problems, and altered mentation, are atypical in the context of critical illness [42, 43].

3. NTIS in Critically Ill Infants and Children Treated in the Pediatric ICU

In critically ill infants and in children, NTIS is also present with normal or low T4, low T3, high rT3 plasma concentrations, and a low T3/rT3 ratio in the absence of elevated TSH (Fig. 3). NTIS in children has been described in pediatric ICU (PICU) populations with varying diagnostic categories [44, 45], in patients undergoing cardiac surgery [46–49], in patients suffering from sepsis or septic shock [50–53], and in those with oncological diseases [54, 55]. The critical illness-induced rise in rT3 was found to be more pronounced in infants than in older children and resulted in a lower T3/rT3 ratio [44]. As in adults, the severity of NTIS in children has been associated with poor clinical outcomes of critical illnesses [44, 45, 50, 52, 56]. Lower T4 and lower T3 have been associated with delayed discharge from PICU [45, 52] and with risk of infections [44] and death [44, 50, 52, 56, 57]. Two small studies found higher TSH plasma concentrations in nonsurvivors than in survivors [58, 59], but this could not be confirmed in two large, more diverse PICU populations [44, 45]. Detailed studies documenting the time course of NTIS—from the acute phase through the chronic phase of pediatric critical illness—are currently lacking.

Whether treating critically ill children with thyroid hormone is beneficial or not remains unclear. Thyroid hormone substitution has mainly been tested in acute critical illness after cardiac surgery with cardiopulmonary bypass. In most studies, T3 treatment did not improve

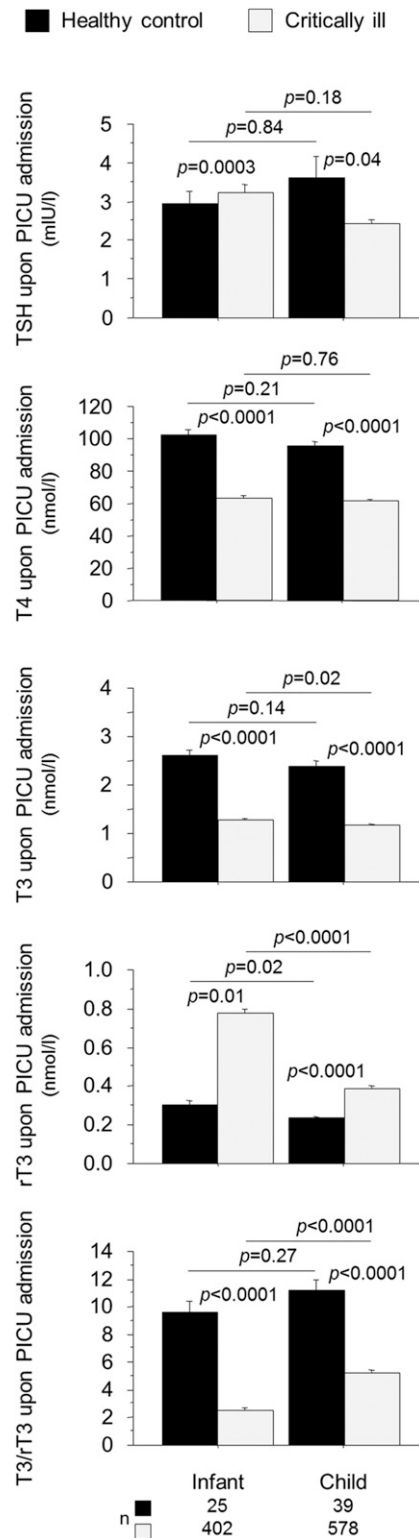


Figure 3. Impact of critical illness on thyroid hormone concentrations upon PICU admission in infants and children. Infants are younger than 1 y old. Bars represent means, and whiskers represent the SE. The black boxplots represent healthy children, and the light-gray boxes represent critically ill patients. [Reproduced with permission from Jacobs A, Derese I, Vander Perre S, van Puffelen E, Verstraete S, Pauwels L, Verbruggen S, Wouters P, Langouche L, Garcia Guerra G et al: Non-thyroidal illness syndrome in critically ill children: prognostic value and impact of nutritional management. *Thyroid*. 2019;29(4):480–492.]

outcome [60–63]. In one randomized control trial (RCT), T3 infusion improved myocardial function and reduced the need for postoperative intensive care [64]. One study of oral T3 also reported shortened time to extubation [65]. No studies have investigated the impact of treatment with thyroid hormone in the chronic phase of pediatric critical illness.

4. NTIS in Premature Newborns Treated in the Neonatal ICU

Premature infants with low birth weight represent a particular and separate subgroup of patients treated in the neonatal intensive care environment. Preterm infants often present with transient hypothyroxinemia of prematurity (THOP), which is characterized by low circulating T4 and T3 without a concomitant rise in TSH [66, 67]. Although the changes in T4, T3, and TSH are quite similar to what is observed in NTIS in adults, children, and term infants, the underlying mechanisms are even more complex, given that the hypothalamus–pituitary–thyroid axis matures until the end of full-term pregnancy. Hence, thyroid axis immaturity likely contributes to the thyroid hormone alterations observed in preterm newborns [66, 67]. The most immature newborns, who suffer from the highest morbidity rates, also have the most pronounced THOP [68]. Also, in the preterm infant population, studies on the impact of thyroxine supplementation did not provide sufficient evidence in favor of thyroid hormone substitution. Indeed, supplementation of preterm infants with levothyroxine during the first 48 hours of life did not improve morbidity or mortality; nor did it improve longer-term neurodevelopment [69, 70]. A *post hoc* analysis of one of these studies, however, showed a neurocognitive benefit among infants born at 25 to 26 weeks gestational age [70]. Levothyroxine treatment of preterm infants suffering from THOP also did not improve acute outcome [71], whereas a neurodevelopmental benefit was observed until a corrected age of 3 years [72].

5. Iatrogenic and Nutritional Factors Interfering With NTIS

Adult, pediatric, and neonatal critically ill patients often receive high doses of glucocorticoids, which can lower serum TSH [73–75]. Moreover, endogenously elevated cortisol levels in response to stress may exert a suppressive effect on TSH [76]. Also, dopamine infusion, prescribed as an inotrope and/or vasopressor for critically ill patients, can severely suppress TSH secretion in adults, children, and infants [77, 78]. Although dopamine is no longer a preferred drug for adults, it is still extensively used in pediatric and neonatal ICUs. Less commonly used drugs, such as antiepileptic medications [79–81], certain antiarrhythmic drugs [82], and lithium, can also affect the hypothalamus–pituitary–thyroid axis. Iatrogenic iodine intoxication [83], through the use of iodine-containing contrast fluids or antiseptic dressings, can affect thyroid hormone availability [84].

Fasting in healthy individuals induces changes in the thyroid axis that are similar to those in NTIS: plasma T3 decreases, whereas plasma rT3 concentrations rise; these changes rapidly return to baseline upon refeeding [85]. Restricted nutrition during adult critical illnesses appears to contribute to NTIS [86–88]. More recently, two large RCTs in adults and in children 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 [89, 90]. Although restricting macronutrient administration in the first week of critical illness reduced complications and accelerated recovery of patients with NTIS, it aggravated the NTIS by further lowering TSH, total T4, T3, and the T3/rT3 ratio (Fig. 4) [44, 88]. Importantly, the clinical benefit of not forcefully feeding early was statistically in part explained by the early further suppression of T3 and T3/rT3 ratio in both the adult and pediatric populations, suggesting that the acute peripheral changes of NTIS likely represent a beneficial adaptation to illness [44, 88]. Such an effect on the peripheral component of NTIS was also shown to be evoked by targeting normal fasting blood glucose levels in critically ill children [45]. This further suppression of T3 and T3/rT3 also in part explained the mortality benefit of tight blood glucose control in this

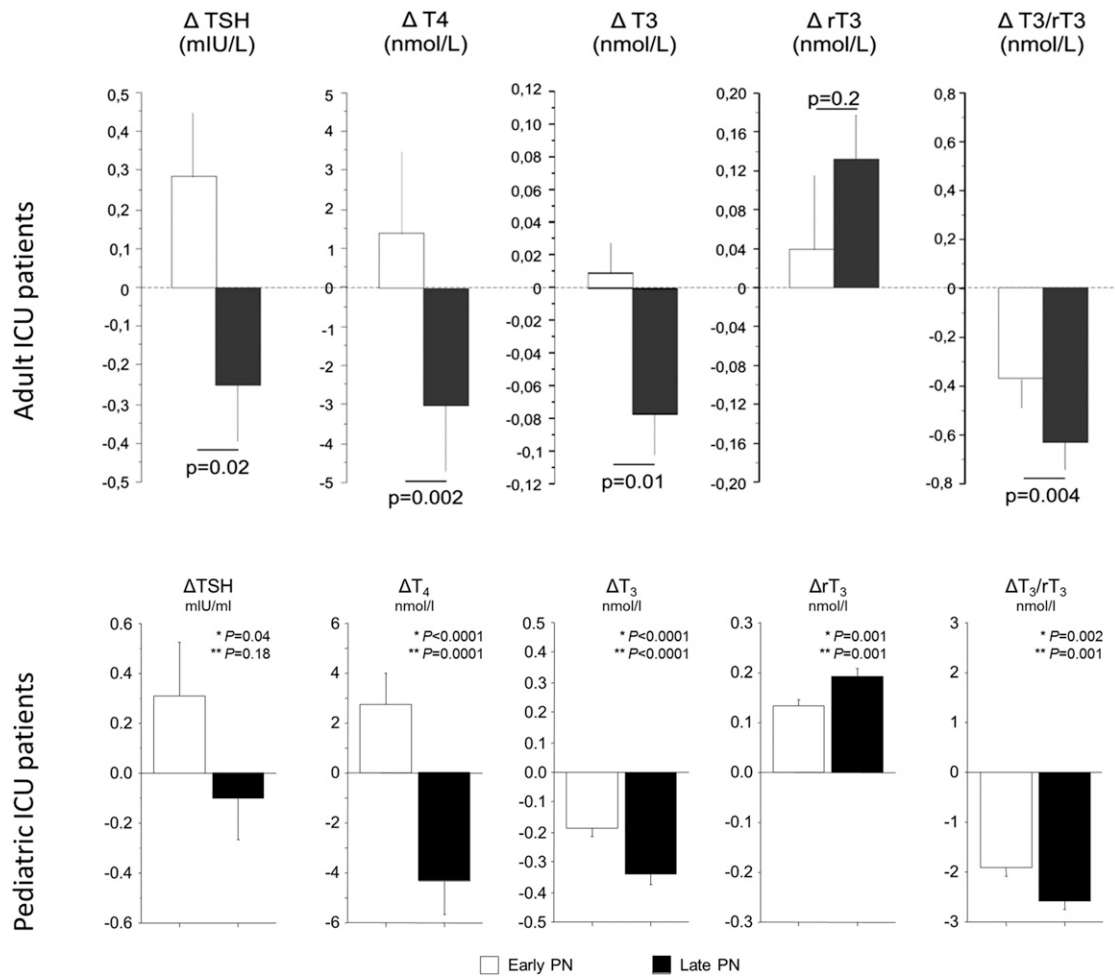


Figure 4. Effect of accepting a very low macronutrient intake, by omitting parenteral nutrition (PN) until beyond the first week in ICU (Late-PN), as compared with early provision of full feeding with PN (early-PN) on NTIS. Bars (mean – SE) represent the changes (referred to as Δ) from the admission values to day 3 in the adult or pediatric ICU (or to the last day for patients with shorter ICU stay) in serum TSH, T₄, T₃, rT₃, and the T₃/rT₃ ratio. The open and filled bars represent the patients randomized to the early-PN and late-PN groups, respectively. [Reproduced with permission from Jacobs A, Derese I, Vander Perre S, van Puffelen E, Verstraete S, Pauwels L, Verbruggen S, Wouters P, Langouche L, Garcia Guerra G et al: Non-Thyroidal Illness Syndrome in Critically Ill Children: Prognostic Value and Impact of Nutritional Management. *Thyroid* 2019, 29(4):480-492; and Langouche L, Vander Perre S, Marques M, Boelen A, Wouters PJ, Casaer MP, Van den Berghe G: Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its relation with outcome: a randomized, controlled clinical study. *J Clin Endocrinol Metab.* 2013;98(3):1006-1013.]

population [45, 91]. In prolonged critically ill adults, however, targeting fasting blood glucose levels did not affect NTIS [8, 92]. The further aggravation of the central component of the NTIS, with further suppression of TSH-induced T₄ release, in critically ill adults and children evoked by not forcefully feeding early appeared to counteract the outcome benefits of the intervention [44, 88]. The central component of the NTIS may thus be a maladaptive response, unlike the acute peripheral component. Whereas virtually all ill patients acutely present with low T₃ and high rT₃ levels, which is interpretable as an immediate adaptation to stress, low T₄ levels are especially pronounced in the more severely ill and prolonged critically ill patients [93, 94]. Because current evidence suggests a potential beneficial peripheral component but a harmful central component of NTI, future RCTs should focus on

treatment of the central part of the thyroid axis in prolonged critically ill patients. Treatment with hypothalamic releasing factors would theoretically also be a safer option than treatment with T3 or T4 because the normal negative feedback exerted by thyroid hormones at the pituitary level would be maintained and excessively elevated thyroid hormone levels could hereby be avoided.

Conclusion

Acute critical illness causes low plasma T3 concentrations and increased rT3 plasma concentrations without a concomitant rise in TSH. This constellation, referred to as NTIS, is present across all ages, from preterm neonates to term critically ill infants and children to critically ill adults. Although the severity of illness strongly correlates with the severity of the NTIS phenotype, causality of this association remains debated, and the pathophysiological mechanisms remain incompletely understood. In the acute phase of illness, NTIS appears to be caused predominantly by an increased peripheral inactivation of thyroid hormones in which reduced nutritional intake plays a role. Current evidence suggests that these acute peripheral changes are part of a beneficial adaptation of the body to reduce expenditure of scarce energy and to activate the innate immune response that is essential for survival. In contrast, in more severely ill and prolonged critically ill patients, an additional central suppression of the thyroid hormone axis alters and further aggravates the NTIS phenotype. Recent studies indicate that this central suppression may not be adaptive. Whether treatment of this central component of NTIS in prolonged critically ill patients, with use of hypothalamic releasing factors, improves outcome remains to be investigated in large RCTs.

Search Strategy

We searched the PubMed database for articles published in English with different combinations of the search terms “critically ill,” “intensive care,” “sepsis,” “paediatric,” “neonatal,” “thyroid,” and “nonthyroidal illness.”

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Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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