

## Non thyroidal illness: to treat or not to treat?

R.P. Peeters

Department of Internal Medicine, Erasmus University Medical Center, Room Ee 502, 50, Dr. Molewaterplein, 3015 GE Rotterdam, The Netherlands

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### Abstract

In critically ill patients, pronounced alterations in the hypothalamic-pituitary-thyroid axis occur without any evidence for thyroid disease. T3 decreases and rT3 increases within a few hours of the onset of disease. Severity and duration of disease are related to the magnitude of these changes. This manuscript discusses whether these changes in thyroid hormone levels during critical illness should be treated, and was in part published elsewhere.

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*Keywords:* Hypothalamic-pituitary-thyroid axis; Thyroxine; Thyrotropin-releasing hormone

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### 1. General introduction

The production of thyroxine (T4) by the thyroid gland is regulated by the classic hypothalamus-pituitary-thyroid axis, in which hypothalamic thyrotropin-releasing hormone (TRH) stimulates the pituitary to release thyroid stimulating hormone (TSH) [19,21,23,24,50]. The biological activity of thyroid hormone, i.e., the availability of the active hormone T3 for nuclear receptors, is largely regulated by different transmembrane transporters and iodothyronine deiodinases [6,23,24,50], which convert T4 to either T3 or to the inactive metabolite reverse T3 (rT3). Via a negative feed-back loop mechanism, T4 and T3 have an inhibitory effect on TRH and TSH secretion.

Within a few hours after the onset of disease, plasma T3 decreases and plasma rT3 increases. The magnitude of these changes is related to the severity of the disease [6,13,36,47]. In severely ill patients, T4 decreases as well and both low T4 and low T3 are associated with a poor prognosis [13,26,31,36]. Circulating TSH usually remains within the normal range, although TSH levels may increase briefly after the onset of disease, [13,17,27,40,41,49].

The thyrotropic profile in chronic critical illness differs from the acute phase. After several days of intensive care, patients have even lower levels of T3 and a low T4 [30,31,44]. Circu-

lating TSH is low to normal and there is hardly any pulsatility in the nocturnal TSH secretory pattern compared with healthy individuals [44]. In addition, hypothalamic expression of the TRH gene is low in patients who died after chronic severe illness compared to patients who died from an acute event [18].

This manuscript, which discusses whether these changes in thyroid hormone levels during critical illness should be treated, was in part published elsewhere [29].

### 2. Thyroid hormone metabolism during critical illness

Thyroid hormone metabolism is mediated importantly by the three iodothyronine deiodinases (D1, D2 and D3), that catalyze deiodination of the different iodothyronines (see refs. [6, 24] for reviews). D1 is present in liver, kidney, and thyroid, and plays a key-role in the production of serum T3 from T4 and in the breakdown of the inactive metabolite rT3 [6,24]. D2 is present in brain, pituitary, thyroid, and skeletal muscle, and also converts T4 to the active hormone T3. D2 is important for local T3 production, but the enzyme in skeletal muscle may also contribute to plasma T3 production [6,24,35]. D3 is present in brain, skin, placenta, pregnant uterus, and various fetal tissues; D3 is the major T3 and T4 inactivating enzyme, by catalyzing the deiodination of T4 and T3 to rT3 and T2, respectively [6,24]. D3 contributes to thyroid homeostasis by protecting tissues from excess thyroid hormone.

The serum T3/rT3 ratio is the parameter that most accurately reflects the peripheral thyroid hormone metabolism dur-

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*E-mail address:* r.peeters@erasmusmc.nl (R.P. Peeters).

ing critical illness, because of the confounding effect of variable concentrations of T4 and T4-binding proteins [30–32]. In recent studies, we analyzed thyroid hormone metabolism in a large number of critically ill patients [30,31,33,34]. Studies in 451 patients who received intensive care for at least 5 days, showed that serum rT3 and the T3/rT3 ratio on day 1 were already prognostic for survival, whereas TSH, T4 and T3 were significantly different between survivors and non-survivors from day 5 onward [31]. Not only the absolute values, but also the time course was completely different between survivors and non-survivors. TSH, T4, T3, and the T3/rT3 ratio increased in patients who survived, whereas there was no such rise in patients who died. However, other than for TSH, T4, and T3, this increase in T3/rT3 in survivors occurred only after day 5, suggesting that the peripheral metabolism recovers at a later stage than the centrally initiated TSH secretion [31] (Fig. 1).

In over 60 patients who had died after intensive care, we analyzed liver and skeletal muscle biopsies. Liver D1 activity in these patients was low compared to values observed in healthy individuals, except for patients who died acutely from severe brain damage [30,31]. Although D2 activity is expressed in normal skeletal muscle [9,37], no D2 activity

could be detected in skeletal muscle samples of these critically ill patients [30,31,34]. On the other hand, D3, which is not present in liver and skeletal muscle in healthy individuals, was markedly induced in both liver and skeletal muscle [30,31,34]. In these critically ill patients, liver D1 activity was positively correlated with the serum T3/rT3 ratio, whereas liver and muscle D3 were positively correlated with serum rT3 levels (Fig. 2) [30,31]. From these data it can be concluded that in addition to a down-regulation of D1, also a down-regulation of D2 and an induction of D3 are important factors in the regulation of serum thyroid hormone levels during critical illness.

Tissue concentrations were also analyzed in these critically ill patients [34]. Serum T4, T3, and rT3 levels in serum showed a strong positive correlation with the respective hormone concentrations in liver and in muscle. Interestingly, a part of these patients were treated with a combination of T4 and T3. The above mentioned correlations were independent of thyroid hormone treatment. Thyroid hormone treatment was initiated when a patient had a serum T<sub>4</sub> concentration below 50 nmol/l in the face of a normal thyroxine-binding globulin, and concomitantly clinical signs of hypothyroidism [34]. In these cases, thyroid hormone treatment consisted of an IV bolus of 150 µg

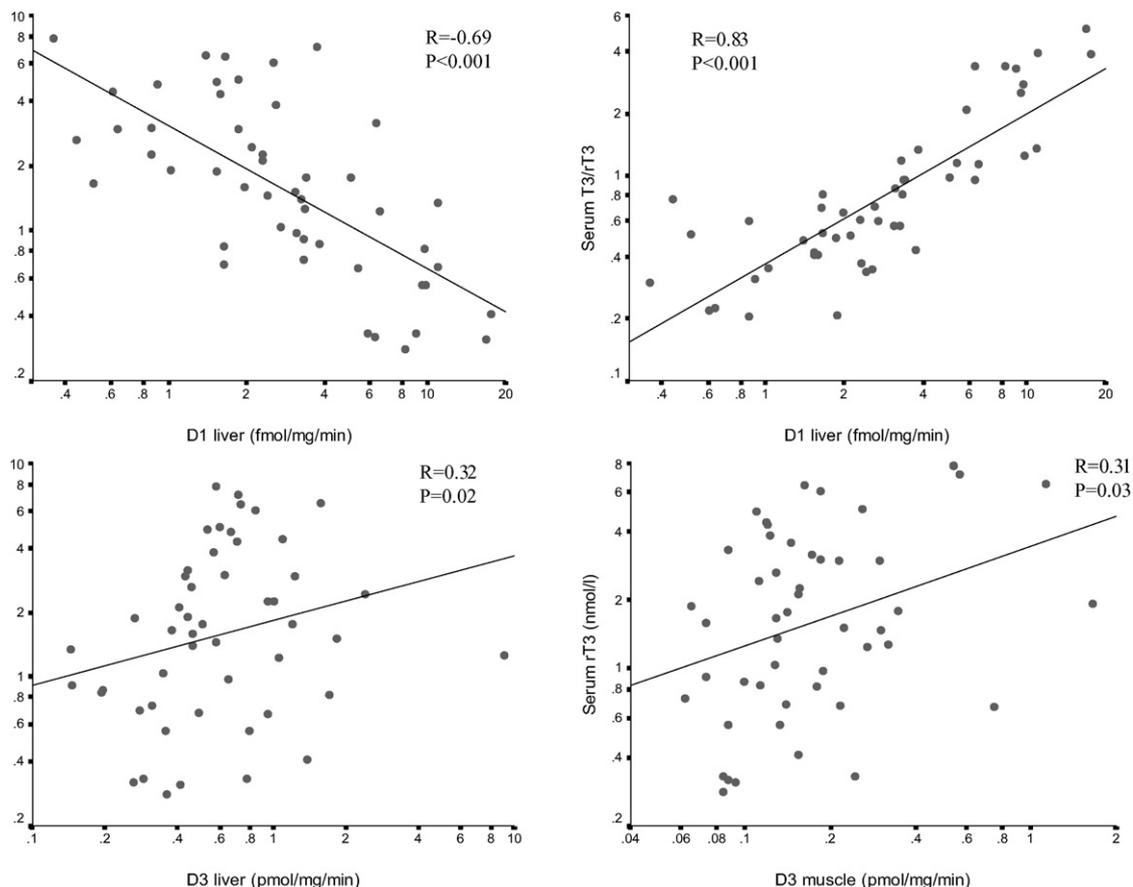


Fig. 1. Correlation analysis of liver D1 activity and serum rT3 (A) and T3/rT3 (B), and of liver D3 activity (C) and skeletal muscle D3 activity (D) and serum rT3. Liver D1 showed a significant negative correlation with rT3 ( $P < 0.001$ ) and a significant positive correlation with T3/rT3 ratio ( $P < 0.001$ ). Both liver and skeletal muscle D3 activity were positively correlated to serum rT3 levels ( $P < 0.05$ ).  $R$  represents Spearman's correlation coefficient. To convert values for rT3 to ng/dL, multiply by 64.9. (From Peeters RP, Wouters PJ, van Toor H, et al. Serum rT3 and T3/rT3 are prognostic markers in critically ill patients and are associated with post-mortem tissue deiodinase activities. *J. Clin. Endocrinol. Metab.* 2005; Aug; 90(8): 4559–65; with permission.)

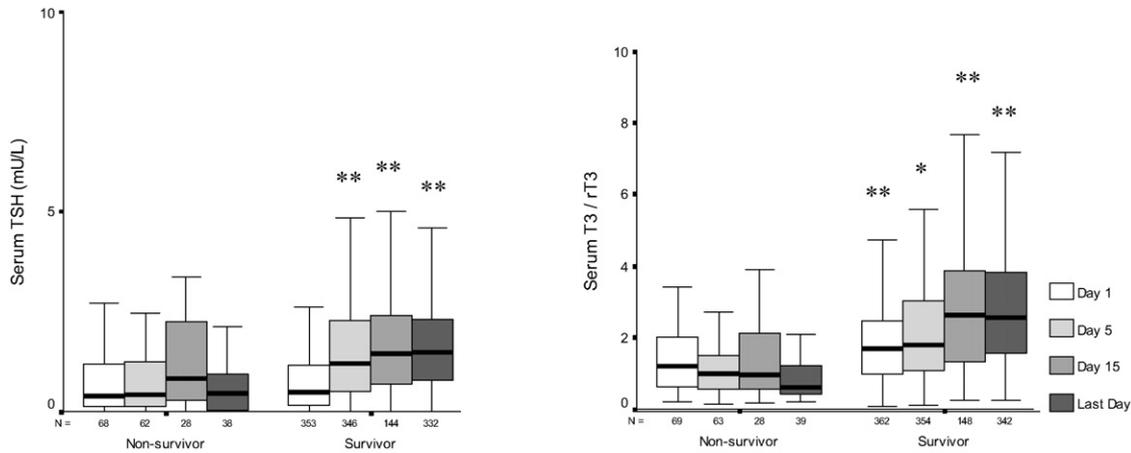


Fig. 2. Serum TSH levels and the T<sub>3</sub>/rT<sub>3</sub> ratio at day 1, 5, 15, and last day of ICU stay between survivors and non-survivors. From day 5 onward, serum TSH increased in patients who survived, whereas there was no such pattern in patients who died (Fig. 3A). The serum T<sub>3</sub>/rT<sub>3</sub> ratio increased in survivors from day 5 to LD, whereas it did not alter or even decreased in non-survivors (Fig. 3D). Box plots represent 10th-25th-50th-75th-90th percentiles. \* = significant difference between survivors and non-survivors ( $P \leq 0.05$ ), \*\* ( $P \leq 0.001$ ). To convert values for T<sub>4</sub> to  $\mu\text{g/dL}$ , multiply by 0.0777, and to convert values for T<sub>3</sub> or rT<sub>3</sub> to ng/dL, multiply by 64.9. (Adapted from Peeters RP, Wouters PJ, van Toor H, et al. Serum rT<sub>3</sub> and T<sub>3</sub>/rT<sub>3</sub> are prognostic markers in critically ill patients and are associated with post-mortem tissue deiodinase activities. *J. Clin. Endocrinol. Metab.* 2005; Aug; 90(8): 4559–65; with permission.).

T<sub>4</sub> daily plus 0.6  $\mu\text{g}$  T<sub>3</sub> per kg body weight per 24 h as a continuous IV infusion.

T<sub>3</sub> levels in patients who were treated with thyroid hormone were still in the low or low-normal range (Table 1). Nevertheless, these patients had a suppressed TSH, which may suggest over-treatment. TSH suppression is potentially harmful in critical illness, since the increase in TSH marks the onset of recovery and concomitantly drives the increase in serum T<sub>4</sub> [3,13,22,31]. This illustrates a major dilemma of thyroid hormone substitution in critically ill patients, since we do not know what appropriate levels of thyroid hormone are in critical illness. Higher serum T<sub>3</sub> levels in these patients were accompanied by higher levels of liver and T<sub>3</sub> and rT<sub>3</sub>, illustrating that the exogenous hormone does indeed enter the tissue. The increased liver T<sub>3</sub> concentration in patients who received thyroid hormone treatment was remarkable, since it was disproportional compared to the increased serum and muscle T<sub>3</sub> concentrations (~4 times higher in liver compared to ~2 times higher in serum and skeletal muscle) [34]. This illustrates another dilemma of thyroid hormone substitution in critically ill patients, and is in line with studies in thyroidectomized rats, in which neither T<sub>4</sub> nor T<sub>3</sub> were able to restore euthyroidism in all tissues and plasma [14–16].

Table 1  
Differences between the patients who were treated with thyroid hormone and the patients who were not

	TH treatment = no	TH treatment = yes	P
No. of patients	48	31	
Serum TSH ( $\mu\text{U/mL}$ )	0.61 (0.13–0.96) <sup>b</sup>	0.01 (0.002–0.08) <sup>b</sup>	< 0.001
Serum T <sub>4</sub> ( $\mu\text{g/dL}$ )	3.01 (1.69–5.17) <sup>b</sup>	3.47 (2.03–5.55) <sup>b</sup>	0.50
Serum T <sub>3</sub> (ng/dL)	51.27 (39.59–72.04) <sup>b</sup>	91.51 (63.60–131.75) <sup>b</sup>	< 0.001
Serum rT <sub>3</sub> (ng/dL)	73.34 (27.91–131.10) <sup>b</sup>	120.07 (64.25–157.71) <sup>b</sup>	0.06
Liver T <sub>4</sub> (ng/g)	23.47 (10.10–61.77) <sup>d</sup>	29.99 (21.83–71.64) <sup>d</sup>	0.14
Liver T <sub>3</sub> (ng/g)	0.72 (0.54–1.26) <sup>d</sup>	2.92 (0.99–3.71) <sup>d</sup>	< 0.001
Liver rT <sub>3</sub> (ng/g)	1.38 (0.75–3.23) <sup>d</sup>	2.76 (1.60–4.57) <sup>d</sup>	0.01
Muscle T <sub>4</sub> (ng/g)	1.63 (0.99–2.68) <sup>c</sup>	2.29 (1.78–3.37) <sup>f</sup>	0.01
Muscle T <sub>3</sub> (ng/g)	0.22 (0.16–0.29) <sup>f</sup>	0.36 (0.26–0.73) <sup>f</sup>	< 0.001
Muscle rT <sub>3</sub> (ng/g)	0.48 (0.35–0.92) <sup>f</sup>	0.75 (0.55–1.10) <sup>f</sup>	0.02

Age and BMI are shown as mean  $\pm$  SD, ICU stay, other data are shown as median (IQR). P values represent Mann-Whitney U tests. TH: Thyroid Hormone; IQR: Interquartile range.

<sup>b</sup> N = 39 vs. 25.

<sup>d</sup> N = 43 vs. 22.

<sup>c</sup> N = 41.

<sup>f</sup> N = 42 vs. 21.

tional compared to the increased serum and muscle T<sub>3</sub> concentrations (~4 times higher in liver compared to ~2 times higher in serum and skeletal muscle) [34]. This illustrates another dilemma of thyroid hormone substitution in critically ill patients, and is in line with studies in thyroidectomized rats, in which neither T<sub>4</sub> nor T<sub>3</sub> were able to restore euthyroidism in all tissues and plasma [14–16].

### 3. Thyroid hormone substitution during critical illness

Whether the reduced serum thyroid hormone levels in critical illness are adaptive, resulting in a decreased metabolic rate and protection against hypercatabolism, or mal-adaptative contributing to a worsening of the disease, is still controversial [12,13,38,41]. In the discussion about the possible role for thyroid hormone substitution in critically ill patients, it is important to realize the differences between the acute and the chronic phase of critical illness [40,41,45]. The changes in the thyroid axis in the acute phase of illness are similar to those observed in fasting, and have therefore been interpreted as an attempt to reduce energy expenditure and protein wasting [20, 39]. Studies in fasting subjects suggest that thyroid hormone replacement results in increased catabolism, as indicated by the increased nitrogen excretion and negative nitrogen balance [8,10,20,46]. It is unclear whether this is also true for critical illness, but studies in rats show no beneficial or even negative effects of thyroid hormone treatment in critically ill rats [11, 25]. So far, it has not been clearly demonstrated that thyroid hormone substitution in critically ill patients has a positive or negative effect on clinical outcome [1,4,5,7,28]. T<sub>4</sub> administration in patients with acute renal failure was associated with an increased mortality, which might be due to the suppressed TSH in the treatment group [1]. Free T<sub>4</sub> and free T<sub>3</sub> levels were not different between the two groups in this study [1]. A randomized clinical trial, in which 11 critically ill patients were treated with T<sub>4</sub>, showed no beneficial effect of T<sub>4</sub> treatment on

survival either [7]. Although T4 levels rose into the normal range in the treated patients, serum T3 concentrations remained low and did not differ between the two treatment groups [7]. This is probably due to the decreased T4 to T3 conversion, which is seen in both the acute and chronic phase of critical illness, and by the accelerated breakdown of T4 and T3 by D3 [30,31]. Therefore, treatment with T3 may be a better choice, although T3 may be detrimental as well and will also be subject of degradation by D3. More recent randomized clinical trials showed an improved cardiac function in adult patients treated with pharmacological doses of T3 for 6 h after cross-clamp removal during elective coronary artery bypass grafting [28], and in dopamine-treated children who received T3 substitution after cardiopulmonary bypass surgery [5]. However, since there was no effect on (peri-operative) survival, those results do not refute the postulated adaptive nature of the acute low T3 syndrome.

With the development of intensive care medicine in the last decades, patients who previously died from serious life-threatening diseases, can now survive. These patients sometimes require intensive care for a very long period. The changes in the thyrotropic profile in this situation seem to be of a more central origin [40,41,45], although the peripheral metabolism is also altered [30,31]. Studies on fasting subjects should therefore not be extrapolated to this situation. In chronic critical illness, many tissues have reduced thyroid hormone levels, although the severity seems to vary from one organ to another [2]. As in the acute situation, also in patients with prolonged critical illness, low levels of thyroid hormone and a low T3/rT3 ratio are associated with a higher mortality rate [31]. Furthermore, serum thyroid hormone levels are negatively correlated with urea production and bone degradation, which are markers of catabolism [41,42]. This suggests that the low levels of T4 and T3 in protracted critical illness reflect the severity of disease, and that it could be either adaptive, protecting against hypercatabolism, or a maladaptation that contributes to the worsening of the disease which should be treated.

If we decide to substitute these patients with thyroid hormone, the major question is what should be used? And should we aim for thyroid hormone levels within or still below the normal range?

Because of the decreased T4 to T3 conversion [30,31], T4 treatment does not seem appropriate and T3 treatment may be a better choice. A recent study, in which patients were treated with a combination of T4 and T3, showed tissue specific effects of thyroid hormone treatment in different tissues, with a disproportional increase in liver T3 levels compared to serum and skeletal muscle T3 concentrations [34]. Furthermore, with T3 levels still in the low normal range, TSH was suppressed which might suggest over-treatment.

A major disadvantage of substitution with thyroid hormone itself, is that the hypothalamus-pituitary-thyroid axis is bypassed. This may result in over-treatment and TSH suppression, whereas an increase in serum TSH marks the onset of recovery and concomitantly drives the increase in serum T4 [3,13,22,31]. If a combination of T4 and T3 (or T3 alone) is

given, the local regulation of thyroid hormone bioactivity by T4 to T3 conversion is also bypassed, which may be an additional argument against giving a combination of T4 and T3. Intervention with hypothalamic releasing factors might therefore be a more successful approach [42,43,48]. Continuous infusion of TRH, combined with a growth hormone secretagogue, restored pulsatile pituitary hormone secretion, restored physiological levels of thyroid hormone and reduced urea production and bone degradation as markers of catabolism in a group of patients with prolonged critical illness [42,43]. Whether this treatment also results in an improved clinical outcome in patients with protracted critical illness, remains to be determined in a randomized clinical trial.

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