Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 239–244
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit

Katharina Plikat, Julia Langgartner, Roland Buettner, L. Cornelius Bollheimer, Ulrike Woenckhaus, Jürgen Schölmerich, Christian E. Wrede*

Department of Internal Medicine I, University Hospital of Regensburg, University of Regensburg, 93042 Regensburg, Germany

Received 17 June 2006; accepted 18 September 2006

Abstract

Acute and chronic critical conditions are associated with reduced serum levels of free triiodothyronine (FT_3), free thyroxine FT_4, and thyrotropin, known as nonthyroidal illness syndrome (NTIS). It is still controversial whether these changes reflect a protective mechanism or a maladaptive process during prolonged illness. However, larger studies to determine the prevalence of the NTIS and its association with outcome in medical intensive care units (ICUs) are missing. Complete thyroid hormone levels from 247 of 743 patients admitted to our ICU between October 2002 and February 2004 were retrospectively evaluated. From these patients, Acute Physiology and Chronic Health II scores, ICU mortality, length of stay, mechanical ventilation, and concomitant medication were recorded. Ninety-seven patients (44.1%) had low FT_3 levels indicating an NTIS, either with normal (23.6%) or reduced (20.5%) serum thyrotropin levels. Of 97 patients with NTIS, 24 (23.3%) also showed reduced serum FT_4 levels. The NTIS was significantly associated with Acute Physiology and Chronic Health II scores, mortality, length of stay, and mechanical ventilation. In a multivariate Cox regression analysis, the combination of low FT_3 and low FT_4 was an independent risk factor for survival. Nonthyroidal illness syndrome is frequent at a medical ICU. A reduction of FT_4 together with FT_3 is associated with an increase in mortality and might reflect a maladaptive process, thereby worsening the disease.
© 2007 Elsevier Inc. All rights reserved.

1. Introduction

It has been shown for more than 30 years that acute and chronic critical conditions are associated with a significant decrease of the serum concentration of total triiodothyronine (T_3) and free triiodothyronine (FT_3) [1]. In prolonged critical illness, a concomitant and gradual decrease of serum thyroxine (T_4) and of thyrotropin (TSH) may also occur [2]. This condition, known as "low-T_3 syndrome," "euthyroid sick syndrome," or "nonthyroidal illness syndrome" (NTIS), has been described in patients with various medical and surgical conditions, such as tuberculosis [3], trauma [4], myocardial infarction [5], general surgery [6], bypass operations [7], and starvation [8]. In fact, it probably occurs in any acute or chronic critical condition.

The pathogenesis of these endocrine alterations is not fully understood yet. The reduction of serum FT_3 is probably due to a decreased conversion of T_4 caused by an impaired activity of the type 1 deiodinase in liver and kidney. In addition, there is an induction of the type 3 deiodinase in liver and skeletal muscle, which prevents conversion of T_4 to T_3 by catalyzing T_4 to the biologically inactive reverse T_3 instead. As a result, there may be an increased level of serum reverse T_3 in these patients [9-11].

Changes in serum TSH levels have been attributed to an altered hypothalamic-pituitary regulation, particularly because the hypothalamic TSH-releasing hormone (TRH) messenger RNA expression has been shown to be reduced in patients with NTIS [12]. This theory is additionally supported by the observation that serum TSH levels are not elevated in the presence of decreased T_4 levels, but increase gradually during recovery from NTIS [13]. Besides this, TSH and T_4 serum levels have been shown to increase after administration of TRH in patients with NTIS [14].

The reduction of serum FT_3 levels occurs in the acute phase and persists in the chronic phase, whereas the drop in

* Corresponding author. Tel.: +49 941 944 7175; fax: +49 941 944 7021.
E-mail address: christian.wrede@klinik.uni-regensburg.de (C.E. Wrede).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.09.020

free T_4 (FT_4) and TSH levels is associated with the prolonged phase of critical illness [13,15]. The inactivation of peripheral hormones in the acute setting of critical illness as well as the down-regulation of hypothalamic-pituitary hormones in the chronic phase have been observed in all hormone axes [15], including the adrenal axis where this process may lead to a relative adrenal insufficiency, requiring hydrocortisone substitution in some patients with septic shock [16].

The hormone changes of the hypothalamic-pituitary-thyroid axis in critically ill patients have often been regarded as a protective mechanism to reduce energy expenditure to avoid worsening catabolism. More recently, some authors challenged this view suggesting that hormonal changes in the chronic phase of critical illness may reflect a maladaptive process, thereby worsening the course of the disease [15,17]. The presence of NTIS seems to correlate with the severity of the underlying disease, and the outcome of patients with low T_3 and T_4 serum levels was worse compared with that of patients with normal thyroid laboratory parameters [18-20]. However, it remains to be proven that the NTIS itself represents an independent risk factor for the increased mortality of critically ill patients, thereby providing a rationale for a substitution with thyroid hormones or hypothalamic peptides.

The question if this association between NTIS and outcome is a causal one can only be answered by a large randomized treatment study. However, the current data published so far do not provide enough information for the design of such a study. Therefore, the aim of our study was to identify subgroups of patients who might benefit from a treatment in the setting of a large randomized study.

2. Materials and methods

2.1. Study population

From October 2002 to February 2004, 743 patients had been admitted to a 12-bed medical intensive care unit (ICU) at the University Hospital of Regensburg (Regensburg, Germany). Demographic data such as age and sex, length of stay at the ICU, duration of mechanical ventilation, and ICU mortality had been recorded for all patients. From 247 patients, complete serum thyroid hormone levels were available, and these patients were further evaluated.

2.2. Laboratory values

All thyroid hormone levels were usually determined within the first 24 to 48 hours of ICU admission (median, 1.0 days). Blood was drawn from nonheparinized central lines. Serum FT_3, serum FT_4, and TSH were measured by chemiluminescent immunoassays on an Advia Centaur instrument (Bayer, Leverkusen, Germany).

2.3. Characterization of patients with complete thyroid laboratory values

Patients with a complete thyroid status (laboratory values for serum FT_3, FT_4, and TSH) were further characterized by retrospective analysis of the ICU charts. The Acute Physiology and Chronic Health II (APACHE II) score was calculated within 24 hours of ICU admission as described by Knaus et al [21]. The main diagnoses as well as any preexisting thyroid disease were recorded (data available from existing medical files). Because certain drugs have been reported to interfere with the hypothalamic-pituitary-thyroid axis, the use of dopamine, epinephrine, amiodarone, and steroids as well as T_4 or thyreostatic agents within 24 hours before the determination of serum thyroid hormone levels was documented. Patients with T_4 or thyreostatic treatment were excluded from further analysis.

2.4. Statistical analysis

All statistical tests were calculated by SPSS software (SPSS for Windows, Rel. 12.0.1, 2003, SPSS, Chicago, IL). A P value of less than 0.05 was considered statistically significant. Descriptive data were presented as median and interquartile range for continuous data and percentages for categorical data. Differences in baseline characteristics were calculated by Mann-Whitney test (continuous data) and χ^2 test (categorical data). For survival analysis, follow-up time was determined by the time patients were last seen in our hospital. The event was defined as death at the ICU. Significance levels were calculated by Cox regression analysis with a 95% confidence interval.

3. Results

Between October 2002 and February 2004, 743 patients had been admitted to our medical ICU. The median age of these patients was 62 years, and 48% of all patients were women. The median length of stay at the ICU was 2.0 days. Of all patients, 40.1% were mechanically ventilated; overall ICU mortality was 17.6% (Table 1). No significant differences between women and men were observed (data not shown). In 247 (33.2%) of 743 patients, all thyroid hormone values were available. These patients were more often mechanically ventilated than those without complete thyroid function tests (49.4% vs 35.5%, $P < .001$). They also stayed longer at the ICU (median, 4 and 2 days, respectively; $P < .001$). There were no significant differences between these groups regarding age (median, 62.5 vs 61.0 years; $P = .48$),

Table 1
Characteristics of the study cohort (mean values ± SD)

	Thyroid laboratory values		Total	P
	Available	Not available		
n	247 (33.2%)	496 (66.8%)	741 (100%)	
Age (y)	58.8 ± 17.0	57.2 ± 19.2	57.8 ± 18.5	.27
Sex (% male)	49.4	53.6	52.2	.28
No. of days at the ICU	9.8 ± 13.2	3.5 ± 5.8	5.6 ± 9.5	<.001
Mechanical ventilation (%)	49.4	35.5	40.1	<.001
Mortality at the ICU (%)	18.4	16.7	17.3	.58

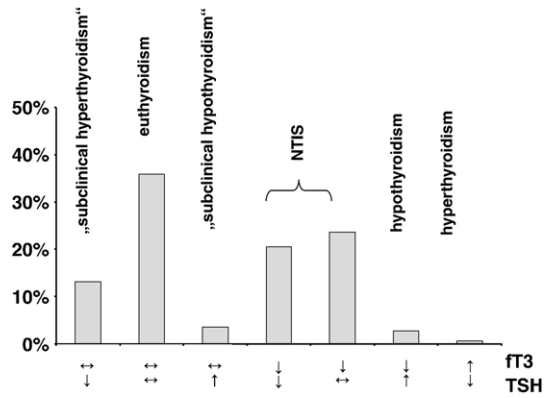

Fig. 1. Combination of thyroid laboratory values in the study population. Values are presented as percentage (n = 220).

sex (49.4% male vs 53.6% female, $P = .28$), and mortality (19.4% vs 16.7%, $P = .37$) (Table 1).

From those 247 patients with complete thyroid hormone levels (TSH, FT_3, FT_4), 5 patients received thyreostatic drugs, and 22 patients were on medication with T_4. These patients were excluded from further analyses.

Of the remaining 220 patients, 79 (35.9%) were euthyroid, defined as having normal thyroid laboratory values for TSH, FT_3, and FT_4. Ninety-seven (44.1%) had low serum FT_3 levels indicating an NTIS, either with normal (52 patients, 23.6%) or reduced (45 patients, 20.5%) serum TSH levels. Twenty-nine patients (13.2%) had reduced serum TSH levels, but normal FT_3 levels. Patients with abnormal TSH and normal peripheral thyroid laboratory values were formally classified as having "subclinical hyperthyroidism" or "subclinical hypothyroidism," although these changes may have a different meaning in critically ill patients, probably also indicating an NTIS. Six patients (2.7%) had manifested hypothyroidism, and 1 (0.5%) manifested hyperthyroidism (Fig. 1). Of the 97 patients with NTIS, 24 (23.3%) showed also reduced serum FT_4 levels.

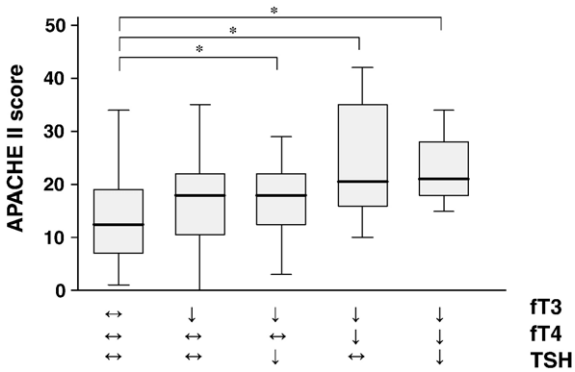

Fig. 2. Acute Physiology and Chronic Health II scores of euthyroid patients and patients with NTIS. Results are depicted as box plots. The top and bottom of each box indicate the 25th and the 75th percentiles. The line through the box is the median, and the error bars are the 5th and 95th percentiles. Significance levels were determined by the Mann-Whitney test (*$P < .05$).

The NTIS was associated with the severity of disease, as expected. The median APACHE II score for patients with normal thyroid laboratory values was 12.5, whereas patients with reduced serum FT_3 levels had median APACHE II scores of 18.0 ($P < .05$). Patients with reduced serum FT_3 and FT_4 levels had the highest APACHE II scores (21.0). These values were significantly higher than those for euthyroid patients ($P < .001$) as well as for patients with reduced FT_3 values ($P < .05$). Surprisingly, additional reduction of TSH did not significantly affect the correlation between NTIS and APACHE II scores (Fig. 2). Therefore, 2 groups of patients with NTIS were built for further analyses, one with low FT_3 levels and one with low FT_3 and FT_4 levels, regardless of the TSH values.

The patients with NTIS had an increased length of stay at the ICU. The median duration for patients with low FT_3 was 5.0 days (interquartile range, 12.0 days) compared with 3.0 days (interquartile range, 6.0 days) for euthyroid patients ($P < .05$). Patients with low FT_3 and FT_4 stayed significantly longer at the ICU (median, 13.0 days; interquartile range, 29.0 days) than euthyroid patients ($P < .001$) and patients

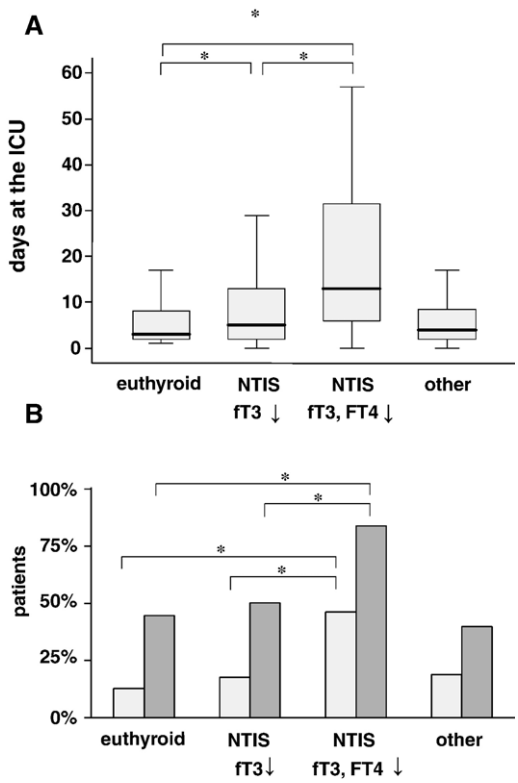

Fig. 3. A, Duration of stay at the ICU for euthyroid patients, patients with NTIS, and patients with other thyroid hormone changes. Results are shown as box plots with the top and bottom of each box indicating the 25th and the 75th percentiles, the line through the box is the median, and the error bars are the 5th and 95th percentiles, respectively. Significance levels were indicated in the figure (Mann-Whitney test, *$P < .05$). B, Intensive care unit mortality (light gray boxes) and percentage of mechanically ventilated patients (dark gray boxes) for euthyroid patients, patients with NTIS, and patients with other thyroid hormone changes. Significance levels were determined by χ^2 test (*$P < .05$).

with only reduced FT_3 ($P < .05$, Fig. 3A). Patients with NTIS were also more often mechanically ventilated (44.3% for euthyroidism, 50.0% for low FT_3, and 83.3% for low FT_3/FT_4, respectively; Fig. 3B). The overall ICU mortality was 12.7% for euthyroid patients; the mortality of patients with low FT_3 levels was nonsignificantly higher (17.6%, $P = .396$). Patients with low FT_3 and low FT_4 had a much higher mortality of 45.8% than euthyroid patients ($P < .001$) and patients with low FT_3 ($P = .005$, Fig. 3B).

Because the mortality of euthyroid patients and patients with low FT_3 was not significantly different, these patients were grouped together and a survival analysis of this group compared with patients with NTIS and low FT_4 was performed (Fig. 4A). The multivariate comparison of hazard rates was done by Cox regression analysis using NTIS as independent variable. Because mortality was both associated with NTIS and APACHE II scores, these scores were categorized by quartiles (first quartile, APACHE II score <11; second quartile, 11-17; third quartile, 18-22; fourth quartile, >22) and used as covariates for Cox regression (Fig. 4B). By this model, NTIS with reduced FT_4 was significantly associated with reduced survival (odds ratio, 2.57; 95% confidence interval, 1.19-5.52; $P = .016$); independent of the APACHE II score ($P = .006$).

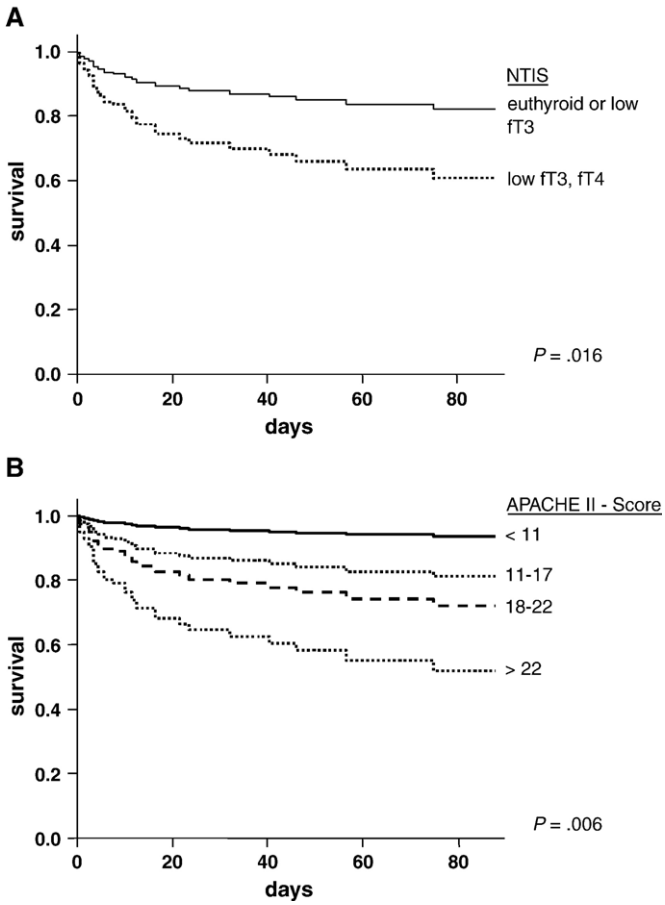

Fig. 4. Multivariate Cox regression analysis of patients with NTIS with low FT_3 and FT_4 compared with patients with euthyreosis and NTIS having only low FT_3 values. The APACHE II scores were used as covariate. A, Survival curve of patients with NTIS. B, Survival curve of patients based on quartiles of the APACHE II score. Significance levels are indicated in the figure.

The main diagnoses were determined to identify patients at risk for NTIS in the medical ICU. Although patients with sepsis, pancreatitis, and pneumonia had the highest NTIS prevalence, the number of patients was too small to assess the influence of main diagnoses on the NTIS (data not shown).

Several drugs have previously been associated with the NTIS, and their associations on survival were determined by univariate Cox regression analysis. The use of epinephrine (n = 51) and dopamine (n = 24) was significantly associated with reduced survival ($P < .001$), whereas no association was found for β-blockers (n = 13, $P = .237$), steroids (n = 40, $P = .649$), and amiodarone (n = 6, $P = .541$). In the multivariate Cox regression analysis, NTIS with low FT_4 was still significantly associated with ICU mortality after correction for dopamine ($P = .004$), but lost significance after correction for epinephrine ($P = .062$). However, when using hospital mortality instead of ICU mortality, the correlation remained significant ($P = .002$ for dopamine and $P = .039$ for epinephrine, respectively).

4. Discussion

In critically ill patients, disturbances of the hormonal axes including the hypothalamic-pituitary thyroid axis occur, leading to an NTIS with reduced FT_3, FT_4, and TSH laboratory values. Although this pattern has been described for many years, it still remains controversial whether and to what extent these changes reflect a protective or a maladaptive process. This question can only be answered in a large prospective, randomized multicenter treatment study. However, several factors important for the design of such a study are unknown. There is a lack of larger studies evaluating the prevalence of the NTIS at ICUs because most studies were based on small numbers of selected patients [1,18,20,22-26]. Our study evaluated thyroid function in 247 patients at a medical ICU, which is one of the largest studies published so far. Although retrospective, this study compared demographic parameters and mortality of patients with thyroid laboratory parameters with those of patients admitted to our ICU, showing that these parameters were not significantly different between patients with and without thyroid laboratory values. A recent study by Peeters et al [11] determined thyroid laboratory values of 451 of 1548 surgical patients initially randomized for intensive insulin treatment. However, the prevalence of the NTIS was not calculated, and several of the patients with NTIS were clinically judged as hypothyroid and treated with T_4.

The reduced outcome of patients with NTIS found by others [11,18-20,25,27,28] could be confirmed in our study. Patients with reduced FT_4 values, independently of TSH,

had the highest mortality rates, consistent with an older study from Slag et al [20] and a recent study by Van den Berghe et al [27], whereas some other publications found T_3 as the main predictor of survival [25,28].

Half of our patients with NTIS also had reduced TSH levels, thereby indicating changes in the hypothalamic-pituitary regulation. Interestingly, this alteration did not seem to affect mortality, whereas concomitant low FT_4 levels, which may also be due to an impaired hypothalamic or pituitary regulation [29], clearly increased mortality. These findings are consistent with previous studies, although the reasons for these results remain not fully understood.

In contrast to previous studies, our study had sufficient patient numbers to correct for the severity of disease by multivariate Cox regression analysis, using the APACHE II score as a marker. In this analysis, only patients with reduced FT_4 values had an increased risk of nonsurvival, indicating that the reduction of FT_4 itself worsen the course of the disease.

Treatment of patients affected by NTIS with thyroid hormones has been controversially discussed, and there are only a few studies in humans with small numbers available so far [14,30-33]. Possible treatment includes the substitution of T_4, which restored serum T_4 levels but reduced TSH levels and failed to show a clinically beneficial effect [30]. Treatment with T_3 has been investigated in burn patients [31] and in coronary artery bypass surgery [32,33], but its clinical benefit has not been repeatedly shown yet. Probably the most promising treatment was the continuous infusion of TRH together with growth hormone–releasing peptide 2, which was found to reduce protein catabolism in patients with NTIS by restoring physiologic hormone levels [14]. In an animal model for critical illness, this treatment has also been shown to restore the tissue levels of type 1 and type 3 deiodinase [34]. However, because hormonal changes in critical illness are dynamic processes [35], not all patients with NTIS may benefit from such a treatment. Because our study showed that only a reduction in FT_4 levels, regardless of the TSH value, is an independent risk factor for mortality, these patients should be treated within controlled studies.

There are some limitations to our study. Thyroid laboratory values were not determined in all patients, and although the mortality of patients without laboratory values was not statistically different, the stay of these patients at the ICU was shorter and a bias cannot be ruled out. Longitudinal measurement of thyroid hormone levels was also not available. Because changes within the thyroid axis during critical illness differ from acute to chronic phases, we might have missed some of the NTIS occurring later during the prolonged phase of critical illness. In addition, equilibrium dialysis is considered as the gold standard for the determination of FT_3 and FT_4. Automated assays such as the ADVIA assay used in this study are not validated for critically ill patients and may overestimate the frequency of reduced free thyroid values in patients with NTIS [36].

Determination of free thyroid hormones instead of total hormone concentrations in patients with NTIS is controversial because the validity of diagnostic tests for FT_3 and FT_4 has not been sufficiently determined for these patients. On the other hand, total hormone concentrations vary significantly with changes in T_4-binding globulin and albumin concentrations, which are frequently seen in these patients [37]. For T_3, most publications reported a concomitant reduction in free and total hormone concentrations [1,3,26,31,38], but the correlation between free and total T_4 is less clear. Whereas total T_4 is often reduced, free T_4 values might be reduced [24,31] or elevated [1,24]. Whether free or total thyroid hormone measurements better reflect the true thyroid function in patients with NTIS remains speculative.

In summary, almost half of the patients treated in our medical ICU had an NTIS. The reduction of FT_4 values, found in about one fourth of the patients with NTIS, was an independent risk factor for mortality in our study. These patients may benefit from a treatment, preferably with hypothalamic peptides, in the setting of randomized studies.

References

[1] Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab 1975;41:27-40.

[2] McIver B, Gorman CA. Euthyroid sick syndrome: an overview. Thyroid 1997;7:125-32.

[3] Chow CC, Mak TW, Chan CH, Cockram CS. Euthyroid sick syndrome in pulmonary tuberculosis before and after treatment. Ann Clin Biochem 1995;32(Pt. 4):385-91.

[4] Phillips RH, Valente WA, Caplan ES, Connor TB, Wiswell JG. Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome. J Trauma 1984;24:116-9.

[5] Eber B, Schumacher M, Langsteger W, Zweiker R, Fruhwald FM, Pokan R, et al. Changes in thyroid hormone parameters after acute myocardial infarction. Cardiology 1995;86:152-6.

[6] Aun F, Medeiros-Neto GA, Younes RN, Birolini D, de Oliveira MR. The effect of major trauma on the pathways of thyroid hormone metabolism. J Trauma 1983;23:1048-51.

[7] Reinhardt W, Mocker V, Jockenhövel F, Olbricht T, Reinwein D, Mann K, et al. Influence of coronary artery bypass surgery on thyroid hormone parameters. Horm Res 1997;47:1-8.

[8] Hennemann G, Docter R, Krenning EP. Causes and effects of the low T3 syndrome during caloric deprivation and non-thyroidal illness: an overview. Acta Med Austriaca 1988;15(Suppl 1):42-5.

[9] Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003;88:3202-11.

[10] Köhrle J. Local activation and inactivation of thyroid hormones: the deiodinase family. Mol Cell Endocrinol 1999;151:103-19.

[11] Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3,3′,5′-triiodothyronine (rT3) and 3,5,3′-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. J Clin Endocrinol Metab 2005;90:4559-65.

[12] Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 1997;82:4032-6.

[13] Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993;39:499-518.
[14] Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 1998;83:309-19.
[15] Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1-13.
[16] Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
[17] De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999;84:151-64.
[18] Leon-Sanz M, Lorente JA, Larrodera L, Ros P, Alvarez J, Esteban AE, et al. Pituitary-thyroid function in patients with septic shock and its relation with outcome. Eur J Med Res 1997;2:477-82.
[19] Silberman H, Eisenberg D, Ryan J, Shofler R, Niland J, Kaptein E, et al. The relation of thyroid indices in the critically ill patient to prognosis and nutritional factors. Surg Gynecol Obstet 1988;166:223-8.
[20] Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981;245:43-5.
[21] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
[22] Baue AE, Gunther B, Hartl W, Ackenheil M, Heberer G. Altered hormonal activity in severely ill patients after injury or sepsis. Arch Surg 1984;119:1125-32.
[23] Custro N, Scafidi V, Costanzo G, Notarbartolo A. Prospective study on thyroid function anomalies in severely ill patients. Ann Ital Med Int 1992;7:13-8.
[24] Kaplan MM, Larsen PR, Crantz FR, Dzau VJ, Rossing TH, Haddow JE. Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am J Med 1982;72:9-16.
[25] Maldonado LS, Murata GH, Hershman JM, Braunstein GD. Do thyroid function tests independently predict survival in the critically ill? Thyroid 1992;2:119-23.
[26] Scoscia E, Baglioni S, Eslami A, Iervasi G, Monti S, Todisco T. Low triiodothyronine (T3) state: a predictor of outcome in respiratory failure? Results of a clinical pilot study. Eur J Endocrinol 2004;151:557-60.
[27] Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Iranmanesh A, et al. The combined administration of GH-releasing peptide–2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. Clin Endocrinol (Oxf) 2002;56:655-69.
[28] Loh KC, Eng PC. Prevalence and prognostic relevance of sick euthyroid syndrome in a medical intensive care unit. Ann Acad Med Singapore 1995;24:802-6.
[29] Kaptein EM, Robinson WJ, Grieb DA, Nicoloff JT. Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. A noncompartmental analysis. J Clin Invest 1982;69:526-35.
[30] Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab 1986;63:1-8.
[31] Becker RA, Vaughan GM, Ziegler MG, Seraile LG, Goldfarb IW, Mansour EH, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med 1982;10:870-5.
[32] Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwinn DA. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. JAMA 1996;275:687-92.
[33] Klemperer JD, Klein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ, et al. Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med 1995;333:1522-7.
[34] Weekers F, Michalaki M, Coopmans W, Van Herck E, Veldhuis JD, Darras VM, et al. Endocrine and metabolic effects of growth hormone (GH) compared with GH-releasing peptide, thyrotropin-releasing hormone, and insulin infusion in a rabbit model of prolonged critical illness. Endocrinology 2004;145:205-13.
[35] Van den Berghe G. Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin North Am 2003;32:385-410.
[36] Sapin R, Schlienger JL, Gasser F, Noel E, Lioure B, Grunenberger F, et al. Intermethod discordant free thyroxine measurements in bone marrow-transplanted patients. Clin Chem 2000;46:418-22.
[37] Laboratory support for the diagnosis and monitoring of thyroid disease. Published guidelines of the National Academy of Clinical Biochemistry; 2003 http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidedlines/ThyroidDisease/.
[38] Surks MI, Hupart KH, Pan C, Shapiro LE. Normal free thyroxine in critical nonthyroidal illnesses measured by ultrafiltration of undiluted serum and equilibrium dialysis. J Clin Endocrinol Metab 1988;67:1031-9.