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Short Communication

Two-step thyroid screening strategy in the critical patient☆,☆☆,★

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ABSTRACT

Background: Thyroid function biochemical tests are known for their usefulness in prognosis of long-term critical patients, although current data are controversial regarding the clinical benefit of both free triiodothyronine and thyroxine as prognostic thyroid markers during the first 48 h after Intensive Care Unit (ICU) admission.

Methods: The aim of this study was to evaluate the usefulness of two strategies for thyroid function assessment in the first 48 h after admission at the ICU. The usefulness of a two-step biochemical thyroid strategy (initial isolated TSH determination, followed by subsequent fT_4 and fT_3) was compared with a complete one-step biochemical profile (TSH + fT_4 + fT_3).

Results: No significant differences were found between the rates of thyroid dysfunction detection when using both strategies (2.8% vs. 2.4%; $p = 0.71$). Using the two-step strategy and a 2.5 μUI/mL cut-off value for TSH, sensitivity and negative predictive value were 100%. Among patients with an altered fT_3 only, mortality was 14% if TSH ≤ 2.5 μUI/mL, whereas it was 7% if TSH > 2.5 μUI/mL ($p = 0.008$).

Conclusions: For patients with critical illness, the early two-step thyroid screening strategy (starting with an isolated TSH determination between 24 and 48 h after admission) led to a saving of 50% in fT_4 and fT_3 tests, with a false-negative rate of 1.3%. This represents an improved diagnostic approach, hence avoiding the performance of unnecessary complementary biochemical measurements.

1. Introduction

During an Intensive Care Unit (ICU) admission, the endocrine system exhibits substantial changes which may hinder the differential diagnosis between preexistent dysfunctions and those induced during the current pathological process. The measurement of tissue levels of thyroid hormones is a tedious work. Conversely, the quantification of their circulating levels in blood is considered the best estimation of tissue function. However, several conditions may seriously modify the concentration of such hormones, especially hypoxia and sepsis [1].

Thyroid hormones serum concentrations are usually altered in the critical patient, with a typically decreased concentration of free triiodothyronine (fT_3) and an increase or transient decrease of free thyroxine (fT_4) [1]. In addition, the decrease in fT_4 levels has been associated with the severity and the prognosis, with an increased risk of death above 50% if they are below 0.5 ng/dL [2]. During admission, thyrotropin (TSH) levels may be initially slightly increased, displaying a subsequent decrease if illness persists [3]. Such alterations have been previously correlated with tissue deiodinase D1 and D3 activities, both of which contribute to the lowering of fT_3 in the critical illness, thus establishing a tissue hypothyroid status [4].

The thyroid function tests are known for their usefulness in prognosis of long-term critical patients, although current data are controversial regarding the clinical benefit of both fT_3 and fT_4 as prognostic thyroid markers during the first 48 h after ICU admission [5].

2. Objective

The aim of this study was to evaluate the usefulness of two thyroid function biochemical strategies in the first 48 h after admission at the Intensive Care Unit, for the early screening of thyroid dysfunction in patients without any medical record of thyroid alteration.

3. Methods

This is a retrospective analysis, including patients between January 2013 and June 2015. The usefulness of a two-step biochemical thyroid strategy (initial isolated TSH determination, followed by subsequent fT_4 and fT_3) was compared with a complete one-step biochemical profile (TSH + fT_4 + fT_3). The study included patients above 18 years old, without previous thyroid pathology and with a morning complete biochemical test performed during the first 48 h after ICU admission, in a tertiary care hospital.

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Table 1a
First step values after TSH determination ($n = 578$).

TSH (μUI/mL)	Free T_4 (ng/dL)			Total
	<0.7	0.7–1.5	>1.5	
<0.35	5 (5%)	85 (85%)	10 (10%)	100 (17.3%)
0.35–5	39 (9.1%)	363 (84.6%)	27 (6.3%)	429 (74.2%)
>5	9 (18.4%)	40 (81.6%)	0	49 (8.5%)
Total	53 (9.2%)	488 (84.4%)	37 (6.4%)	578 (100%)

Serum quantifications of TSH, fT_4 and fT_3 were performed by a chemiluminescent immunoassay, according to manufacturer instructions (Architect i2000, Abbott Diagnostics, IL). The reference intervals in our laboratory were 0.35 to 5.0 μUI/mL for TSH; 0.7 to 1.5 ng/dL for fT_4 and 1.7 to 3.7 pg/mL for fT_3.

The percentages of thyroid dysfunction detection between strategies were compared, defined as TSH alterations together with a clinically significant decrease in fT_4 and fT_3 levels. The Chi-squared test was used to compare the two-step strategy versus the complete one-step profile. Statistical significance was set at 5%. We totally adhered to the ethical guidelines approved by the Ethics Board of our institution.

4. Results

A total of 578 patients were included. The sample consisted of 51% male, with a mean age of 59 years (range: 18–83 years). The female group had a mean age of 60 years (range: 18–89 years). No age or gender differences were detected.

The reasons for admission were: neurological disorder including stroke (24%), infectious complications and sepsis (22%), oncological patients (17%), acute coronary syndrome and myocardial infarction (13%), kidney disease (12%), surgical intervention and polytraumatism (12%).

When the complete one-step biochemical profile (TSH + fT_4 + fT_3) was used, up to 16 patients (2.8%) had a significant thyroid dysfunction, and most of them presented infectious complications of the base disease (81%). When the two-step strategy was used, 2.4% of true thyroid dysfunction was detected. No significant differences were found between the rates of thyroid dysfunction detection when using both strategies (2.8% vs. 2.4%; $p = 0.71$). Altogether, 25.8% of patients ($n = 149$) had an altered TSH value, 67% of which were above the upper reference limit and 33% below the lower reference limit (Table 1a).

4.1. TSH elevation

Up to 18.4% of the patients with a TSH elevation, showed a decreased fT_4. All patients with a decreased fT_4 also showed low fT_3 (Table 1b).

4.2. Decreased TSH

Among those patients with a TSH decrease ($n = 100$), up to 5% showed low fT_4, and all patients with a decreased fT_4 also showed low fT_3 (Table 1b). In contrast, in the patient group with altered TSH and normal fT_4 ($n = 125$), a total of 56% had a decreased fT_3.

Table 1b
Second step values after fT_4 determination ($n = 149$).

Free T_4 (ng/dL)	Free T_3 (pg/mL)			Total
	<1.7	1.7–3.7	>3.7	
<0.7	14 (100%)	0	0	14 (9.4%)
0.7–1.5	70 (56%)	55 (44%)	0	125 (83.9%)
>1.5	5 (50%)	4 (40%)	1 (10%)	10 (6.7%)
Total	89 (59.7%)	59 (39.6%)	1 (0.7%)	149 (100%)

Table 2a
Detection rate of thyroid dysfunction after isolated TSH determination without 2.5 μUI/mL cut-off value of the normal range to TSH.

TSH (μUI/mL)	Thyroid dysfunction		Total
	Yes	No	
<0.35 or >5	14	135	149
0.35–5	2	427	429
Total	16	562	578

4.3. Normal TSH

Among all screening patients, 429 showed a TSH concentration within the reference interval (74.2%), and 9.1% of them had a low fT_4. From this subgroup, fT_3 was reduced in 31% of cases ($n = 12$). Therefore, the percentage of the total patients with a within-interval TSH and decreased fT_4 and fT_3 is 2% (Table 1a and 1b).

A quantitative analysis of these 12 patients with normal TSH and decreased both fT_4 and fT_3 yielded a median TSH value of 1.04 μUI/mL (percentile-10: 0.50 μUI/mL; percentile-90: 2.50 μUI/mL). Among all patients with a TSH value within the reference interval, up to 145 had TSH below 2.50 μUI/mL, and 2 of them had a clinical thyroid dysfunction (Table 2a and 2b).

According to our results, using the two-step screening strategy and a cut-off value for TSH, sensitivity was 100%, for a specificity of 50% (confidence interval 95%: 46–54%), and the negative predictive value was 100% (Table 2b).

4.4. Mortality

From patients with decreased fT_3 and fT_4, those with normal TSH values showed a 75% mortality, whereas the mortality among patients with altered TSH was 63% ($p = 0.48$). If only fT_3 was reduced, mortality was 21% in patients with normal TSH, while 30% in patients with altered TSH ($p = 0.06$). Thus, regardless of TSH value, when mortality was compared between the "low fT_3 fT_4" group (68%) and the "low fT_3 only" group (24%), statistically significant differences were found ($p < 0.001$).

Among patients with an isolated fT_3 alteration, mortality was lower in patients with TSH concentrations above 2.5 μUI/mL (14% if TSH ≤ 2.5 μUI/mL vs. 7% if TSH > 2.5 μUI/mL, $p = 0.008$).

5. Discussion

Up to 15% of patients included in our study showed a low serum fT_3, while <18% of them had a true thyroid dysfunction. This fact reveals the need of an adequate laboratory request management of hormone biochemical tests in critical illness. Previous studies recommend the measurement of both fT_3 and fT_4 in every critically ill patient in which thyroid dysfunction is suspected [6].

Free thyroxine levels may exhibit an initial increase, although its circulating concentration is essentially reduced in cases of severe illness [7]. The decrease in T_4 together with T_3 and an increase in the concentration of its inactive metabolite (rT_3), without an increase in TSH,

Table 2b
Detection rate of thyroid dysfunction after isolated TSH determination with 2.5 μUI/mL cut-off value of the normal range to TSH.

TSH (μUI/mL)	Thyroid dysfunction		Total
	Yes	No	
≤2.5 or >5	16	279	295
>2.5–5	0	283	283
Total	16	562	578

Sensitivity and negative predictive value: 100%.