IN VITRO NUCLEAR MEDICINE

Low T_4 and Low FT_4I in Seriously Ill Patients: Concise Communication

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Of 128 euthyroid hospitalized patients with nonthyroidal illnesses (NTI), 33% had a low total thyroxine (T_4). Forty-three percent of the latter patients had a low free thyroxine index. In euthyroid patients with NTI, free T_4 was, with rare exceptions, within the range for well euthyroid controls. The free T_4, as determined by two different radioimmunoassays, was diagnostically low in 34 of 37 hypothyroid patients without NTI. However, in hypothyroid patients with NTI, the free T_4 determination was less informative. Only four of ten patients had a low free T_4 by the Corning test, and none of ten were low by the Clinical Assays test.

Our data suggest that patients with NTI frequently have low T_4 and low FT_4I, despite being euthyroid. Low free T_4 strongly suggests hypothyroidism, but normal free T_4 in patients with NTI does not exclude hypothyroidism.

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Depression of total serum triiodothyronine (T_3) has been well characterized in numerous nonthyroidal illnesses (*1,2*), but only mild or no depression of total thyroxine (T_4) has been described in similar circumstances (*2–9*). The decreased T_4 in these conditions is frequently associated with decreased thyroid-binding proteins, and has been generally assumed, but not shown, to be corrected by a high resin triiodothyronine uptake (RT_3U) to give a normal free thyroxine index (FT_4I). The FT_4I has been shown to vary directly with the free T_4 (FT_4), hence a low FT_4I is generally considered a diagnostic criterion of hypothyroidism (*10*). Basal TSH and TSH response to thyrotropin-releasing hormone (TRH) have been reported to be useful in separating euthyroid, primary hypothyroid, and pituitary/hypothalamic hypothyroid patients (*11*).

We have recently encountered diagnostic problems in many seriously ill patients with low T_4, low-normal or low FT_4I, and normal TSH, in whom pituitary/hypothalamic hypothyroidism had to be seriously considered. The obvious question was whether these patients should be treated with thyroid hormone. We undertook this survey of seriously ill patients to characterize the thyroid profile of the "sick-euthyroid" syndrome, to ascertain the prevalence of this diagnostic problem, and to evaluate the utility of FT_4 determinations in euthyroid and hypothyroid patients with nonthyroidal illnesses (NTI).

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MATERIALS AND METHODS

In our retrospective study we included all intensive care unit (ICU) patients from our hospital, who, during a 6-mo period, had thyroid-function tests performed and had not had known thyroid disease. Serum T_4, T_3, TSH, RT_3U, and FT_4I had been routinely determined. Free T_4 was determined in patients with abnormal serum T_4 for whom frozen serum was available. A prospective series of patients was randomly selected from all noncardiac, seriously ill medical patients. Serum T_4, T_3, TSH, RT_3U, FT_4I, and FT_4 were determined, as was the TSH response to 500 μg of intravenous TRH.

Total T_4, total T_3, RT_3U, and TSH were assayed with Corning radioimmunoassay kits. Elevated TSH levels were confirmed using Abbott materials. The FT_4I was calculated as RT_3U (%) $\times$ T_4 $\div$ 100. FT_4 was assayed with a double-antibody technique (Corning) and in 91% of patients also with an antibody-coated tube technique (Clinical Assays). The Corning FT_4 was corrected for binding-protein alterations as directed by the manufacturer. Normal values for all routine thyroid tests were

TABLE 1. LOW T_4 PATIENTS WITH NTI

	RT_3U*	T_4*	FT_4I*	T_3*	TSH
Normal ranges	30–40%	5.3–11.3 μg/dl	1.5–4.5	69–192 ng/dl	1–10 mIU/ml
Euthyroid					
Low FT_4I (18)	43.7 ± 7.0†,§	2.2 ± 0.3‡,‖	0.9 ± 0.1‡,‖	10.5 ± 3.7‡,‖	3.8 ± 1.9†,‖
Normal FT_4I (24)	41.0 ± 1.0§	4.6 ± 0.1‖	1.9 ± 0.4‖	46.9 ± 7.3§	4.4 ± 2.0‖
Hypothyroid (10)	38.6 ± 1.5	3.3 ± 0.6	1.3 ± 0.2	56.4 ± 16.4	23.4 ± 3.8

* Mean ± s.e.m.
† NS compared with normal FT_4I group.
‡ $P < 0.05$ compared to normal FT_4I group.
‖ $P < 0.05$ compared to hypothyroid group.
§ NS compared to hypothyroid group.

derived from 100 euthyroid ambulatory controls tested by our laboratory. Normal values for FT_4 were derived also from 50 euthyroid ambulatory controls tested by our laboratory. A final diagnosis of hypothyroidism was made upon integrating the clinical findings, the clinical course, and the serum T_4, TSH, and FT_4I, before obtaining special investigative studies (FT_4 and TRH-TSH stimulation test). Patients who were euthyroid clinically, had no clinical evidence of hypothalamic or pituitary dysfunction, and had a normal TSH were classified as euthyroid. Euthyroid patients, except for seven who subsequently died of their primary illness, improved clinically without thyroid-hormone therapy. Hyperthyroidism was diagnosed by clinical examination supported by routine thyroid tests. Retrospective patients (N = 118) and prospective patients (N = 28) were considered together for further analysis. Statistical analysis was performed with the paired Student's t-test.

RESULTS

During the survey of 146 seriously ill patients, three were found to be hyperthyroid, ten hypothyroid, and five unclassifiable. Of the remaining 128 seriously ill, euthyroid patients, 33% had a low T_4. Forty-three percent of the latter patients had a low FT_4I.

Table 1 shows the means of thyroid functions of euthyroid patients with NTI and with a low T_4, subdivided according to low or normal FT_4I. Also included are hypothyroid patients with NTI. In euthyroid patients with a low FT_4I, the mean T_4 and the mean T_3 were significantly lower than in patients with a normal FT_4I. The mean RT_3U appeared higher in those with a low FT_4I than in the normal FT_4I group, but was not significantly so. The mean T_4 and the mean FT_4I in those euthyroid patients with a low FT_4I were significantly lower than in the hypothyroid group.

Table 2 shows the means and ranges of FT_4, as measured by Corning and by Clinical Assays, in our euthyroid and hypothyroid patients with and without NTI. The mean FT_4, as measured by both Corning and Clinical Assays, was not different among any of the groups of euthyroid patients except for those with a low FT_4I, in which Corning FT_4 was significantly lower ($P < 0.05$). However, the FT_4 values of hypothyroid patients with NTI overlapped considerably with those seen in euthyroid patients with NTI. The FT_4 values in hypothyroid patients without NTI were readily separated in most instances from those of euthyroid patients without NTI

TABLE 2. FREE T_4* IN EUTHYROID AND HYPOTHYROID PATIENTS WITH AND WITHOUT NTI

	Corning (ng/dl)	Clinical Assays (ng/dl)
Euthyroid with NTI		
Low FT_4I, low T_4 (18)	1.1 ± 0.1 (0.9–1.5)	1.4 ± 0.2 (0.7–2.4)
Normal FT_4I, low T_4 (24)	1.5 ± 0.1 (1.2–1.9)	1.8 ± 0.1 (1.0–2.2)
Normal FT_4I and T_4 (47)	1.8 ± 0.1 (1.3–2.2)	1.7 ± 0.1 (1.1–2.3)
Hypothyroid with NTI (10)	1.1 ± 0.1 (0.6–1.3)	1.4 ± 0.1 (0.9–2.0)
Euthyroid without NTI (50)	1.7 ± 0.1 (1.0–2.3)	1.6 ± 0.1 (0.9–2.2)
Hypothyroid without NTI (37)	0.6 ± 0.1 (0.3–1.2)	0.5 ± 0.1 (0.2–1.1)

* Mean ± s.e.m. (range).

by both Corning and Clinical Assays.

Overall, FT_4 as measured by Corning and Clinical Assays agreed very well (r = +0.90). The coefficient of correlation (r) between FT_4I values with FT_4 for hypothyroid, hyperthyroid, and euthyroid patients without NTI was +0.88 when measured by Corning and +0.82 by Clinical Assays. There was a poor correlation, however, between FT_4I and FT_4 in patients with NTI, whether measured by Corning (r = +0.42) or by Clinical Assays (r = +0.34).

The maximum TSH response to TRH in euthyroid patients with NTI ranged from 0 to 28 mIU TSH with three of 16 being less than the age- and sex-corrected normal range reported by Utiger (*11*). The mean baseline TSH in those three euthyroid patients with a blunted response was 3.1 ± 0.6 mIU/ml. This was not different from the mean baseline TSH (4.6 ± 1.6 mIU/ml) of those 13 euthyroid patients with a normal response. In only one of three hypothyroid patients with NTI was the TSH response to TRH above the reported euthyroid range. The baseline TSHs in those two hypothyroid patients with euthyroid responses were 11.1 and 17.9 mIU/ml, compared with a baseline TSH of 12.3 mIU/ml in the patient with a supranormal response.

The two most common nonthyroidal illnesses in our series were Laennec's cirrhosis (42%) and acute or chronic cardiopulmonary disease (40%). Other major diagnoses included alcoholism, malnutrition, renal failure, and diabetic ketoacidosis. There was no diagnostic difference between euthyroid patients with low FT_4I or normal FT_4I. However, those patients with low FT_4I were generally the most ill.

DISCUSSION

Thirty-three percent of our seriously ill patients had a low T_4, and 43% of these had a low FT_4I. Our findings indicate that a low FT_4I occurs more often than has been suspected, and poses a diagnostic dilemma. Indeed, since the submission of this paper, additional confirmation of this dilemma has appeared in the literature (*12*). The combination of low T_4 and low FT_4I in the absence of elevated TSH raises the possibility of pituitary/hypothalamic hypothyroidism. The use of thyroid hormone in these patients, if they were indeed hypothyroid, could be potentially lifesaving. However, administration of thyroid hormone to euthyroid patients, particularly those with heart disease, could be detrimental.

The extremely low levels of T_4 seen in those patients with a low FT_4I were apparently too low to be arithmetically corrected by the RT_3U. These patients would have been incorrectly classified as hypothyroid if the FT_4I had been used diagnostically.

The very low T_4 levels in our patients may have been caused by decreased thyroid-binding proteins (*2,3,13,14*). Another possibility is the in vivo displacement of T_4 from binding proteins by various substances (*12,15*). Whatever the mechanism, it is obvious that the T_4 and FT_4I alone can not be relied upon in seriously ill patients for diagnosing hypothyroidism.

In our search for the cause of hypothyroidism, the TSH response to TRH was of little diagnostic value in our seriously ill patients. A "normal" TRH-TSH response has been described in anorexia nervosa (*4*), long-term fasting (*5*), and chronic liver disease (*16*). Other studies have shown a blunted TRH-TSH response in chronic renal failure (*6*), acute starvation (*7,17*) and cirrhosis (*8*). In agreement with these latter reports, our data suggest that the occurrence of a less-than-expected TRH-TSH response may be seen in euthyroid patients with NTI. However, we also observed a less-than-expected TRH-TSH response in hypothyroid patients with NTI, hence this test may not be helpful in diagnosing hypothyroidism in patients with NTI. An elevated baseline TSH was helpful in diagnosing hypothyroidism. In the absence of an elevated TSH, however, we have no evidence that we can exclude primary, secondary, or tertiary hypothyroidism.

FT_4 has been shown to correlate well with FT_4I under various clinical conditions (*10*) and to differentiate euthyroid, hypothyroid, and hyperthyroid patients. We confirmed these results only in patients without NTI. In our patients with NTI, FT_4 correlated poorly with FT_4I. We have no good explanation for the significantly lower mean Corning FT_4 seen in euthyroid patients with NTI and low FT_4I, when compared with euthyroid patients with normal FT_4I, with or without NTI.

Although FT_4 was able to distinguish hypothyroidism from euthyroidism in patients without NTI, the FT_4 assay could not distinguish the hypothyroid from the euthyroid state in patients with NTI. It was possible to obtain either a normal or low FT_4 in a hypothyroid patient with NTI. This problem was seen with both Corning and Clinical Assays materials. It is likely that a problem would occur if equilibrium dialysis were used to measure FT_4, because it has been demonstrated previously that euthyroid patients with NTI may also have high FT_4 levels by this method (*2,3,5,12–14*). It is possible that the same phenomenon may explain our observed higher FT_4 levels in hypothyroid patients with NTI when compared with those hypothyroid patients without NTI.

Our results suggest that the free T_4 determination, by either Corning or Clinical Assays, may be useful in diagnosing hypothyroidism only if the FT_4 is low and the patient does not have a readily identifiable nonthyroidal illness. As is summarized in Fig. 1, the occurrence of a normal FT_4I or a normal FT_4 in sick patients, and rarely in well patients, does not appear to rule out hypothyroidism. We did not observe an elevated FT_4 in any of our hypothyroid patients. However, Fig. 1 shows the entire full range of results, but does not convey the

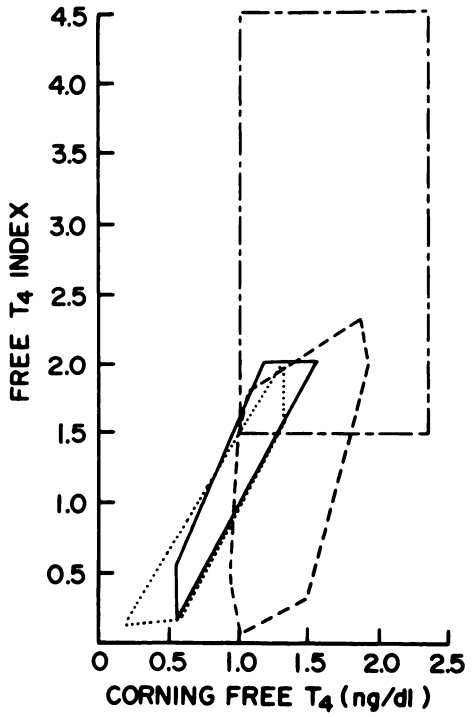

FIG. 1. Ranges of free T_4 and free T_4 index in euthyroid and hypothyroid patients with and without NTI. Diagram incorporates the *range*, for all patients in each set of patients, for combined plotting of free T_4 and free T_4 index. Although overlap between various sets is well demonstrated by this technique, approximate number of patients in overlapping areas is better indicated by Table 2. For example, only 3 of 37 hypothyroid patients without NTI had normal FT_4 levels, whereas 6 of 10 hypothyroid patients with NTI had normal FT_4 levels. - - - Euthyroid patients with low T_4 and NTI. —— Normal range. ····· Hypothyroid patients without NTI. —— Hypothyroid patients with NTI.

numbers of patients within overlapping groups. The latter information is given in statistical terms in Tables 1 and 2. Low reverse T_3 levels have been suggested as helpful in diagnostic problems of hypothyroidism (*12*). However, our preliminary data (unpublished) do not support a diagnostic role for reverse T_3 in our hypothyroid patients with NTI.

Our patients with NTI, low T_4, low FT_4I, and normal TSH are regarded as euthyroid because of their clinical features and generally favorable course without thyroid-hormone administration. The FT_4 in these patients does not appear to be a valid way to confirm their apparent euthyroid status.

In conclusion, low T_4, frequently accompanied by a low FT_4 I, occurs commonly in seriously ill patients. FT_4 determinations by Corning or by Clinical Assays, although useful in the diagnosis of hypothyroidism without NTI, cannot be relied upon to distinguish hypothyroidism in the presence of NTI.

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