Variable Thyrotropin Response to Thyrotropin-releasing Hormone after Small Decreases in Plasma Free Thyroid Hormone Concentrations in Patients with Nonthyroidal Diseases

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ABSTRACT Although a normal serum thyrotropin (TSH) concentration is generally considered to be the most important finding to support the clinical impression of euthyroidism in patients with nonthyroidal diseases and decreased serum triiodothyronine (T₃), the regulation of TSH secretion in sick patients has not been studied previously. Accordingly, we studied the regulation of TSH secretion in 23 patients with nonthyroidal diseases; 15 of the patients had decreased serum T₃. TSH regulation was studied by measuring the TSH response to injected thyrotropin-releasing hormone (TRH) before and after effecting a small decrease in serum thyroxine (T₄) and/or T₃ concentrations by iodide treatment, 262 mg daily for 10 d. Iodide treatment significantly decreased (>10%) the free T₄ index (FT₄-I) and/or free T₃ index (FT₃-I) in all patients. FT₄-I values were correlated (0.611, P < 0.001), with free T₄ concentration determined by equilibrium dialysis. Despite decreased FT₄-I and/or FT₃-I after iodide treatment in all patients, the TSH response to TRH after iodide treatment was augmented in only 8 of 15 patients who had decreased serum T₃ (group 1) and in only 5 of 8 patients who had a normal serum T₃. Mean base-line TSH concentration was increased significantly (P < 0.05) from 0.9±0.1 to 1.5±0.3 μU/ml in group 1 only. Comparison of the mean TSH response to TRH showed that there was no significant difference between groups 1 and 2. Moreover, no significant difference in thyroidal parameters was observed between patients who had augmented TSH response to TRH after iodides and those who had either similar or decreased TSH response irrespective of the initial serum T₃. These studies show that an augmented TSH response to TRH in response to a small reduction in serum T₄ and T₃ concentration occurred in only 57% of the entire group of patients with nonthyroidal diseases and that the presence or absence of a normal TSH response to this stimulus did not seem to be related to the base-line serum T₃ concentration. Because an increase in serum TSH in response to decreased serum T₄ and T₃ did not occur in about one-half of patients with nonthyroidal diseases, normal serum TSH may not be a reliable index of the euthyroid state in these patients.

INTRODUCTION
Changes occur frequently in peripheral thyroid hormone metabolism and in results of tests of thyroid function in patients with acute and chronic nonthyroidal diseases (1–12). Characteristic laboratory data in such patients include normal or slightly decreased serum thyroxine (T₄)¹ concentration and decreased serum T₄ binding. Free T₄ concentration is within the normal range or increased. Decreased serum triiodothyronine (T₃) concentration is found in most patients, and although serum T₃ binding is decreased, free T₃ concentration is generally decreased as well. Inasmuch as it is probable that T₃ affects most of the biological activities of the thyroid hormones in human subjects (13–15), these measurements in sick patients could readily be interpreted as consistent with hypothyroidism. It is interesting, therefore, that on the basis of

¹Abbreviations used in this paper: FT₄-I, free triiodothyronine index; FT₃-I, free thyroxine index; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

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clinical evaluation, most patients with nonthyroidal diseases are considered euthyroid. The latter interpretation is supported by the consistent finding that serum thyrotropin (TSH) concentration remains within the normal range in most patients. In healthy euthyroid subjects, TSH secretion is very closely regulated by serum thyroid hormone concentrations. Even a small decrease in serum T₄ and T₃ stimulates TSH secretion and increases serum TSH concentration (16, 17). Indeed, an increase in serum TSH is generally considered to be the most sensitive indicator of hypothyroidism due to thyroid disease (18, 19). Although normal serum TSH concentration provides the principal laboratory evidence to support the diagnosis of euthyroidism in these patients, the regulation of TSH secretion by thyroid hormones in patients with nonthyroidal diseases has not been examined. The possibility exists, for example, that a decrease in thyroid hormone concentrations in these patients does not increase TSH secretion and serum TSH concentration. If so, sick patients with decreased serum T₉ might be hypothyroid despite normal serum TSH concentrations.

METHODS

Studies of TSH secretion were carried out in 12 male and 11 female patients hospitalized with nonthyroidal diseases at Montefiore Hospital and Medical Center or in Beth Abraham Hospital, Bronx, New York (Table I). Most patients suffered from neoplastic diseases, but several had cerebrovascular or hepatic disorders. Each subject was informed of the nature of the study and gave informed and written consent according to institutional guidelines. Patients with a history of thyroid disorders or medications were excluded from the study, as were patients with thyroid enlargement, renal failure, or those treated with corticosteroid or estrogenic medications. Patients who were severely malnourished or

<p>| TABLE I |
| Effect of Iodide Administration on the Plasma Concentration of T₄, T₃, and TSH in Patients with Nonthyroidal Diseases |</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>T₄</th>
<th>FT₄</th>
<th>T₃</th>
<th>FT₃</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yr</td>
<td>μg/dl</td>
<td></td>
<td>ng/dl</td>
<td>μU/ml</td>
</tr>
<tr>
<td>Group 1</td>
<td>1</td>
<td>R.A. 81 F</td>
<td>Carcinoma of ovary</td>
<td>10.2 10.9</td>
<td>10.2 8.7</td>
</tr>
<tr>
<td>Decreased</td>
<td>2</td>
<td>C.K. 75 M</td>
<td>Carcinoma of lung</td>
<td>9.0 7.9</td>
<td>8.8 6.9</td>
</tr>
<tr>
<td>serum T₃</td>
<td>3</td>
<td>M.K. 76 F</td>
<td>Cerebrovascular accident</td>
<td>7.6 6.2</td>
<td>8.0 5.7</td>
</tr>
<tr>
<td>4</td>
<td>J.R. 78 F</td>
<td>Cerebrovascular accident</td>
<td>9.0 7.5</td>
<td>6.1 5.5</td>
<td>59 71</td>
</tr>
<tr>
<td>Group 2</td>
<td>5</td>
<td>E.C. 79 F</td>
<td>Carcinoma of breast</td>
<td>6.0 7.0</td>
<td>12.8 9.5</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>C.D. 62 F</td>
<td>Carcinoma of breast</td>
<td>9.7 8.1</td>
<td>8.5 6.0</td>
</tr>
<tr>
<td>serum T₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M.S. 69 F</td>
<td>Carcinoma of breast</td>
<td>7.1 6.5</td>
<td>3.4 2.9</td>
<td>97 97</td>
</tr>
<tr>
<td>Decreased</td>
<td>8</td>
<td>L.L. 72 F</td>
<td>Cerebrovascular accident</td>
<td>8.3 8.3</td>
<td>9.7 5.9</td>
</tr>
<tr>
<td>9</td>
<td>R.S. 76 F</td>
<td>Fever unknown origin</td>
<td>9.0 6.8</td>
<td>6.4 5.4</td>
<td>89 65</td>
</tr>
<tr>
<td>10</td>
<td>G.G. 58 M</td>
<td>Carcinoma of lung</td>
<td>7.3 6.5</td>
<td>7.0 4.5</td>
<td>49 55</td>
</tr>
<tr>
<td>11</td>
<td>J.K. 70 M</td>
<td>Carcinoma of lung</td>
<td>6.8 8.6</td>
<td>8.1 7.5</td>
<td>66 67</td>
</tr>
<tr>
<td>12</td>
<td>H.K. 76 M</td>
<td>Diabetes mellitus</td>
<td>5.0 3.7</td>
<td>4.5 4.2</td>
<td>84 75</td>
</tr>
<tr>
<td>13</td>
<td>T.A. 27 M</td>
<td>Carcinoma of lung</td>
<td>6.0 5.5</td>
<td>9.9 6.5</td>
<td>47 56</td>
</tr>
<tr>
<td>14</td>
<td>D.W. 50 M</td>
<td>Carcinoma of esophagus</td>
<td>9.1 6.4</td>
<td>12.6 7.1</td>
<td>48 40</td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>C.G. 70 M</td>
<td>Carcinoma of mandible</td>
<td>10.6 6.3</td>
<td>9.4 9.2</td>
</tr>
<tr>
<td>67.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM (±)</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.025</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Group 1 vs. Group 2 | P | <0.05 | NS | NS | <0.001 | <0.001 | <0.001 | NS | NS |

The statistical analysis was performed by the paired t test. The table values are the averages of two or three determinations during the control period (C) or after iodide treatment (I). The limit of detection for serum TSH is 0.6 μU/ml for most assays. All TSH determinations in the undetectable range were assigned a value of 0.6 μU/ml to facilitate statistical analysis. Statistical analysis was done by paired t tests for comparisons between the control period and after iodide treatment. Two-tailed (independent) t tests were done to compare the mean values for each parameter of group 1 with those of group 2.
who appeared moribund were not selected for this study. Two patients, 10 and 11, were moderately cachetic at the initiation of the study and died 2 mo and 2 wk, respectively, after the study was completed. Patient 21 was placed on cancer chemotherapy during the study. All other patients were stable without specific new treatment during the study. Assessment of patient status 4 mo after the study was completed revealed that patients 1 and 20 died 2 and 4 mo, respectively, after the study was completed. The remaining 19 patients were being monitored by the oncology clinic or were permanent residents of Beth Abraham Hospital for their chronic illness.

Studies of TSH secretion in response to small decreases in plasma thyroid hormone concentrations were carried out according to the general procedures described by Vagenakis et al. (16) and Saberi and Utiger (17). Serum was obtained for measurement of thyroid hormone concentration, binding, and TSH concentration on 2 control days. On the 2nd control day, blood was obtained at 10, 0, 10, 20, 30, 60, and 120 min after an intravenous bolus injection of 500 μg thyrotropin-releasing hormone (TRH) (Thyphrinone, Abbott Diagnostics, Diagnostic Products, North Chicago, Ill.) as previously described (20). All patients were then treated with iodides, 262 mg 1/d, in the form of supersaturated potassium iodide, 8 drops (1 drop = 0.05 ml) per os twice each day for 10 d. Blood samples for hormone measurements were obtained on the 5th, 7th, and 9th days of iodide treatment. On the 10th day, two samples were obtained and a second TRH test was performed. Serum was obtained rapidly by centrifugation and stored frozen at -20°C until required for hormone assays. Duplicate measurements of all samples for each patient were carried out in the same assay.

Hormone concentrations were measured by radioimmunoassay. Serum T4 concentration was measured by the Corning method (Immophase, Corning Medical, Corning Glassworks, Medfield, Mass.); the normal range was 4.5-12.0 μg/dl. Serum T3 was measured as previously described (21); the normal range was 90-180 ng/dl. Serum TSH concentration was measured by modifications of the double-antibody technique of Odell et al. (22), as described previously (3, 20). Human TSH and TSH antisera were gifts from the National Pituitary Agency of the National Institutes of Health, and human TSH Standard 68/38 was a gift of the Division of Biological Standards, National Institutes of Medical Research, Mill Hill, London. The limit of detectability in the TSH assay was generally 0.6 μU/ml, and the normal range was <0.6-5.0 μU/ml. At the present time, ~50% of subjects without thyroid disease have undetectable TSH in our laboratory. For the three hormone measurements, the intraassay coefficients of variation were 5.7% for T4, 6.3% for T3, and 11.3% for TSH.

The intensity of hormone binding by serum proteins was determined by the Res-Q-Mat T3 Micro Test (Mallinkrodt Inc., St. Louis, Mo.). Free/bound ratios were calculated and corrected for interassay variability using the free/bound ratios for two control pools of serum that were measured concurrently with the unknowns, as previously described (23). The corrected free/bound ratio was divided by the mean free/bound ratio for control patients to yield a binding index, and the product of the binding index and the T3, T4, or T3 concentration was defined as the free T3 index (FT3-I) or free T4 index (FT4-I). Plasma free T3 concentration was also determined by equilibrium dialysis (BioScience Laboratories, Van Nuys, Calif.); normal range was 1.0-2.3 ng/dl in a single plasma sample obtained from each patient during the control period.

Patients were grouped according to their base-line FT3-I and response to TRH as outlined in Table I. Data for the various groups were expressed as a mean±SEM. Statistical analysis was by two-tailed t test or by t tests of paired observations when appropriate (24).

RESULTS
The clinical and laboratory data in the control period and after iodide therapy are listed in Table I. The age range of the patients was between 27 and 82 yr and the mean age of the entire group was 65.0 yr. Despite the fact that all patients appeared euthyroid clinically, serum T3 or FT3-I were decreased to values below the normal range in 15 of the 23 patients (Table I), patients 1-15 (group 1). Although the range in age was wide, the mean age of patients with decreased T3, 67.9±4.6 yr, was significantly greater than the mean age of the eight patients with normal serum T3 (group 2), 59.5±7.2 yr (P < 0.05). None of the patients studied was moribund or severely malnourished as judged by clinical evaluation. Four patients died after the study was completed: patient 11, after 2 wk; patients 1 and 10, after 2 mo; and patient 20, after 4 mo. Aside from the decrease in mean T3 and FT3-I in patients in group 1, no significant difference in any of the other parameters of thyroid function was observed between group 1 and group 2 (Table I). Free T4 concentration determined by equilibrium dialysis was correlated with FT4-I measurements, r = 0.611, P < 0.001. The mean free T4 concentration of group 1, 2.0±0.4 ng/dl, was not significantly different from group 2, 2.7±0.4 ng/dl. The TSH response to TRH during the control period was also similar (Fig. 1, filled symbols). A significant difference between the groups was noted only at 10 min after TRH injection. The mean serum TSH at that time for group 2, 5.1±1.3 μU/ml, was significantly greater than that of group 1, 2.2±0.4 μU/ml, P < 0.025. Moreover, there was no difference in the mean integrated TSH response to TRH between the two groups.

Treatment with iodide decreased mean serum T4 in all groups, but this change was significant statistically for group 1 only (Table I). Similarly, mean serum FT4-I decreased significantly after iodide therapy only in group 1. Mean serum T3 concentration and FT3-I decreased after iodide treatment in most patients and a significant decrease in mean serum T3 and FT3-I was noted in both groups after iodide treatment. Treatment with iodide resulted in a 10% or greater decrease either in FT3-I and/or FT3-I in all patients (Table I).

A small increase in mean base-line serum TSH was observed after iodide treatment in both groups, but the increase was significant statistically (P < 0.05) only in group 1 (Table I). The TSH response to TRH before and after iodide treatment is shown in Fig. 1. As indicated in the lower panel for the patients with normal serum T3 (group 2), the TSH response to TRH after treatment was not different statistically from the response before treatment. Similar results.
were obtained for the group with decreased serum T₃ (Fig. 1, upper panel) although the base-line and 10-min mean value for serum TSH was minimally but significantly increased after iodide treatment. There was no difference in the mean integrated TSH response to TRH after iodide treatment for either group.

Examination of individual patients’ responses to TRH showed that 8 of the 15 patients in group 1 and 5 of the 8 patients in group 2 had the anticipated increase in TSH response to TRH after iodide treatment. To determine whether patients with an appropriate increase in TSH response to TRH after treatment could be identified on the basis of other thyroidal parameters, we analyzed statistically the parameters listed in Table 1 for subgroups within groups 1 and 2. No significant differences in mean serum T₄, FT₄-I, T₃, or FT₃-I were evident between groups of patients who exhibited an augmented TSH response to TRH after iodide treatment and those who had either the same or a decreased TSH response to TRH after treatment in groups 1 and 2. Our results do not provide a guide for selection of patients who respond appropriately to iodide treatment.

DISCUSSION

Our studies suggest that there is abnormal regulation of TSH secretion in many patients with nonthyroidal diseases and that a normal TSH concentration may not be a valid index of the euthyroid state, as considered previously. Despite the decrease in serum T₃ and FT₃-I, and variable changes in serum T₄ and FT₄-I, serum TSH and the TSH response to TRH have been normal in most reports of patients with nonthyroidal diseases (1–12). However, Bermudez et al. (3) showed that a small increase in the TSH response to TRH occurred in sick patients with decreased serum T₃ as compared with similar patients with serum T₃ in the normal range; and Burroughs et al. (11) reported that the TSH response to TRH was blunted in about one-third of euthyroid geriatric patients with a variety of nonthyroidal diseases. A principal question raised in all of these studies is whether or not patients with nonthyroidal diseases and decreased serum T₃ are euthyroid. Euthyroidism could be sustained (a) by downward regulation of the thyrotroph set point for T₃ so that, despite decreased serum and pituitary T₃, TSH secretion remains normal; (b) by an increase in the intrapituitary conversion of T₄ to T₃, resulting in normal pituitary T₃ despite decreased serum T₃ concentration; or (c) by a combination of these changes.

Irrespective of the underlying biological mechanisms, it seems clear that if euthyroidism is maintained in these patients, TSH secretion should be responsive to small changes in serum thyroid hormone concentrations in a fashion similar to healthy controls. In normal subjects, Vagenakis et al. (16) and Saberi and Utiger (17) have shown that a small reduction in serum T₄ and T₃ concentration after iodide treatment augments basal and TRH-induced TSH release. Conversely, a small elevation of T₄ and T₃ concentrations, with values still within the normal range, decreases the TSH response to TRH (25). The close regulation of TSH secretion by thyroid hormones also occurs in some patients with decreased serum T₃. In normal subjects with decreased serum T₃ after a short-term fast, Gardner et al. (26) showed that TSH secretion is augmented after iodide treatment and suppressed after T₃ supplementation in a manner similar to controls. Because these changes in TSH secretion were demonstrated with T₃ concentrations within the normal range (in the case of T₃ supplementation) or with only a small decrease in serum T₃ below that already present in the fasted state, the authors suggested that the set point for TSH secretion was decreased in these patients and that, even at the lower set point, TSH secretion was normally sensitive to small changes in thyroid hormone concentrations.

Although we did not test the sensitivity of TSH secretion to suppression by administered thyroid hormones, 10 of 23 patients studied in this investigation failed to augment TSH secretion in response to a small decrease in FT₃-I and FT₄-I induced by iodide treatment. Because determination of thyroidal state was a principal focus of these studies, we grouped our patients according to the serum FT₄-I concentration. For groups of
patients with either normal or decreased serum $T_3$, the mean TSH response to TRH after iodide treatment was not significantly different from the TSH response before iodides. 53% of patients with decreased $FT_3$-I and 63% of patients with normal $FT_3$-I failed to augment TSH secretion after iodide. Thus, on the basis of these studies, abnormal TSH regulation seemed to be unrelated to serum $T_3$ concentration in patients with nonthyroidal disease. Those patients who did not augment TSH secretion after iodide consisted of eight males and two females. Although the groups are small, the disproportionate sex distribution suggests that abnormal regulation of TSH secretion may be more common in sick male than in sick female patients. Although TSH responsiveness after iodide has not been studied as a function of age or sex, published reports indicate that the TSH response to TRH may be decreased in elderly males (27). In our studies, the TSH responders and nonresponders after iodide could not be distinguished on the basis of age, serum $T_3$, or $FT_3$-I concentrations, or on our clinical impression of the severity of the illness. Decreased serum TSH concentration and TSH response to TRH have been reported in some studies of short-term fasting (28, 29) but these findings do not appear to be consistent, as pointed out by Gardner et al. (26). The inability of some patients with nonthyroidal diseases to augment TSH secretion in response to decreased serum $FT_3$-I and $FT_3$-I after iodide suggests altered regulation of TSH secretion, and raises the possibility that such patients might not be able to increase TSH secretion in response to decreased serum thyroid hormone concentrations due to thyroid failure. Thus, the lack of an increase in serum TSH concentration may not be taken as clear-cut evidence for euthyroidism in all patients with nonthyroidal diseases who have decreased serum $T_3$.

The results of our study complicate the interpretation of the already confusing laboratory findings in patients with nonthyroidal diseases. Earlier studies indicated that although serum protein-bound iodine was decreased, serum free $T_4$ concentration was either normal or increased, and the free $T_4$ concentration was considered to support the interpretation of euthyroidism. The more recent finding of a decreased serum $T_3$ in sick patients again raises the possibility of underlying hypothyroidism in these patients, but a normal serum TSH concentration has been interpreted to indicate that the pituitary at least is euthyroid. Our studies suggest that the normal serum TSH may not be a reliable index for the euthyroid state in all patients. An additional feature that warrants consideration is the fact that the diagnosis of primary hypothyroidism is occasionally made in patients who also have nonthyroidal diseases. Serum TSH concentration is appropriately increased in such patients, although it may be argued that the magnitude of the serum TSH might be greater in the absence of the nonthyroidal disease. Thus it is likely that most patients with nonthyroidal diseases who also have significant primary hypothyroidism would have sufficient symptoms and signs of hypothyroidism to suggest the diagnosis, and that the diagnosis would be supported by an elevation in serum TSH. Until a biological measure of thyroidal activity is developed that is not influenced by other factors that occur in nonthyroidal diseases, it would still appear prudent to rely on clinical evaluation as well as an increase in serum TSH to establish a diagnosis of primary hypothyroidism in these patients.

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