Diagnostic Performance of Sensitive Measurements of Serum Thyrotropin during Severe Nonthyroidal Illness: Their Role in the Diagnosis of Hyperthyroidism

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Serum thyrotropin (TSH) concentrations were measured serially in 14 heart-transplant recipients (group 1) and 21 patients undergoing coronary artery bypass surgery (group 2), all without thyroid disease, and randomly in 158 patients hospitalized for various other nonthyroidal illnesses, including 144 judged euthyroid (group 3), six with increased FT4 and (or) T3 (group 4), and eight classified hypothyroid by conventional tests. The serial measurements indicated profound fluctuations. In group 1, TSH was subnormal in 21% of studies and increased in 10%. In group 2, corresponding abnormalities were found in 7% and 13%, respectively. Transiently low or high TSH tended to be associated with normal free thyroxin (FT4), prolonged subnormal TSH (>1 week) with subnormal FT4. By contrast, subnormal TSH plus elevated FT4, or high TSH plus low FT4, were not encountered, making it unlikely that they occur by chance in severely ill patients who are not also hyper- or hypothyroid. In group 3, a suppressed TSH (plus borderline high FT4, T3/FT3) identified four cases of subclinical hyperthyroidism; however, another 11% of patients had subnormal and 10% had above-normal TSH, paired with normal FT4 and no evidence of thyroid disease. In group 4, suppressed TSH confirmed hyperthyroidism in five of six patients, and all in group 5 had increased TSH. We conclude that, in the hospital setting, sensitive TSH measurement can help to detect or confirm mild hyperthyroidism, but the positive predictive value of TSH alone may be as low as 35%.

In outpatients, it is now fairly well established that the new "sensitive" immunometric assays for thyrotropin (TSH) can discriminate between normal concentrations in serum of euthyroid individuals and the suppressed concentrations typical of hyperthyroidism, if the assays meet certain criteria for analytical performance (I, 2). Many studies have shown that, in patients without systemic disease, basal TSH concentrations accurately predict the response to thyrotropin-releasing hormone (TRH) and are clinically helpful, not only in confirming overt hyperthyroidism but also in detecting mild or borderline (subclinical) hyperthyroidism (2-5). (It is undisputed that TSH is of diagnostic value in hypothyroidism.)

Consequently, several investigators have advocated this type of TSH measurement as an initial screening test for evaluation of thyroid function (6-11). It is, however, not yet entirely clear whether this strategy is equally applicable to patients hospitalized with various severe nonthyroidal illnesses (NTI).

TSH concentrations in sera of patients with NTI, when measured by conventional assays, have generally been within the normal reference interval for healthy, euthyroid individuals. In the past, a normal TSH concentration was considered to be the best single test to distinguish severely ill patients, with low circulating thyroid hormone concentrations (euthyroid sick syndrome), from hypothyroid patients.

Wehmann et al. (12), among the first to use sensitive TSH measurements in critically ill patients, observed a drastic fall in serum TSH after bone marrow transplantation, a procedure that often results in subnormal TSH concentrations. By contrast, other groups have reported abnormally high TSH during severe illness (13-15).

These data raise the question as to how reliable sensitive TSH measurements are in hospitalized patients with severe NTI. Surveys have shown that many hospitalized patients undergo evaluation of thyroid function, which underscores the clinical relevance of such a question. For example, in our own laboratory, 32% of all thyroid tests requested are for hospitalized patients.

The aim of the present study was several fold: (a) to investigate further the extent to which serum TSH is affected by major surgery and (or) severe systemic illness; (b) to assess the clinical utility of sensitive TSH measurements in the hospital setting, particularly in the diagnosis of mild hyperthyroidism; (c) to look at the relationship between FT4 and TSH concentrations in serum during serious illness; and (d) to try to establish some guidelines for the interpretation of disparate results for TSH and FT4.

Subjects and Methods

In the first part of this study we followed serum TSH prospectively in two groups of patients with heart disease who underwent major cardiac surgery: Group 1, 14 heart-transplant recipients (11 male, three female; age 43 ± 9 y) and group 2, 21 patients who underwent coronary artery bypass graft surgery or cardiac valve replacement (17 male, four female; age 57 ± 9 y). None of these patients had a history of thyroid dysfunction or had received treatment with thyroid or antithyroid medications. There was no thymomegaly or any clinical features that might have suggested thyroid disease. Blood specimens for serial hormone measurements were obtained on the day before and at intervals after surgery. Patients in group 1 were tested typically twice in the first postoperative week and then once per week. Patients in group 2 were tested daily the first week and twice in the second week.

In the second part of this investigation, we performed sensitive TSH measurements retrospectively on consecutive hospitalized patients for whom routine thyroid-function tests had been ordered. After reviewing the medical charts, the following patients were excluded from the study, to facilitate the interpretation of results: (a) patients who had a prior record of thyroid disease and (or) had been on any

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4 Nonstandard abbreviations: TSH, thyrotropin (thyroid-stimulating hormone); NTI, nonthyroidal illness; TRH, thyroliberin (thyrotropin-releasing hormone); FT4, free thyroxin; T4, total thyroxin; T3, total 3,3',5-triiodothyronine; and FT3, free T3.

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thyroid medication, (b) patients with psychiatric disorders, and (c) pregnant women. At our institution, approximately 7% of all hospital admissions have at least one thyroid-function test ordered routinely, and the 158 patients finally selected for the study represented approximately 5% of all patients hospitalized during the period of recruitment.

The selected patients (59 male, 99 female; age 59 ± 17 y) included 32 (18%) in the intensive-care unit. A relatively large percentage of patients (35%) had cardiac or cardiovascular disease, frequently with arrhythmias; the rest suffered from a wide variety of other NTI. None of them was overtly hypo- or hyperthyroid. Based on the results of routine free thyroxin (FT4), total 3,3',5-triodothyronine (T3), and TSH measurements by conventional RIA, the selected patients were subdivided into three groups: Group 3, 144 patients classified clinically and biochemically as probably euthyroid. The vast majority of them had FT4 and TSH concentrations (by RIA) within normal limits, as will be described in detail below, but many had subnormal values for total thyroxin (T4) and (or) subnormal values for T3 (Table 1 below). Group 4, six patients who had an abnormally high value for FT4 or T3 and, thus, by conventional biochemical criteria were suspected of being mildly hyperthyroid, although there was little or no clinical evidence to support it. Group 5, eight patients who were biochemically hypothyroid on the basis of either a subnormal FT4 plus increased TSH of >10, or only an increased TSH of >20 milli.int. units/L. In groups 3–5 we used for the sensitive TSH measurement one specimen selected from each patient without conscious bias, as submitted for the routine thyroid evaluation.

In groups 1 and 2, TSH was measured by a two-step immunoassay using a commercial kit for FT3 from Abbott Laboratories (normal range 0.4–3.7 milli-int. units/L) (4) and most of the results were confirmed by an enzymeimmunometric assay from Abbott Laboratories (normal range 0.4–6.2 milli-int. units/L) (16). There was an excellent correlation between TSH results by the two assays, and in groups 3–5 only the latter assay was used. The performance characteristics for both the Hybritech assay (4) and the Abbott assay (1) have been described previously. All values of <0.4 milli-int. unit/L stated here refer to the Abbott assay.

Other thyroid-function tests were performed as described previously (4). Free T3 (FT3) was measured in all patients with subnormal TSH with a kit for FT3 ("Cost-A-Count," Diagnostica Product Corp., normal range 13–36 ng/L), which we found to be least affected by variations in albumin concentrations when compared with other clinical methods.

Statistical analysis: Preoperative results were compared to controls by unpaired Student's t-test. In the case of TSH results, log TSH was used to fulfill the requirement of a normal distribution. Postoperative results were compared to the corresponding preoperative values by the paired t-test. All P values refer to the area in two tails.

Results

Sequential Sensitive TSH Measurements in Patients Undergoing Cardiac Transplantation or Coronary Artery Bypass Graft Surgery (Groups 1 and 2, Figures 1A, 1B, and 2)

At the outset, all patients in group 2 had values for serum TSH within normal limits, and the mean TSH concentration was similar to that in healthy controls. In group 1, the presurgery mean TSH was significantly higher than in controls. (Five patients had a slightly increased TSH of 6.2–12, one had a TSH of 18 milli-int. units/L.)

Postoperatively, serum TSH fell sharply in both groups when compared to preoperative values. In group 1 significantly lower TSH concentrations were found at four intervals of sampling (days 4–7, 8–14, 15–21, and 21–28) with the nadir during days 8–14. In group 2, with daily sampling, the decline in TSH was statistically significant on days 1 and 2, and the nadir was seen already on the second day.

Two heart-transplant recipients who started out with a somewhat increased TSH (Figure 1B) even had intermittently subnormal TSH after surgery. In one additional patient, with a clearly abnormal basal TSH of 30 milli-int. units/L and a history of head and neck irradiation (excluded from statistical analysis and graphs), the TSH concentration declined after surgery to concentrations well within the normal reference interval (<3.2 milli-int. units/L), thus masking a thyroid insufficiency.

After the initial postoperative decline, serum TSH tended to increase again as the patients' clinical status improved, but continued to vary strongly in individual patients (Figures 1 and 3). The majority of the patients had typically only transiently subnormal TSH concentrations, but there were three patients in whom TSH remained subnormal for a prolonged period (longer than one week), while their clinical course worsened. All three (two in group 1, one in group 2) died subsequently. At discharge, mean TSH was lower than initially in group 1, and similar to controls in both groups.

Overall, in group 1, 43% of the patients had a subnormal TSH value at least once after surgery and, conversely, 21% had a mildly increased TSH. In group 2, the corresponding percentages were 24% and 43%, respectively. In terms of all TSH studies, 21% were low and 10% were high in group 1, and 7% were low and 13% were high in group 2. The magnitude of the postoperative intradividual variations was such that TSH frequently exceeded the normal range on the low as well as on the high side (Figures 1 and 3).

Relationship between TSH and Free/Total Thyroid Hormone Concentrations in Groups 1 and 2

Mean pre-surgery FT4, total T4, and T3 concentrations in both groups were similar to those in healthy controls. Postoperatively, a large number of patients had subnormal total T4 and (or) total T3 (Table 1), and both mean total T3 and total T4 were significantly lower than preoperatively for the duration of four weeks in group 1 and during two days in group 2, largely in parallel with the decline in TSH concentrations.

In contrast, mean postoperative FT4 values were comparable with those before surgery at various time intervals. The only exception was a lower mean FT4 in group 1 between the eighth and 14th day, which reached barely

Table 1. Prevalence of Abnormal Values for Total T4 and Total T3 in Groups 1–3

<table>
<thead>
<tr>
<th>Group</th>
<th>Pts (Stds)</th>
<th>% patients (% studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>T4</td>
</tr>
<tr>
<td>1. Transplant</td>
<td>14 (70)</td>
<td>57</td>
</tr>
<tr>
<td>2. CAGB</td>
<td>21 (109)</td>
<td>33</td>
</tr>
<tr>
<td>3. Misc. NTIs</td>
<td>(a) ICU</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(b) Ward</td>
<td>114</td>
</tr>
</tbody>
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CABG, coronary artery bypass graft; ICU, intensive-care unit.

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Fig. 1. Intraindividual variations in serum TSH concentrations after heart transplantation (group 1): comparison with corresponding fluctuations in FT4 and T4

A: Patients with a normal value for TSH preoperatively; B: patients with a slightly high initial TSH value. Shaded areas indicate normal reference intervals.

Fig. 2. Serum TSH concentrations before and one to 10 days after coronary artery bypass graft surgery (group 2)

Fig. 3. Amplitude of fluctuations of serum TSH and thyroid hormone concentrations in individual patients undergoing coronary artery bypass graft surgery (group 2)

The triangles indicate preoperative hormone concentrations, the lines the range of postoperative values, the shaded areas the normal reference intervals.

statistical significance ($P < 0.02$), and temporally coincided with the nadir of TSH. Also, the percentage change in serum FT4 for group 1 was generally less than 25%, while that of TSH was greater than 50% (Figure 4). The vast majority of patients in both groups had FT4 values continuously within normal limits throughout the period of observation. We found only two patients (14%) in group 1 and one (5%) in group 2 in whom FT4 became clearly subnormal, and one borderline case. All three patients with subnormal FT4 values had a subnormal TSH value for more than one week and died subsequently. On the other hand, one patient in group 1 had consistently high FT4 (Figure 1B) and two in group 2 had temporarily increased FT4 (probably drug effects), while their TSH value was within the normal reference interval.

It is noteworthy that, despite the prevalence of abnormal
TSH concentrations, none of the patients had, at any time, either a subnormal TSH and concomitantly increased FT4 (typical of hyperthyroidism), or a high TSH associated with a low FT4 (characteristic of hypothyroidism). Moreover, from the percentages of abnormal data we estimated a probability of only 0.002–0.015% that a subnormal TSH and an abnormally high FT4, both due to NTI, would coincidently be associated in a sick euthyroid patient.

TSH Concentrations in a Representative Cross-Section of Hospitalized Patients with Miscellaneous NTI (Groups 3–5, Figures 5 and 6)

In group 5, all eight patients characterized as hypothyroid by conventional thyroid-function tests also had abnormally high TSH values by the sensitive assays. In group 4, patients suspected of being "subclinically hyperthyroid" because they had increased FT4 and (or) increased total T3 (FT4, 24 to >50 ng/L; T3, 2.5 to 3.35 μg/L), we found a completely suppressed (undetectable) TSH in four, and a subnormal TSH (0.16 milli-int. unit/L) in one patient. The sixth patient had a normal TSH of 1.4 milli-int. units/L (FT4, 25 ng/L).

In group 3, patients judged to be "euthyroid" on the basis of conventional tests, we observed a striking shift of TSH concentrations to lower values, when compared with healthy individuals (Figure 5) and a total of 23 (15%) patients had subnormal TSH. Two of the latter patients had an undetectable TSH together with a borderline-high FT4 that was within the upper five percentile of FT4 results for the group (19 and 22 ng/L). Two others were found to have an increased or borderline-high FT3 (36 and 38, normal 13–36 ng/L) upon further testing. However, aside from these four cases—i.e., in the majority of cases—the subnormal TSH was found to be associated with normal FT4 concentrations, corresponding to the middle or lower end of the normal range, and low to normal total/free T3, and there were no other biochemical (thyroid antibody tests) or clinical criteria to support a diagnosis of hyperthyroidism. Conversely, the sensitive TSH assay produced slightly above-normal results in 14 (10%) of patients in group 3, all of whom had a normal value for FT4, and only four of them had a slightly increased TSH value by our conventional RIA (10–25 milli-int. units/L). Two (1%) of the most gravely ill patients had a subnormal FT4 and a subnormal TSH value.

Overall, the pattern of TSH and FT4 concentrations obtained by random measurements in group 3 was similar to that from serial measurements in groups 1 and 2 (Figure 6). For example, the proportion of abnormal TSH results in patients with normal FT4 was similar and the subnormal TSH concentrations associated with normal FT4 were, in general, still measurable, rather than suppressed to undetectable values (0.05–0.4 milli-int. unit/L by the Abbott assay). Undetectable TSH was encountered only in 3% of
studies in group 1, 4% in group 2, and 1% of patients in group 3 (exclusive of the four found to be borderline hyperthyroid).

Discussion

Our observations further underscore the fact that pituitary TSH secretion can be profoundly affected by major surgery and (or) severe systemic illness.

Judging from our serial measurements, however, it seems unlikely that a subnormal TSH plus supranormal FT4 or a supranormal TSH plus subnormal FT4 are found in a patient with NTI unless that patient is also hyper- or hypothyroid, respectively. Rather, it appears that inverse abnormalities in both TSH and FT4 are indicative of thyroid dysfunction and that their interpretation in hospitalized patients is virtually the same as in outpatients.

Consequently, we interpreted the finding of a subnormal TSH value in five of six patients with abnormally high thyroid hormones (group 4) as a confirmation of hyperthyroidism, and the finding of a subnormal TSH in four other patients with borderline high FT4 and FT3 (group 3) as a sign of subclinical hyperthyroidism.

Clinically, sensitive TSH measurements may, e.g., be useful in hospitalized patients with unexplained tachycardia who routinely undergo evaluation of thyroid function to establish, or rule out, mild hyperthyroidism. During this study, one patient with atrial fibrillation and a high FT4 value of 33 ng/L was found to have a subnormal TSH of 0.01 milli-int. unit/L, which provided further evidence for subclinical thyroid disease.

On the other hand, our data also indicate that "sensitive" TSH assays readily detect minor, temporary abnormalities of serum TSH in sick patients and, thus, generate a significant number of abnormal (low or high) results, while FT4 tends to remain normal, consistent with the longer biological half-life of T4 in plasma and previous observations from single FT4 measurements during NTI (17–19). The disparate TSH and FT4 results are difficult to interpret.

In (untreated) outpatients, a suppressed TSH paired with a normal FT4 is virtually synonymous with early stages of hyperthyroidism (3–5), while an increased TSH plus normal FT4 is characteristic of compensated hypothyroidism. By contrast, these sets of results, per se, in patients with NTI are inconclusive. They can either reflect a mild intrinsic thyroid disorder, or they can be entirely manifestations of the systemic illness (temporary fall in pituitary TSH secretion and rebound phenomenon, 13, 14), or they can be combinations thereof. However, we encountered these abnormalities relatively frequently in the serial studies, where thyroid disease was ruled out to the extent possible, and so it appears that in severely ill patients with no history of thyroid disease these results are more often than not caused by the NTI. Therefore, as described in Table 2, an abnormal TSH plus a normal FT4, or the reverse, has to be interpreted differently in severely ill patients than is customary in outpatients.

Estimates for the diagnostic performance of sensitive TSH measurements in hospital settings like ours are shown in Table 3. Estimates are based on the data obtained for groups 3–5. We assumed that abnormal TSH results were true-positive results for intrinsic thyroid disease when they were coupled with complementary thyroid hormone abnormalities (subnormal FT4, in the case of hypothyroidism, and elevated FT4/FT3/FT3, in the case of hyperthyroidism), but that a slightly abnormal TSH (<20 milli-int. units/L) plus a normal FT4 result, or the reverse, in a patient with no evident thyroid disease, constituted a false-positive result (worst-case scenario). We found a high diagnostic sensitivity, a relatively poor specificity, and a very low positive predictive value, approximately as low as 35% for both hypo- and hyperthyroidism. The latter two can be vastly improved, with only minor sacrifices in sensitivity, if one uses for hospitalized patients TSH values of 0.05 and 12 milli-int. units/L as cutoff points (Figure 6, shaded areas), instead of the reference interval designated for clinic patients (0.4–6.2). However, we emphasize that a wider reference interval would probably not be indicated if TSH were to be used as a single initial screening test in the hospital setting.

As illustrated by our cumulative data in Figure 6, abnormal TSH values associated with NTI were clustered just above and below the normal reference interval. On the low side, they were typically (although not exclusively) still measurable, rather than undetectable (above 0.05 milli-int. unit/L).
Table 2. Associations of TSH and FT4 Results Observed in Patients with NTI: Tentative Interpretation of Abnormal Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ FT4 + ↓ TSH or BL FT4/FT3 + ↓ TSH</td>
<td>(A) highly probable Hyperthyroid</td>
</tr>
<tr>
<td>↓ FT4 + ↑ TSH or normal FT4 + ↑ TSH &gt;20</td>
<td>(B) less probable Prim. hypothyroidism</td>
</tr>
<tr>
<td>Normal FT4 + normal TSH</td>
<td>No thyroid dysfunction</td>
</tr>
<tr>
<td>Normal FT4 + ↓ TSH</td>
<td>NTI-related transient fall in TSH secretion, no thyroid disease*</td>
</tr>
<tr>
<td>Normal FT4 + ↑ TSH &lt;20</td>
<td>NTI-related rebound phenomenon</td>
</tr>
<tr>
<td>↓ FT4 + ↓ TSH</td>
<td>Severe NTI with long impaired TSH secretion</td>
</tr>
<tr>
<td>↓ FT4 + normal TSH</td>
<td>Mild hypothyroid or NTI-related acceler. T4 loss and NTI-related fall in TSH</td>
</tr>
<tr>
<td>↑ FT4 + normal TSH</td>
<td>NTI-related T4-binding inhibitors</td>
</tr>
</tbody>
</table>

*In patients receiving T4 replacement therapy: excessive T4. BL: borderline

Table 3. Diagnostic Sensitivity, Specificity, and Positive Predictive Value of Sensitive TSH Measurements in Hospitalized Patients: Comparison with FT4

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Posit. predict. value, %</th>
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<tbody>
<tr>
<td></td>
<td>Hyper-</td>
<td>Hypo-</td>
<td>Hyper-</td>
</tr>
<tr>
<td>TSH</td>
<td>0.4–6.2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>0.05–12.0</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>FT4</td>
<td>56</td>
<td>88</td>
<td>99</td>
</tr>
</tbody>
</table>

Estimates are based on final patient classification and data on groups 3–5.

unit/L; and on the high side, they ranged predominantly from 6.2 to 12 milli-int. units/L.

Our findings in heart–transplant recipients confirm previous data of Wehmann et al. (12) on bone-marrow recipients. We, however, observed a higher prevalence of abnormal TSH values in our cross-section of hospitalized patients undergoing routine thyroid-function testing (group 3) than has been reported recently by two other groups (2, 20). This discrepancy could be explained by differences in the analytical performance of the sensitive TSH assays used, but much more probably by differences in patient selection, in the nature and severity of the systemic illnesses, and (or) in the timing of the tests. For example, we measured TSH when routine thyroid-function tests were ordered, quite often when a patient’s status got worse. In the other reports (2, 20), all patients admitted to the hospital were screened on admission. From our longitudinal studies we would predict that some of the NTI-related abnormalities can be avoided if tests were performed exclusively on admission, i.e., before surgical procedures and before administration of drugs that are known to affect thyroid function.

The unexpected finding of an increased TSH preoperatively in patients with end-stage cardiac failure (group 1) remains unexplained. It might have been due to repeated administration of iodine-containing contrast agents for angiography. Klee and Hay (2) also found five patients with cardiopulmonary failure with TSH values ranging from 11.8 to 52.4 milli-int. units/L, but who had no obvious thyroid disease.

In conclusion, sensitive TSH measurements during NTI were found to be of clinical value in the diagnosis of hyperthyroidism. TSH identified borderline cases and allowed a more definitive biochemical assessment than could be made solely on the basis of increased thyroid-hormone concentrations, especially since T4 binding inhibitors may cause misleadingly high FT4 (21). We recommend sensitive measurements of TSH plus FT4 for initial evaluation of thyroid function in selected hospitalized patients, rather than TSH as a single screening test. If a suppressed TSH, or in particular if an undetectable TSH is found, measurement of FT3 may be helpful.

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References