Exaggerated TSH Responses to TRH in Depressed Patients With "Normal" Baseline TSH

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Background: Subclinical hypothyroidism (elevated thyroid-stimulating hormone [TSH] with normal thyroid hormone levels) can present with depression. This may be confirmed by an exaggerated TSH response to thyrotropin-releasing hormone (TRH) on the TRH stimulation test (TRH-ST). The objective of this study was to determine the prevalence of exaggerated TRH-ST results in a sample of depressed patients with "high-normal" screening TSH levels.

Method: Depressed patients with TSH levels of 3.00–5.50 mIU/L underwent a TRH-ST. After baseline TSH was drawn, TRH 400 µg was injected intravenously, and TSH samples were drawn at +20 min, +30 min, and +40 min postinjection. A rise in TSH after TRH (peak value minus baseline) of > 25 mIU/L represented an exaggerated TSH response.

Results: Twenty-three (38%) of 60 patients had an exaggerated TSH response to TRH. The 38% prevalence is significantly ($\chi^2 = 59.65$, df = 1, $p < .001$) greater than the 6% prevalence of positive TRH-ST results reported in the euthyroid general population. The prevalence of positive TRH-ST results was not attributable to differential patterns of psychotropic or thyroid hormone treatment. Unexpected observations were a lack of correlation in TSH levels week to week (r = .17, N.S.) and a lack of correlation between screening TSH value and subsequent TRH-ST results (r = .28, N.S.).

Conclusion: Subtle thyroid underfunction may be contributing to depression in some patients with TSH in the upper half of the range usually considered normal. If so, then the TRH-ST may be more sensitive in identifying this than measurement of TSH alone.

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Since depression may be associated with thyroid dysfunction,[1,2] routine screening for thyroid disease is advised in patients with depressive disorders.[3] Currently, the recommended thyroid screening test is TSH concentration, with the accepted normal range at most laboratories being 0.35–5.50 mIU/L. However, this range is based on observations in nonpsychiatric populations.

Subclinical hypothyroidism is a mild form of hypothyroidism, usually defined by mild elevations of basal thyrotropin (TSH) concentration in the face of normal thyroid hormone levels (free T_4 and free T_3) and an absence of somatic manifestations of thyroid hormone deficiency.[4] It can be present for many years before progressing to more overt hypothyroidism.[5] Many patients with subclinical hypothyroidism show symptoms typical of depression,[6] as well as nonspecific symptoms such as mental slowing, inefficiency, lethargy, and apathy. Furthermore, the depressive symptoms in subclinical hypothyroidism may respond suboptimally to antidepressant treatment, with such patients then being labeled as treatment resistant.[7]

A sensitive means of detecting subclinical hypothyroidism may be the finding of an exaggerated TSH response to thyrotropin-releasing hormone (TRH) on the thyrotropin-releasing hormone stimulation test (TRH-ST).[8] A normal maximal change in TSH (ΔMAX TSH) in response to TRH (defined as the peak TSH value after TRH minus the baseline TSH value pre-TRH) is less than 25 mIU/L.[8] Any ΔMAX TSH > 25 mIU/L confirms hypothyroidism.

In this study we sought to prospectively determine the prevalence of exaggerated TSH responses to TRH on the TRH-ST in depressed patients in whom screening TSH concentrations were in the upper half of the "normal range" (3.00–5.50 mIU/L). We report here on the initial 60 subjects who undertook the TRH-ST.

PATIENTS AND METHOD

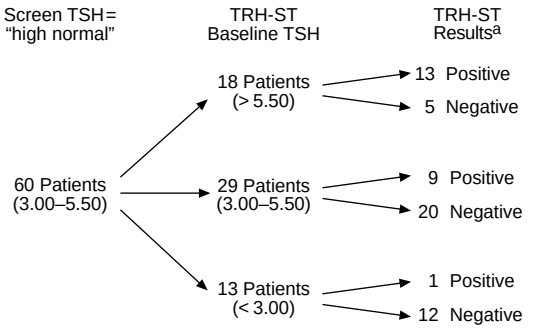
Nonpregnant women and men aged 18 years or older were studied as outpatients or inpatients through the Affective Disorders Program in a general hospital. Subjects underwent a psychiatric assessment, and a DSM-IV[9] diagnosis was assigned. A physical examination and a series of standard lab tests, including TSH concentration, were performed. Subjects had to meet one of the DSM-IV depressive disorders criteria as their primary diagnosis to be eligible for the study. Patients on stable doses (unchanged for a minimum of 1 month) of psychotropic drugs (e.g., lithium, antidepressants, benzodiazepines)[8] and routine medical drugs were eligible for the study. Patients on stable doses (minimum of 3 months) of thyroid hormone replacement were also eligible.

Excluded from the study were patients with active (within 6 months) substance abuse, significant medical or neurologic illness, body weight less than 80% of ideal weight, pregnancy, known primary endocrinological disorder (other than hypothyroidism on stable replacement with thyroid hormone), or those being treated with drugs known to accelerate hepatic metabolism (e.g., phenytoin, carbamazepine).

Severity of depressive symptoms was rated at screening by a series of subjective (Beck Depression Inventory,[10] Beck Anxiety Inventory,[11] Sheehan Disability Scale[12]) and objective (Hamilton Rating Scale for Depression [HAM-D],[13] Montgomery-Asberg Depression Rating Scale,[14] Reversed Vegetative Symptom Scale[15]) measures. In addition, the level of functioning was rated on the Global Assessment of Functioning (GAF) scale.[9] Those patients with a screening TSH value in the upper half of the normal range (i.e., 3.00–5.50 mIU/L) were approached to provide written informed consent to undertake the TRH-ST.

For the purpose of the TRH-ST,[8] patients were made to fast from 2300 hours the evening before the test. Patients lay recumbent during the test, which began at 0730 hours. An intravenous solution (0.9% NaCl running at 75 cc/h) was started, and blood was drawn to establish a baseline TSH along with free T_4 and antimicrosomal and antithyroglobulin antibodies. Protirelin TRH (Relefact, Hoechst-Roussel Canada, Inc., Laval, Quebec) 400 µg was then rapidly injected intravenously. Post-TRH TSH samples were drawn at +20, +30, and +40 minutes. Vital signs and temperatures were monitored before the intravenous TRH injection, then every 30 minutes until test completion.

Figure 1. Screening TSH and Subsequent TRH-ST Results in Depressed Patients*



*Abbreviations: TRH-ST = thyrotropin-releasing hormone stimulation test, TSH = thyroid-stimulating hormone. Units are mIU/L. Considerable fluctuation in TSH from screen to baseline (r = .17, NS). Lack of correlation between screen TSH and TRH-ST result (r = .20, NS).
[a]ΔMAX TSH > 25.00 mIU/L = positive TRH-ST result; ΔMAX TSH < 25.00 mIU/L = negative TRH-ST result.

TSH was measured by a two-site cheminoluminescent immunoassay on the ACS-180 analyzer (Ciba Corning, Medfield, Mass.).[16] Antimicrosomal and antithyroglobulin antibodies were measured by hemagglutination method by Commercialized Kits (Murex Diagnostics Ltd., Dartford, England).

RESULTS

Sixty-one (13%) of the consecutively screened patients were within the TSH range of 3.00–5.50 mIU/L, and all but 1 provided informed written consent for the TRH-ST study. The 60 studied patients consisted of 47 women and 13 men with an age range of 19 to 75 years (mean = 44 years). Fifty-three were outpatients and 7 were inpatients.

This was a moderately depressed (mean HAM-D score = 20.84) and moderately dysfunctional (mean GAF score = 57.26) group of patients. The results of the TRH-ST determinations in this population are illustrated in Figure 1. The major finding was that 23 (38%) of these 60 subjects had positive TRH-ST results (20 women, 3 men) with ΔMAX TSH > 25 mIU/L (range, 25.80–61.57; mean = 43.69). The 38% prevalence of positive TRH-ST results in this depressed population is significantly ($\chi^2 = 59.65$, df = 1, $p < .001$) greater than the 6% prevalence reported in the normal TSH general population.[16]

Removing the 7 inpatients from analysis (3 with positive TRH-ST results) left the same 38% (20/53) prevalence of outpatients with positive TRH-ST results. Similarly, eliminating the 5 patients who were on thyroid replacement therapy (2 with positive results) from the total group left 21 (38%) of 55 with positive TRH-ST results. Finally, 43% (20/47) of the women (mean age = 40) had positive results, versus 23% (3/13) of the men (mean age = 46).

We observed no significant differences in the severity-of-depression or anxiety scales on the seven rating instruments between the TRH-ST positive and negative groups. We also observed no significant differences in patterns of psychotropic medication treatment between the two groups. Specifically, there were 6 (26%) of 23 patients in the TRH-ST positive group taking lithium, compared with 9 (24%) of 37 in the TRH-ST negative group. Three of the TRH-ST positive group (13%) were taking low doses of dopamine-blocking neuroleptics versus 8 (22%), taking higher doses, in the TRH-ST negative group. Two TRH-ST positive subjects (9%) were on thyroid replacement therapy versus 3 (8%) in the TRH-ST negative group. The precision of the TSH assay was determined at TSH levels of 0.08, 1.14, 9.55, 22.98 mIU/L, with 20 samples analyzed at each respective point. Precision was not determined within the 3.00–5.50 range. For the mean TSH of 1.14, the within-run standard deviation (SD) was 0.065 and the percent coefficient of variation (%CV) was 5.70; the between-run SD was 0.08 with a %CV of 7.02. For the mean TSH of 9.55, the within-run values were SD = 0.286 and %CV = 2.99, and the between-run values were SD = 0.65 and %CV = 6.81.

Considerable fluctuation was noted in TSH values from the screening TSH to the baseline TSH of the TRH-ST, resulting in a lack of correlation between the values (r = .17, N.S.) (see Figure 1). In addition, an absence of correlation between the screening TSH value and subsequent TRH-ST results was observed (r = .28, N.S.). In other words, it was not possible to predict from the earlier screening TSH values which patients would have a positive TRH-ST. Baseline TSH, on the day of the TRH-ST, was correlated with the ΔMAX TSH (r = .40, $p < .05$). However, this TSH value still could not reliably predict the TRH-ST results, as shown in the breakdown of results in Figure 1. Of the 42 patients whose TRH-ST baseline TSH was below 5.50 mIU/L, 13 (31%) had positive TRH-ST results.

The TRH-ST was well tolerated by subjects. In keeping with the physiologic actions of TRH, approximately 60% of subjects experienced transient nausea, flushing, or urges to micturate immediately after the TRH administration.[8] Slight (up to 0.2°C) temperature rises were occasionally noted, but no other changes in vital signs or untoward events were observed.

DISCUSSION

Clinicians and researchers dealing with depressed patients routinely seek to exclude hypothyroidism as a factor contributing to depressive symptoms. Exclusion has meant determining a TSH result of less than 5.5 mIU/L,[17] observing an absence of physical stigmata of hypothyroidism, and concluding that such patients are euthyroid. Our results suggest that such conclusions may be invalid in some of these patients with screening TSH concentrations in the upper half of the "normal range" (3.00–5.50 mIU/L). We found that 38% of 60 such patients demonstrated an exaggerated (> 25 mIU/L) TSH response to TRH on the TRH-ST, a prevalence that is significantly greater than the 6% "false-positive" rate reported in the euthyroid general population. The TRH-ST results may provide evidence of a very mild degree of subclinical hypothyroidism in these patients that is not identified reliably or sensitively by screening TSH levels alone. If so, then subclinical hypothyroidism might be contributing to depressive symptoms in such patients.

Some limitations and weaknesses of this study must be acknowledged. First, caution should be exercised in interpreting the significance of the 38% prevalence of positive TRH-ST results, as there was no true comparator group. The 6% prevalence of similar results in the general population was for subjects with a screening TSH throughout the normal range, not just the upper half of the range.[16] In the normal population, at least, the prevalence of exaggerated TSH response to TRH rises with higher baseline TSH,[8] and it is possible that the prevalence of positive TRH-ST results in a normal, nondepressed population with high-normal TSH might not differ significantly from our findings. Another group to compare our results with might be depressed patients with *low-normal* screening TSH. This could address the question of whether or not the positive TRH-ST results are associated with the depressed state alone, in which case depressives with low-normal TSH would be expected to have TRH-ST results similar to those with high-normal TSH. Studying depressives who have low-normal screening TSH would also determine the stability of TSH results in that group, in contrast to the lack of stability in the group in our study. For example, some patients with low-normal screening TSH who then underwent the TRH-ST might demonstrate a high-normal baseline TSH. If depressed patients with exaggerated TSH responses to TRH do have a subtle degree of thyroid dysfunction contributing to depressive symptoms, then such patients should be less likely to respond to antidepressant therapies (in the absence of thyroid function normalization) than similarly treated patients with normal responses. Ideally, a study of the TRH-ST in untreated depressed patients who are then prospectively followed through treatment could address this question, especially if TRH-ST findings were correlated with treatment outcome.

A number of potential factors, including the use of psychotropic drugs and thyroid replacement, might have confounded these results. Lithium and neuroleptics can raise basal TSH,[8] but it is unclear if they can produce false-positive TRH-ST results. There were no significant differences in the proportions of TRH-ST positive or negative patients taking these drugs. Similarly, there were no significant differences between the positive or negative

groups in the proportion on thyroid replacement. Many patients were taking antidepressants, but neither noradrenergic nor serotonergic antidepressants are thought to influence TSH or the TRH-ST.[18]

The TRH-ST methodology used was in accordance with that employed in psychiatric studies of the test.[19] Using the 400 μg instead of 500 μg dose of TRH might have resulted in some false-normal TRH-ST results if any patients had a less than maximal TSH rise. The ΔMAX TSH threshold (> 25 mIU/L) was applied equally to both men and women of all ages in this study. Euthyroid women tend to have higher TSH levels than men,[20] and a greater amplitude of TSH response to TRH than men.[21] Some researchers have suggested that the threshold for men should be a ΔMAX TSH no higher than 20 mIU/L.[21] We did not use a lower threshold for men in this study. There were six men whose ΔMAX TSH was between 20 and 25 mIU/L. Including these 6 results as positive would have raised the prevalence to 48%, with the positive prevalence rate for men raised to 69% (9/13). Although the small numbers make it difficult to draw conclusions, it is possible that high-normal TSH values are more likely to be of significance with respect to thyroid axis dysfunction in men than in women.

The observations of week-to-week fluctuations in TSH in many of these patients, and lack of predictability of TRH-ST results based on the screening TSH values, bear some comment. These fluctuations did not seem a result of medication or clinical state changes in patients. Furthermore, the SD and %CV assay results make it unlikely that laboratory error was responsible. We are not aware of studies of TSH concentrations week to week in serial fashion in the general population or in depressed patients. This variability and lack of TRH-ST predictability was not confined to the TRH-ST positive group. It is possible that the depressed state itself confers some instability to the hypothalamic-pituitary-thyroid axis, or that patients whose TSH values fluctuate are exhibiting a prodromal sign of later development of more overt hypothyroidism. This might be analogous to the situation of hypertension, where inconsistently raised borderline high systolic blood pressure predicts later development of clinically significant hypertension.[22]

The TRH-ST was frequently employed by researchers studying neuroendocrine regulation in depression during the early-to-mid 1980s,[19] with the emphasis having been on investigating *blunted* (ΔMAX TSH < 7.0 mIU/L) TSH response to TRH. However, in one such TRH-ST study of 47 melancholic depressives, Targum et al.[23] noted that 8/47 (17%) demonstrated augmented (defined as ΔMAX TSH > 23 mIU/L) responses. The patients in that study were screened to ensure normal thyroid indices (including TSH). That report appears to indicate that all of the 8 depressed patients with an augmented TRH-ST had a high-normal basal TSH. It is not clear what total number of patients had high-normal TSH, and thus it is difficult to calculate the prevalence of positive TRH-ST results in a population analogous to that reported in this study. However, our results are in keeping with those in this earlier report, again suggesting that unidentified subclinical hypothyroidism may be contributing to depressive symptoms in some of these patients.

Most practitioners rely on TSH determination alone in ruling out hypothyroidism.[23] Yet 31% (13/42) of the patients whose baseline (rechecked) TSH on the TRH-ST was still less than 5.50 mIU/L had a positive TRH-ST. Therefore, a 31% false-negative rate would have resulted if a TSH recheck less than 5.50 mIU/L was used as indication of a euthyroid state. These results, although provocative, do not prove that the patients with an exaggerated TSH response to TRH have subclinical hypothyroidism. The TRH-ST may not be a "gold standard" test for subclinical hypothyroidism. It is possible that the results in these patients represent false positives, albeit at a much greater prevalence than that reported in the general population.[16] Prospective data in terms of the specificity and reliability of these test findings (in both TRH-ST positive and negative patients), in appropriate comparator groups, and in correlation with clinical course and outcome, would help clarify these issues. If future studies do confirm the clinical and prognostic value of positive TRH-ST results in such depressed patients, then these would also confirm the relative insensitivity of the TSH alone.

Until much further clarification work is performed, it is premature to speculate on any potential impact on the therapeutic management of such patients. However, it should not be assumed, at least in patients suffering from depression, that the proof of clinically relevant subclinical hypothyroidism must lie with evidence that depressive symptom improvement is contingent on normalization of thyroid status alone.[24] There is evidence of interactions between thyroid hormones and catecholamine receptors in euthyroid patients.[25] If some depressed patients also have mild subclinical hypothyroidism, they may require a combination of adequate thyroid replacement and full antidepressant treatment.[24–26] In any event, if treatment studies with such patients demonstrate that thyroid hormone therapy is a necessary (even if not sufficient) therapeutic intervention, it will provide strong support for the notion that these patients indeed suffer from "true" subclinical hypothyroidism.

Drug names: carbamazepine (Tegretol and others), phenytoin (Dilantin and others).

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