Serum Thyrotropin Measurements in the Community

Five-Year Follow-up in a Large Network of Primary Care Physicians

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Background: Subclinical thyroid disease is common; however, screening recommendations using serum thyrotropin (TSH) level determinations are controversial.

Methods: To study the use of serum TSH by primary care physicians and define populations at risk for having an abnormal TSH level at follow-up, based on initial TSH levels, we conducted an observational study of a large health care database in the setting of a health management organization. All outpatients without thyroid disease or pregnancy or taking medication that may alter thyroid function in whom the TSH level was measured in 2002 and during 5-year follow-up were included in this study. Repeated TSH level determinations were compared with the initial TSH level values.

Results: In 422,242 patients included, 95% of the initial serum TSH concentrations were within normal limits (0.35-5.5 mIU/L), 1.2% were decreased (<0.35 mIU/L), 3.0% were elevated (>5.5 to ≤10 mIU/L) and 0.7% were highly elevated (>10 mIU/L). In 346,549 patients without thyroid-specific medications, the TSH levels became normal in 27.2%, 62.1%, and 51.2%, whose initial serum TSH level was highly elevated, elevated, and decreased, respectively, and remain normal in 98% of the patients with normal initial TSH levels. When the initial serum TSH level was elevated, patients in the highest quintile of this group, who had a shorter interval between the first and second measurements, had a higher probability of a second highly elevated TSH concentration (P < .001).

Conclusions: When the serum TSH level is normal, the likelihood of an abnormal level within 5 years is low (2%). More than 50% of patients with elevated or decreased serum TSH levels have normal levels in repeated measurements.

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Although subclinical thyroid disease is common in the general population, screening recommendations for hypothyroidism using serum thyrotropin (TSH) determinations are controversial.1 While recent expert panels published evidenced-based recommendations against generalized screening for thyroid disease,2,3 others recommend selective screening of certain sectors of the population such as women at 35 years of age and every 5 years thereafter1 and patients older than 60 years.4,5 Moreover, there are no clear recommendations for how often serum TSH level measurements should be repeated after finding a normal result or when the result is abnormal but does not require initiation of medical treatment.

Primary care physicians (PCPs) order large numbers of TSH level measurements and repeat these tests often despite finding an initial normal TSH concentration.6,7,8 The effect of multiple TSH level determinations on clinical outcomes is unknown.9 We used a centralized computerized database of 3.7 million persons (2.3 million of them aged ≥21 years) insured in the Clalit Health Medical Organization (CHMO), Tel Aviv, Israel, to analyze PCP practices for the use of serum TSH level determinations in routine clinical care. This study was approved by the CHMO Ethics Committee.

The purposes of this study were 3-fold: to study the current use of serum TSH tests by PCPs in clinical practice, to define populations at greater risk for having an abnormal follow-up serum TSH level during a 5-year follow-up when the initial serum TSH level was elevated, and to determine the course of thyroid disease in those patients with abnormal initial TSH levels who were not treated with thyroid or antithyroid medications.

METHODS

The CHMO insures the health care of 2.3 million persons 21 years or older. It has a state-of-the-art computerized data warehouse that stores demographic and medical data. Data are aggregated by input from health service providers and physicians documenting patient-physician interactions and from laboratory data and phar-
The study population included all individuals insured by the CHMO 21 years or older who had at least 1 serum TSH level determination in 2002 and for whom follow-up data were available to December 31, 2006. The TSH level determinations included in the analyses were ordered by PCPs during routine clinical care of outpatients only.

Excluded from the study were patients with thyroid disease that was diagnosed before 2002 or who had an abnormal serum TSH measurement during 2001: patients treated with lithium, amiodarone, or interferon during the 5-year study; pregnant women, identified by a delivery between January 1, 2002, and December 31, 2006; subjects lost to follow-up; and patients who died before December 31, 2006. A total of 80,061 patients were excluded as a result of these criteria. A thyroid illness was defined when a diagnosis of hypothyroidism (TSH concentration >10 mIU/L) or hyperthyroidism (TSH concentration <0.35 mIU/L) was made, when thyroid-specific medications (levothyroxine or thionamides) were dispensed for a minimum of 2 consecutive months per year, or when radioactive iodine therapy was given. To study the natural history of patients who had TSH determinations in 2002, patients who received treatment with levothyroxine or antithyroid drugs after the initial serum TSH determination were also excluded (n = 15,081).

### LABORATORY ANALYSIS

Serum thyrotropin level determinations were performed using a continuous random access analyzer (Immuliite 2000; Diagnostic Products Corp, Los Angeles, California) and an immunoassay (ADVIA Centaur; Bayer HealthCare LLC, Diagnostics Division, Tarrytown, New York) apparatus, with upper and lower limits of 0.35 and 5.5 mIU/L, respectively, as previously described. Free thyroxine (FT$_4$) level determinations were performed as described, with upper and lower limits of 10.3 and 20 pmol/L, respectively.

### RESULTS

A total of 422,242 persons with no known thyroid disease or previous consumption of thyroid or antithyroid medications had at least 1 serum TSH measurement during 2002. Patients who had serum TSH level determinations, 65.9% of whom were women, comprised 18% of the enrollees in the CHMO. The rate of TSH testing generally increased with age (Table 1). Testing was performed in approximately 8% of men and 14% of women younger than 40 years. The rate of TSH testing increased in women older than 40 years; approximately one-third of the female patients insured in the CHMO in this age group had a serum TSH level determination during 2002. The TSH testing rate remained relatively low (approximately 8%) in men until 40 years of age, when it gradually increased to include 20% of men aged 60 to 80 years.

Ninety-five percent of the 422,242 initial TSH concentrations determined in 2002 were within normal limits (0.35-5.5 mIU/L), whereas 1.2% were decreased (<0.35 mIU/L), 3.0% were elevated (>5.5 to ≤10 mIU/L), and 0.7% were highly elevated (>10 mIU/L, Table 2). Abnormal test results were more frequent in women (5.8%) than in men (3.4%). A highly elevated TSH level was detected in 0.5% of all tested men and in 0.8% of all tested women. Of all patients whose initial TSH level determination was above the upper limit of the normal range, the concentration was elevated in 80.7% of the entire group (81% of men and 80% of women).
The serum FT₄ level was measured in 89% of patients with abnormal serum TSH levels. Thirty percent of patients with highly elevated TSH concentrations had lower than normal FT₄ levels (overt hyperthyroidism) and 93% of subjects with elevated TSH concentrations had normal FT₄ values (subclinical hypothyroidism). Nine percent of subjects with TSH concentration below the lower limit of the normal range had elevated FT₄ values (overt hyperthyroidism).

Overall, 422,242 subjects had slightly more than 1.5 million TSH level determinations during the 5-year follow-up (mean, 3.73 tests per patient). Of our cohort of patients, PCPs started treatment with thyroid or antithyroid medications in 15,081 patients (3.57%). Approximately 25% of those patients had a single TSH level determination before initiation of medical treatment. Patients given thyroid hormone or antithyroid medications were excluded from the subsequent analysis. Of the remaining patients, 60,612 (15%) had only 1 TSH determination and 346,549 patients had repeated TSH level measurements during follow-up. Of the retested patients, 98% had normal TSH levels at initial TSH testing. The mean (SD) time between repeated TSH measurements (first and second tests) was 18.93 (13.11) months. The rates of repeated TSH measurements were related to the initial TSH category and are shown in Figure 1. Approximately 90% of patients in each abnormal TSH category had 2 TSH measurements or more within 5 years. Patients whose first TSH level determination was in the normal range had a lower rate of repeated TSH determinations. Nevertheless, 84.9% of those patients had 2 TSH level determinations or more within 5 years.

We assessed the results of the second TSH level determination by analyzing the distribution of the second concentration in relation to the initial TSH category in 346,549 patients who were not taking any thyroid-specific medications or other medications that may affect thyroid function. In 98% of patients with a normal initial TSH concentration, the second TSH concentration was also normal (Figure 2). Thirty-five percent of patients with a highly elevated initial serum TSH level (>10 mIU/L) had a repeated TSH level that was also highly elevated. However, 36.5%, the second TSH level was decreased but still elevated, and in 27.7%, the second serum TSH level was within the normal range. For patients with elevated serum TSH levels, 62.1% had normal TSH levels at the second determination and only 2.9% of the patients had a second highly elevated TSH concentration. Almost half of the patients with a decreased (<0.35 mIU/L) TSH concentration at the first determination had a decreased level when the test was repeated. Serum TSH became normal in 51.5% of these patients. Of patients with serum TSH concentrations, 81% were in the group with elevated levels. We divided this group into quintiles for further analysis (Figure 3). The upper values of each quintile were 5.78, 6.13, 6.63, 7.47, and 10.0 mIU/L, respectively. When the initial serum TSH level was elevated, patients whose results were scaled on the fifth quintile, and who had a shorter interval between the first and second measurements, had a significantly higher probability of having a second highly elevated TSH concentration (P < .001). Comparisons between the first and the fifth quintiles of the first test result indicated that the probability of a second serum TSH concentration in the normal range decreased from 73.7% to 43.6%. Moreover, the likelihood of a second highly elevated TSH level changed from 0.7% to 7.7% when the first and fifth quintiles were analyzed.

Using the Pearson product moment correlation between the initial and second TSH test results revealed a higher correlation in the groups including patients with shorter times between the 2 tests. In each of these groups, the correlation was statistically significant (P < .01). Application of the marginal homogeneity test demonstrated a difference between first and second TSH test results (P < .01).
We examined the way PCPs use TSH test determinations while caring for patients with no known thyroid illness. For this purpose, we used the CHMO computerized database containing data for 2.3 million insured persons 21 years and older. After excluding subjects with previously diagnosed thyroid disorders, we obtained data for 422,242 persons with 5-year follow-up, analyzing data for approximately 2.1 million person-years. Our results indicate that about 18% of the population had a TSH level determination during 2002. Moreover, PCPs ordered a mean (SD) 3.73 (2.24) additional TSH determinations per person during the 5-year follow-up. Almost all of the test results (95%) were within normal limits and remained so during the study. In addition, when the initial TSH test result was elevated, even without levothyroxine treatment, the likelihood of having a second abnormal TSH level within 5 years was 37.6%.

Subclinical hypothyroidism is common in the general population (4%-8%) and increases with age. Seventy-five percent of patients with subclinical hypothyroidism have elevated (>5 to ≤10 mIU/L) TSH concentrations. In a previous smaller study of 107 patients older than 55 years, elevated serum TSH levels returned to normal in 37% of the patients. However, approximately 50% of the patients they studied had received radioactive iodine treatment or undergone thyroid surgery, whereas our patients had no history of thyroid disease. Others, in smaller studies, have also reported a high frequency of normalization of serum TSH levels in patients with elevated TSH levels. In patients older than 60 years, Parle et al16 showed that 15% of abnormal levels became normal in 12 months, and Gussekloo et al,17 in a 3-year study of octogenarians, showed that serum TSH levels became normal in 11 of 21 patients with subclinical hypothyroidism.

Our findings extend those of a previous report14 from a large primary care practice; elevated serum TSH levels became normal in 62% of our patients, remained elevated in 35%, and were highly elevated in only 2.9% when the test was repeated during 5-year follow-up. Our findings differ from those reported by Huber et al,15 who observed 82 patients with subclinical hypothyroidism for a mean of 9.2 years. They reported that TSH levels returned to the normal range in only 4 (3%) of their patients. However, approximately 50% of the patients they studied had received radioactive iodine treatment or undergone thyroid surgery, whereas our patients had no history of thyroid disease. Others, in smaller studies, have also reported a high frequency of normalization of serum TSH levels in patients with elevated TSH levels. In patients older than 60 years, Parle et al16 showed that 15% of abnormal levels became normal in 12 months, and Gussekloo et al,17 in a 3-year study of octogenarians, showed that serum TSH levels became normal in 11 of 21 patients with subclinical hypothyroidism.

Our data from this large population also support and extend previous observations about the rate of progression from subclinical hypothyroidism (TSH >5.5 to ≤10 mIU/L) to overt hypothyroidism (TSH >10 mIU/L). Vanderspomp et al18 reported, in a 20-year follow-up study of the Whickham Survey, that the rate of progression from subclinical to overt hypothyroidism in untreated patients was 2.6% per year in the absence of thyroid peroxidase autoantibodies and 4.3% per year in their presence. We could not analyze data for antithyroid antibodies in our study. However, the rate of progression from subclinical to overt hypothyroidism during the 5-year follow-up in our study was only 2.9%. Other smaller studies of selected patients report a much higher rate of progression to overt hypothyroidism: 27% during a 32-month follow-up19 and 28% after a mean of 9 years of follow-up.20

Our findings also indicate that decreased (<0.35 mIU/L) serum TSH levels became normal in more than 50% of patients during the 5-year follow-up in this study. Similar results were reported by Sawin et al19 in a study of 101 patients, 51 of whom were treated with levothyroxine. Our findings suggest that the initial decreased serum TSH concentration may have been measured during an episode of transient hypothyroidism, possibly as a result of thyroiditis or Graves disease.

Our data, combined with those of other reports, add to the controversial discussion about whether patients with subclinical hypothyroidism routinely require treatment. Before considering treatment, PCPs should first take an appropriate history, perform a physical examination, and then determine whether the elevated TSH concentration is a consistent finding. When the TSH concentration is elevated, clinicians should consider that serum TSH levels may become normal with time in more than half of patients. In the appropriate clinical setting, a second serum TSH measurement should be made after several months. If the concentration remains elevated for 1 to 3 years, mild hypothyroidism may be considered permanent. However, even when mild hypothyroidism persists with time, patients may continue under observation with occasional determination of serum TSH.
concentration. The rate of progressively increasing TSH seems to be relatively slow; thus, levothyroxine treatment may be introduced when progression is documented. With observation alone, there seem to be few or no adverse health consequences.2 Recent reports further indicate that patients with mild hypothyroidism do not have impairment of neuropsychological function20 or associated depression or deficits in cognitive function.21 Concerns previously reported22-25 about adverse cardiovascular outcomes have been allayed to some extent by the recently published results of the Cardiovascular Health Study, in which almost 500 patients with subclinical hypothyroidism who were at least 65 years of age were followed up for a mean of 12.5 years.26 Their outcomes for coronary heart disease or all-cause mortality were comparable to those in control subjects.

Our findings and those of others indicate that the rate of progression from mild to overt hypothyroidism seems to be very slow. Our findings support that conclusion because elevated (>5.5 to ≤10 mIU/L) TSH levels progressed to highly elevated (>10 mIU/L) in only 2.9% of patients during this 5-year study. Similarly, we found that 51.5% of patients having decreased (<0.35 mIU/L) serum TSH levels initially had a second TSH concentration within the normal range (0.35-3.5 mIU/L) during this study without any specific treatment. Therefore, depending on the clinical setting, it would seem prudent to repeat the serum TSH determination after several months before considering antithyroid treatment in patients with similarly decreased TSH levels. The cause of subclinical hyperthyroidism should always be determined before any specific treatment is considered. For example, antithyroid drugs should not be prescribed in patients with transient thyroiditis.

Primary care physicians have increased the number of routine blood tests ordered, and measurement of the serum TSH concentration is one of the most frequently ordered tests.6,7 In addition, the clinical yield of these tests is low both diagnostically and therapeutically.8-11 Our results are in accord with these reports. The CHMO PCPs ordered serum TSH level determinations frequently, even in the absence of a primary thyroid disorder or an initial abnormal value. Eighty-five percent of 393,905 patients with initial normal TSH results had at least 1 additional TSH level determination within 5 years. The frequent measurement of TSH might be explained by vague symptoms frequently expressed by patients that might raise the possibility of a thyroid disorder.10

The major strength of our study is that it analyzes the actual clinical practices of approximately 2800 PCPs with different medical education, experience, and personalities. Because we excluded patients with known thyroid disorders, we assumed that the TSH level determinations ordered by PCPs were part of standard clinical care. Our data, therefore, may be used to generalize the clinical routine of PCPs. Our study is based on data summarizing 2.1 million patient-years, and, to our knowledge, there is no similar study of such magnitude.

Our study has several weaknesses. First, because of the low rate of FT4 level determination (12%) by our PCPs, we could not provide a detailed analysis of these data. Therefore, we could not exactly categorize our patients as having overt or subclinical thyroid disease, as defined elsewhere.2 Nevertheless, the FT4 level was measured in 98% of our patients with elevated TSH concentrations and was within normal limits in almost all of these patients, which strongly suggests that hypothyroidism in this group of patients could be considered subclinical. Previous reports also suggest that the large majority of patients with elevated serum TSH levels have subclinical hypothyroidism.2 In theory, we also could have missed a few patients with normal TSH levels but low FT4 levels, indicating secondary hypothyroidism. Second, we could not refine the prediction of our patients’ risk for developing progressive thyroid failure because we do not know their antithyroid antibody status or their family history of autoimmune thyroid disease. Third, because this was a retrospective study, we could not determine the reason for measurement of TSH or other aspects of clinical state of the tested patients. Fourth, we do not know the time of day of the TSH level determinations. Thus, influence of time of day could be a confounding factor, as previously discussed.23 Fifth, we are cognizant of the current discussion about whether the TSH reference range should be narrowed.23-24 However, before further discussion and consensus on this issue, we believe it is premature to provide further analysis of our data using a narrower range of normal. Sixth, 37% of patients with abnormal TSH levels were treated with medication and excluded from analysis. Since we do not have clinical information about these patients, we cannot be sure that the group we studied is representative of the entire population with normal or abnormal TSH levels.

When the serum TSH concentration is normal and there are no new clinical indications for a thyroid disorder, there is only a 2% probability that another TSH determination obtained within 5 years will be abnormal. This finding supports recent evidence-based recommendations against population-based TSH level testing. In such patients, we suggest ordering additional TSH measurement only if warranted by the clinical evaluation. In patients with abnormal serum TSH levels after full clinical evaluation, we suggest obtaining at least 2 TSH measurements before considering treatment.

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