Hypothyroidism is linked to depression, hypercholesterolemia, coronary artery disease, and a decrease in quality of life, and it increases the financial burden for the health system. Currently, there are varying guidelines on screening for hypothyroidism. The American Thyroid Association and the American Association of Clinical Endocrinologists have deemed screening to be cost-effective and recommend screening after 35 years of age and every 5 years thereafter. The American College of Physicians and the Institute of Medicine of the National Academy of Sciences, on the other hand, do not recommend screening. Regardless of these general screening recommendations, symptoms suggestive of hypothyroidism, such as depression, fatigue, and weight gain are extremely common, and patients presenting to their family physicians with these symptoms may warrant testing/screening for hypothyroidism.

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**Background and Objectives:** Hypothyroidism is linked to heart disease and decreased quality of life. Since screening guidelines for the general population are controversial, and physicians use clinical judgment in deciding to order thyroid stimulating hormone (TSH), high-normal levels of TSH pose a dilemma. This study’s objective was to compare rates of positive anti-thyroid peroxidase antibodies (antiTPO) tests in persons with high-normal versus low-normal TSH levels. Methods: Physicians at a publicly funded family medicine outpatient clinic used a standard clinical set of criteria to identify patients in need of TSH testing. Patients with non-thyroid diseases or conditions that affect TSH were excluded. A total of 143 patients over 18 years of age presented with symptoms necessitating TSH testing and had levels that fell between 0.36 and 5.49 IU/ml. They were allocated into two groups: 100 patients with TSH levels between 0.36–2.49 IU/ml (low-normal TSH) and 43 patients with TSH levels between 2.5–5.49 IU/ml (high-normal TSH), and they all had measurements of antiTPO levels. Primary outcomes were rates of antiTPO and demographics comparisons between the two groups. Results: The prevalence of the antiTPO antibody in the high-normal group was 18.6% versus 3% in the low-normal range TSH. The antiTPO prevalence was higher in females than in males and had a racial predominance in Hispanics compared to African Americans; however, these differences were not statistically significant. Conclusions: AntiTPO measurement may be appropriate for patients with high-normal TSH to help distinguish those at risk of developing true hypothyroidism.

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Hypothyroidism is linked to depression, hypercholesterolemia, coronary artery disease, and a decrease in quality of life, and it increases the financial burden for the health system. Currently, there are varying guidelines on screening for hypothyroidism. The American Thyroid Association and the American Association of Clinical Endocrinologists have deemed screening to be cost-effective and recommend screening after 35 years of age and every 5 years thereafter. The American College of Physicians and the Institute of Medicine of the National Academy of Sciences, on the other hand, do not recommend screening. The Royal College of Physicians, the American Academy of Family Physicians, and the US Preventive Service Task Force state that there is insufficient data to recommend for or against routine screening. Other recommendations include screening the elderly, pregnant women, and patients with Down Syndrome as specific target populations. Regardless of these general screening recommendations, symptoms suggestive of hypothyroidism, such as depression, fatigue, and weight gain are extremely common, and patients presenting to their family physicians with these symptoms may warrant testing/screening for hypothyroidism.

Since a patient’s symptoms may be non-specific, hypothyroidism is a laboratory diagnosis, and thyroid stimulating hormone (TSH) is the most sensitive single test to diagnose the condition. Discussion has centered, however, on the appropriate normal range of TSH, because the current TSH range is based on values that may include individuals with diseases that may have
influenced TSH secretion, for example, patients with goiter or a family history of thyroid disease.

In several studies, 95% of the normal population has a TSH below 2.5 IU/ml.3-7,10 Other studies have suggested lowering the range of normal.7,11 These studies indicate that the real mean normal value of TSH is between 1.18 to 1.5 IU/ml.7,11

There is a well-documented association between the presence of anti-thyroid peroxidase (antiTPO) antibodies and the development of autoimmune hypothyroidism.1,4,12,13 The progression of subclinical hypothyroidism (borderline elevated TSH with normal thyroid hormone levels) to clinical hypothyroidism has been estimated at 5% per year in a 4-year follow-up.7

The prevalence of antiTPO antibodies in patients with TSH in the 3 to 4.49 IU/ml range was determined to be around 22.2% 9 There is no literature available on the prevalence of antiTPO in the low-normal range of TSH. Estimates of the prevalence of antiTPO in the general population range from 4.4% to 25%.1,14 If the population with high-normal TSH has a greater prevalence of antiTPO antibodies, this finding would suggest that these patients have a higher risk of developing overt hypothyroidism and at least deserve closer follow-up and occasionally even a trial of treatment for potential relief of symptoms.

The purpose of the present study was (1) to evaluate the prevalence of antiTPO antibody in a community-based population of patients predominantly presenting with symptoms necessitating exclusion of hypothyroidism and (2) to determine if the prevalence of antiTPO was significantly different in patients with upper-normal TSH as compared with those whose TSH values were in the lower-normal range.

**Methods**

**Study Design**

Subjects for this study were patients 18 years of age or older who had a TSH drawn for clinical indications based on a clinical guideline. They were recruited between November 2007 to January 2009 by 10 residents and six attending physicians working at a publicly funded community health center in Houston. Physicians involved were requested to obtain consent for the study if their patients were to have TSH testing performed. Charts were reviewed, and patients were excluded with the following conditions: Hashimoto’s Thyroiditis, known thyroid disease (goiter), pregnancy, diabetes type I, other autoimmune diseases (such as lupus and rheumatoid arthritis), radiation treatment for hyperthyroidism, pituitary disease, patients presenting with acute illnesses such as those that require hospitalization that could affect TSH (sick euthyroidism), and subacute thyroiditis. Also excluded were patients on the following medications: steroids, dopamine, iodine, amiodarone, lithium, donperidone, thyroid hormone, and phenytoin. Patients with a family history of thyroid disease and patients who work at night were also excluded.

During the study period, 187 samples were obtained from patients who met the inclusion criteria. In the majority of patients, the TSH was drawn secondary to symptoms like weight gain, fatigue, hyperlipidemia, irregular menses, constipation, hair changes, depression, and the remaining percentage for metabolic syndrome and anxiety. In a few patients, it was drawn as part of a well-patient exam (Table 1). Five were then excluded from further study because their TSH was outside the normal range of 0.36–5.49 IU/ml (three hypothyroidism, two hyperthyroidism range), leaving 182 for further study.

Patients were separated into two groups, 139 patients with low-normal TSH (0.36–2.49 IU/ml) and 43 patients with high-normal TSH (2.5–5.49 IU/ml). AntiTPO was measured in the first 100 of the 139 samples from patients with low-normal TSH, designated as group LN-TSH. AntiTPO was measured in all 43 high-normal TSH subjects, designated as group HN-TSH. Thus 143 patients formed the final study sample, and the demographics are shown in Table 2.

An extra sample of blood was taken from patients at the time of the original TSH blood draw and stored for up to 14 days to be used for measurements of antiTPO antibody testing for participants meeting the inclusion criteria. In 16 patients the extra blood sample was not drawn at the time of TSH (11 patients in group LN-TSH

<table>
<thead>
<tr>
<th>Reasons for Testing</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>61</td>
<td>39.10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>16.03</td>
</tr>
<tr>
<td>Irregular menses</td>
<td>13</td>
<td>8.33</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>6.41</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18</td>
<td>11.54</td>
</tr>
<tr>
<td>General checkup</td>
<td>8</td>
<td>5.13</td>
</tr>
<tr>
<td>Hair changes</td>
<td>10</td>
<td>6.41</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2</td>
<td>1.28</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2</td>
<td>1.28</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>4.49</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>156</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

TSH—thyroid stimulating hormone

Note: Some of the patients had multiple reasons for testing.
and five patients in group HN-TSH). In these patients, the sample was drawn less than 3 months from the original collection of TSH.

The study met the Committee for the Protection of Human Subjects approval for the University of Texas Health Science Center. Informed consent was obtained and available in Spanish and English as appropriate.

**Laboratory Methods**

The antiTPO tests were performed by Quest Laboratories. The test name was antiThyroid Peroxidase Antibodies using DPC Immulite 2000 by the method Chemiluminescent by Siemens (immunoassay using two phases, the first one with beads of human reagent buffer with alcohol phosphate and the second part with a monoclonal murine antihuman IGG with 30 minutes of centrifugation). Specimens were stable at room temperature for up to 4 days and for 2 weeks in refrigeration. The detectable values are between 10 to 10,000 IU/ml, and the reference range value is <35 IU/ml.

The TSH had the following characteristics: The ADVIA Centaur® TSH assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a monoclonal mouse anti-TSH antibody labeled with acridinium ester. The second antibody, in the Solid Phase, is a polyclonal sheep anti-TSH antibody that is covalently coupled to paramagnetic particles.

For specimen storage and stability the following guidelines were met: Samples were stored at room temperature for less than 8 hours and refrigerated at 2 to 8°C if the assay was not completed within 8 hours. Samples were frozen at or below -20°C if the sample was not assayed within 48 hours. The reference Interval is Euthyroid: 0.36–5.49 IU/ml (mIU/L), and the reportable range of the ADVIA Centaur TSH assay is 0.010 IU/ml (mIU/L) to 150 IU/ml (mIU/L).

**Data Analysis**

Analyses were conducted using SPSS v. 17.0. Evaluation of continuous variables used t test or one-way analysis of variance procedures. Analysis of dichotomous dependent variables included cross-tabulation and logistic regression.

**Results**

**Subject Characteristics**

The mean age of the 143 participants was 43.4 (SD =13.0) years, and 87.4% were female; 76.2% were Hispanic, 14% were African American, 4.2% were Caucasian, and 5.6% were self-identified as Asian or “other.” The mean body-mass index (BMI) was 32.2 (SD=7.59), and the mean TSH level for the entire 182 original samples was 1.88 (1.1).

Physicians’ reasons for ordering the TSH test are listed in Table 1. The two most common indications were weight gain and fatigue. Indications for obtaining a TSH did not significantly differ by group.

There were no significant differences between the LN-TSH and the HN-TSH groups on sex, age, or BMI. There were group differences on ethnicity (Table 2). A higher proportion of Hispanic patients were in the HN-TSH group (35.8%) relative to the other ethnic categories, with a very low proportion of African Americans having high normal TSH levels (5%).

Subject characteristics were also compared for patients who were positive versus negative for antiTPO (Table 3). No differences were found on ethnicity, age, or BMI. No male patients had a positive antiTPO test while 8.8% of females were positive, but this gender difference was not statistically significant ($\chi^2$(1) = 1.72, $P=.19$); only 12.6% of the subjects were male.

**Table 2**

**Demographics**

<table>
<thead>
<tr>
<th>Group</th>
<th>LN-TSH (TSH 0.36–2.49)</th>
<th>HN-TSH (TSH 2.5–5.49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=100</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.4 (12.0)</td>
<td>45.6 (14.9)</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Americans</td>
<td>19 (19.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Hispanics</td>
<td>70.0 (70.0)</td>
<td>39 (90.7)</td>
</tr>
<tr>
<td>Caucasians</td>
<td>5 (5.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (6.0)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>87 (87.0)</td>
<td>38 (88.4)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (13.0)</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>32.1 (7.5)</td>
<td>32.3 (8.0)</td>
</tr>
</tbody>
</table>

* $P=.04$

LN-TSH—low-normal thyroid stimulating hormone
HN-TSH—high-normal thyroid stimulating hormone
M (SD)/n (%)—mean (standard deviation)/number (percent)
BMI—body mass index

The second antibody, in the Solid Phase, is a polyclonal sheep anti-TSH antibody that is covalently coupled to paramagnetic particles.

Overall, 7.7% of the sample had a positive antiTPO test. Group differences were revealed on antiTPO status ($\chi^2$(1)=10.31, $P=.001$). Our findings indicate that 3% of the LN-TSH group was antiTPO positive, while 18.6% of the HN-TSH group had a positive test for antiTPO.
Evaluation of Lowering the Upper-Normal TSH Value

In clinical practice the upper limit for the normal TSH range is 5.49 IU/ml. Based on this value, no patients from the current sample would be referred by their physician for antiTPO testing. With our sample we explored the effect of lowering the upper limit value of normal to 3.49 IU/ml. Using this cutoff value, 15 patients (10.5% of the sample) would be considered above normal (>3.5) and would typically be referred for further antiTPO testing. Of these 15, three patients were antiTPO positive. Thus, in our sample, lowering the high normal cutoff value would result in testing only 10% more patients to identify 20% more (versus 0% using the currently accepted upper limit value) who are at risk of developing hypothyroidism.

Discussion

Physicians in primary care settings need to be aware of a potentially high-risk population that should be identified and more closely followed. Patients with high-normal TSH and positive antiTPO are at potentially greater risk of developing true hypothyroidism over time. We propose detecting these people in the earlier stages of the disease. We designed a prospective study whereby subjects in a primary care setting complaining of general symptoms, prompting the physician to order a TSH, were given an antiTPO test, although not indicated by current guidelines. The prevalence of antiTPO in our study was consistent with the reported percentage in the literature (4.4% to 25%).11,14 For those in the upper-normal TSH group (group HN-TSH), we found that the prevalence of antiTPO was significantly different compared to the lower-normal TSH group. These findings challenge the currently accepted upper limit for a normal TSH result. Several studies have suggested that the real mean of TSH is between 1.18 and 1.5 IU/ml and that 95% of the population has a TSH level below 2.5 IU/ml.

While positive antiTPO status was not significantly different by gender, this is likely a result of the small number of participating males (n=18). In our sample, none of the males had positive antiTPO while almost 9% of females were positive. It may be that high-normal TSH has more clinical relevance for women.11 Previous studies have reported higher prevalence of antiTPO in Hispanics and whites versus African Americans, who typically have the lowest prevalence.11 Although we found no differences in race with respect to positive antiTPO status, 82% of antiTPO positive patients were Hispanics and none were African American. Further, 90% of the high TSH group was Hispanics versus 2.5% of African Americans, despite the fact that African Americans comprise 15% of the whole study. It is possible that being of Hispanic background is a risk factor for developing hypothyroidism.

Our results should be reviewed within the context of study limitations. Our sample was drawn from patients seen by a subset only of residents and attending physicians at a large, community-based family medicine clinic. We have no reason to believe, however, that the patients in our study were substantially different from patients seen by other doctors in the clinic. Another limitation of our study was our small sample size, which likely lowered power to detect differences among various sub-groups of the sample.

Conclusions

Our finding that the prevalence of antiTPO is higher in a TSH range between 2.5 to 5.49 IU/ml may be important for clinicians to consider in their clinical practice. For example, based on our data, if a patient has a high-normal TSH, it may be appropriate to order an antiTPO test. If the antiTPO is positive, physicians may follow up patients more closely to determine if and when treatment is necessary for overt hypothyroidism. If the antiTPO is negative, there may be less concern about TSH values in the high-normal range. If the person is in the lower range TSH (0.36 to 2.49 IU/ml) a longer range follow-up would be appropriate.

Further, the results of this study have broader implications for the normal limit range used in evaluating a TSH level. Using current guidelines, almost 20% of the people in our sample with a positive antiTPO
would not be identified. Using a cut off value of 3.5 IU/ml, only 10% more patients needed testing to identify patients at potentially greater risk for hypothyroidism, perhaps suggesting a high benefit to cost ratio for testing patients with high-normal TSH levels. Each test cost is $85.75 in our clinical laboratory. One hundred tests would thus cost $8,575 to identify 20 patients potentially at risk. The additional cost of screening is offset by the improved health and productivity of patients who are followed up more closely and treated earlier in the course of their illness. Future studies are needed to further investigate and validate these recommendations.

By measuring the prevalence of antiTPO antibodies in high-normal range TSH individuals, and comparing them to individuals in the low-normal range, we have identified a specific population that are potentially at risk and that needs to be more closely followed. Future research can establish specific recommendations to guide physicians in helping patients to prevent and reduce the potential symptoms and consequence of hypothyroidism, as well as decrease the financial burden for the health system resulting from this disease.

Acknowledgments: This research project was presented as a poster at the 2008 Society of Teachers of Family Medicine Annual Spring Conference in Baltimore.

We want to acknowledge two key people that helped us with this article. Without them it would have been nearly impossible to have accomplished this project: David Zelaya for his editing and technical skills and Rose Young for her administrative support.

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