Reference limits for serum TSH differ significantly between races and with age, potentially causing erroneous diagnosis in a substantial number of patients

Boucai L, Surks MI. Reference limits of serum TSH and free T_4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf) 2009;70:788-93.

SUMMARY

BACKGROUND The upper reference limit of serum thyrotropin (TSH) is the subject of considerable controversy. As a result, the TSH reference limits derived from national databases have not yet been uniformly applied to clinical practice. This study is aimed at determining whether race and age influence the distribution of TSH and free thyroxine (FT_4). Although serum TSH reference limits have traditionally been established in individuals free of thyroid disease without antithyroid antibodies, more recent studies of thyroid disease–free subjects have found no difference in the median TSH and the 97.5th centile when individuals with antithyroid antibodies and even ultrasound abnormalities were excluded. Furthermore, analysis of the National Health and Nutrition Examination Survey III (NHANES III) found that age-related shifts in TSH distribution were not significantly altered by excluding individuals with antithyroid antibodies. These new findings thus suggest that TSH reference limits can now be assessed in populations deemed not to have thyroid disease on clinical grounds, without knowing the individual's antithyroid antibody status.

METHODS This is a cross-sectional study of the outpatient medical practices of the Montefiore Medical Center, Bronx, New York. Among 119,361 outpatients seen from January 1 through December 31, 2006, a total of 46,183 (38%) had TSH determinations. A total of 22,116 patients comprised the study group after excluding patients with International Classification of Diseases, 9th edition (ICD-9) codes for all thyroid diseases and those taking medications that affect FT_4 and TSH. Of the study group, 16,343 were female (74%) and 5773 were male (26%), and all were older than 10 years of age. The adult population was represented by 18,243 patients (83%) older than 20 years of age, only 3.8% of whom had tests for antithyroid antibodies. The median age of the adult group was 44 years, and of this group, 17,787 (98%) had simultaneous TSH and FT_4 determinations. Self-designated race/ethnicity, which was available in 11,604 patients (52.5%), was designated as black or African American in 32.8%, white in 14.7%, Hispanic in 5%, and undesignated in 47.5%. The Bronx has different demographics than occur nationally, reflected by the median age (31.2 years vs. 36.2 years), the percentage <44 years of age (71 vs. 65.5), and the percentage of whites (29.2 vs. 75%), blacks (35.6 vs 12.3), and Hispanics (48.4 vs. 12.5%), comparing Bronx demographics with national demographics.

RESULTS After dividing patients into arbitrary TSH categories ≤0.30, 0.31 to 2.49, 2.50 to 4.50 and >4.50 μIU/ml, the percentage of patients in the 0.31 to 2.49 category progressively declined with age, decreasing from 83.7% in the 20-to-29-year-old group (young) to 67.9% in the >80-year-old group (old), which was associated with a progressive increase in the percentage of patients with TSH levels in the 2.50 to 4.50 μIU/ml category (Figure 1). Approximately 90% of the patients in the TSH >4.50 μIU/ml category had serum TSH concentrations <10 μIU/ml, which suggested a shift to higher TSH levels with aging. A comparable shift in TSH distribution with age occurred in the major racial subpopulations within the study. In whites, the percentage of patients in the 0.31 to 2.49 μIU/ml TSH category decreased from

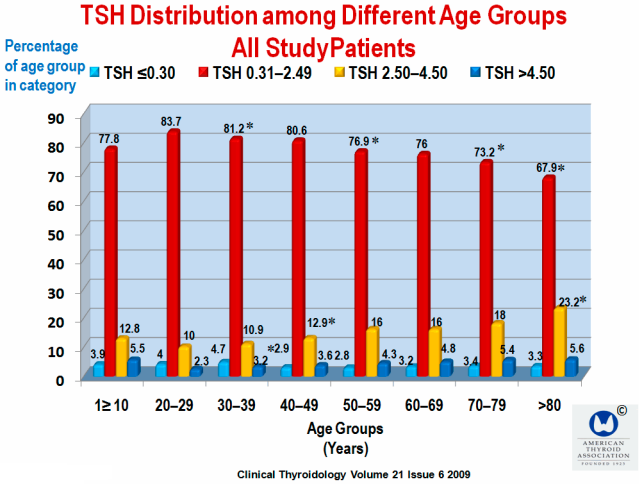

Figure 1. The percentage of patients in the 0.31 to 4.50 μIU/ml TSH category decreased progressively with increasing age. *P<0.05 for difference from prior age decile. (Derived from data in Table 1 of Boucai and Surks.)

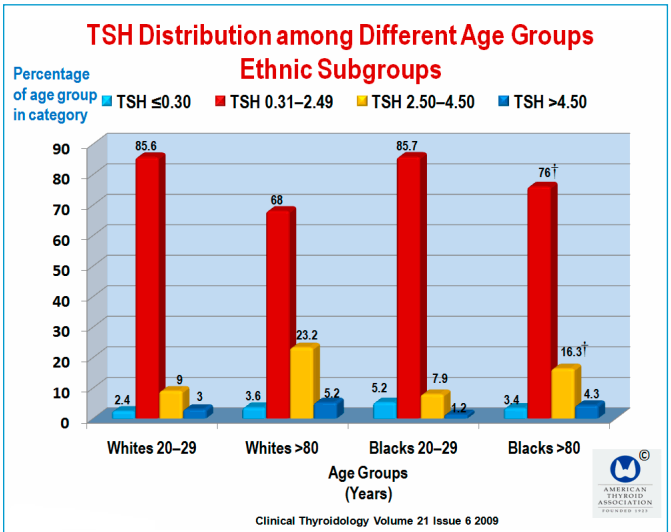

Figure 2. The percentage of patients in the 0.31 to 2.49 μIU/ml TSH category decreased significantly, from 85.6% to 76%, with age. †P<0.05, comparing white and black patients.

85.6% in the young to 68% in the old group, which was associated with an increase in patients in the 2.50 to 4.50 and >4.50 μIU/ml categories with age (Figure 2). Furthermore, the TSH distribution of whites shifted significantly to higher TSH levels than those in blacks, including the peak TSH levels. The median and 97.5th centile for TSH in whites (1.54 and 7.46 μIU/ml), were significantly higher than those in blacks (1.18 and 5.25 μIU/ml) (P<0.001). The TSH distribution in 1103 Hispanic patients was identical to that of blacks. Furthermore, the TSH distribution curves for men and women were superimposable for all patients, including blacks, whites, and Hispanics. In all patients combined (22,116), the TSH was found to shift to the right (higher levels) with age, with a median TSH of 1.13 μIU/ml and 1.61 μIU/ml, and the 97.5th centile 5.13 μIU/ml and 6.77 μIU/ml for young and old, respectively (P<0.001) (Figure 3). Moreover, there were similar population shifts in TSH distribution to higher concentrations with aging in each racial group (Figure 4). The median TSH level was significantly different among young and old whites (1.24 and 1.74 μIU/ml, respectively; P<0.007) and between young and old blacks (1.01 and 1.45 μIU/ml, respectively; P<0.001) (Figure 5).

The mean FT_4 decreased progressively as TSH increased (P for trend <0.001) (Figure 6). This occurred in all patients, including the subgroups young, old, blacks, and whites. The increment in FT_4 when the TSH was ≤0.3 μIU/ml, in comparison with the 0.31 to 2.49 μIU/ml category, indicating that some patients may have thyroid hormone hypersecretion. The mean (±SD) FT_4 was not significantly different in the young and old groups (18.02±4.5 vs.17.76±3.6 pmol/L; P = 0.11). However, mean FT_4 was higher in the white population than in the black population (18.3±3.99 vs.17.5±4.38 pmol/L; P<0.001). In a separate analysis, whites had significantly higher mean FT_4 levels than blacks in all TSH categories. Using the 2.5th centile for TSH from NHANES III (0.45 μIU/ml) 5.7% of all patients and 8% of blacks and 3.7% of whites

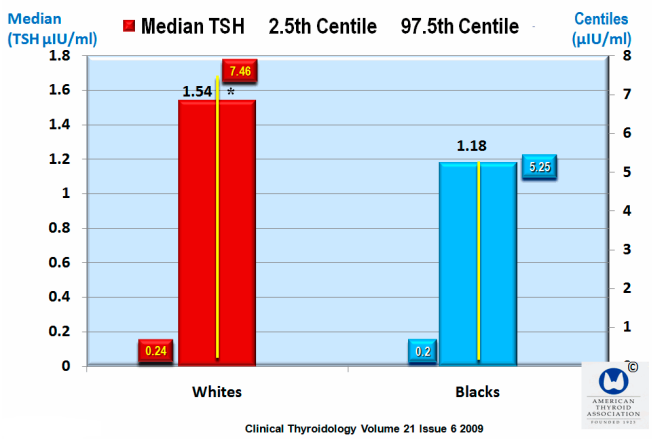

Figure 3. The median and 97.5th centile for TSH in whites were significantly higher than the median and 97.5th centile in blacks. *P<0.001. The yellow lines represent the 25th and 97.5th centiles.

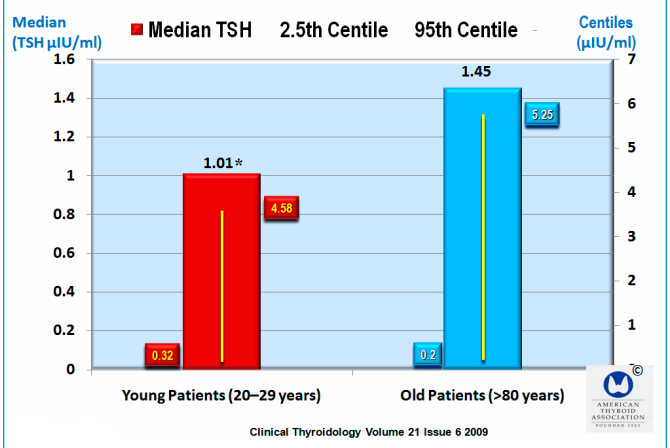

Figure 5. The median TSH and 97.5th centiles were higher in young black patients than in old black patients. *P<0.001. The yellow lines represent the 25th and 97.5th centiles.

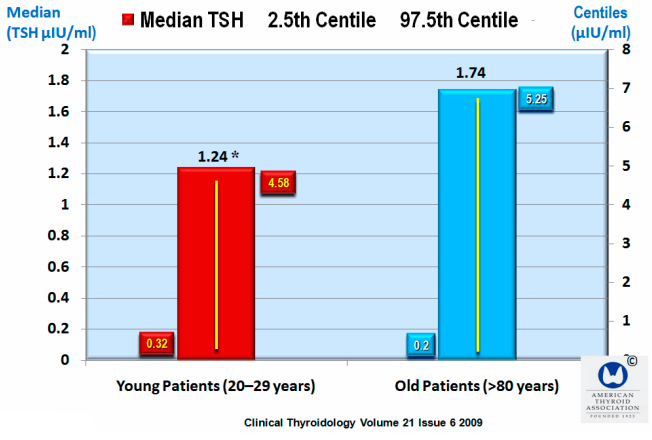

Figure 4. The median TSH and 97.5th centile were higher in older patients than in young patients *P<0.001. The yellow lines represent the 25th and 97.5th centiles.

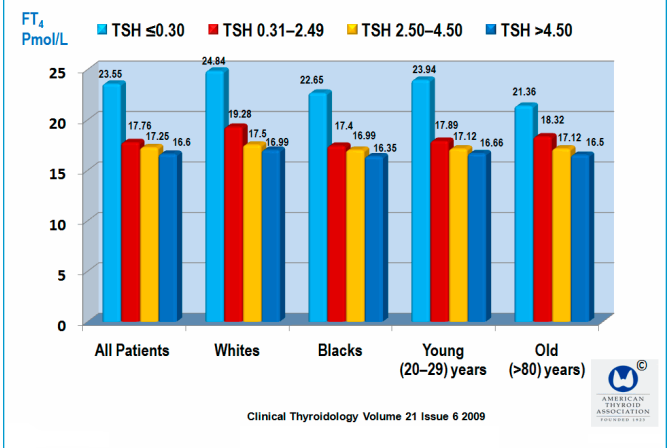

Figure 6. The mean FT_4 was significantly lower in blacks than in whites (P<0.001) and did not differ between young and old, but decreased progressively (average, 7%) as TSH increased to >4.50 μIU/ml.

would be misclassified as having elevated serum TSH levels. Using the 97.5th centile from NHANES III (4.12 μIU/ml), 4.1% of blacks and 5.8% of whites would be misclassified as having elevated serum TSH levels.

CONCLUSION Reference limits for TSH differ between races and with age and unless age-specific limits for TSH are used, the clinical diagnosis is misclassified in a significant number of patients.

COMMENTARY

This important study has major implications for the diagnosis of thyroid dysfunction. The study shows that the reference limits for TSH differ significantly with age and between races, indicating that race- and age-specific reference limits should be routinely used in practice. The patients in this study were judged to be clinically free of thyroid disease without excluding patients with antithyroid antibodies. This was done on the basis of three studies (1-3) that found no difference in median TSH and the 97.5th centile when individuals with antithyroid antibodies were excluded. Furthermore, the NHANES III survey showed that age-related shifts in TSH distribution were not significantly changed when individuals with antithyroid antibodies were excluded. Moreover, analysis of the NHANES III survey found that age-related shifts in TSH distribution were not significantly changed when individuals with antithyroid antibodies were excluded (3).

The main findings in this study were that TSH was higher in whites as compared with blacks, and in old patients(>80 years) as compared with young patients (20 to 29 years). Using TSH limits from national databases resulted in a significant misclassification that raised or lowered TSH concentrations. In all patients, blacks, and whites, 3%, 8% and 5%, respectively, of those older than 80 years were misclassified as having high TSH as compared with those 20 to 29 years of age. The NHANES III data suggest that blacks may have lower TSH levels than whites; blacks had a significant decrease in the median, 2.5th and 97.5th centiles as compared with whites, which was confirmed by this study.

The mean FT_4 decreased progressively as TSH increased to >4.50 μIU/ml and was lower in blacks than in whites but did not differ between young and old. As TSH increased to the >4.50 μIU/ml category, the decrement in mean FT_4 was 6.5% for all patients, 7% for whites, 6% for blacks, and 8.4% for young and old. The authors suggest that when the TSH was ≤0.30 μIU/ml, in comparison with the 0.31 to 2.49 category, some patients may have hypersecretion of thyroid hormone. The implications of this are not clear and require further study. Nonetheless, regardless of the TSH level, the mean FT_4 concentration was not significantly different from that in the old group (>80 years). However, mean FT_4 was significantly higher in whites than in blacks and was significantly higher in all TSH categories.

The debate concerning the diagnosis of subclinical thyroid disease began in 2004 when Surks et al. (4) published a review and guidelines for the diagnosis and management of subclinical hypothyroidism and hyperthyroidism. Since then, the debate has swirled around the upper reference limits for TSH, which directly translates into the threshold for thyroid hormone–replacement therapy. However, in the past several years, Surks and his associates have been carefully studying the features that weave the fabric of our knowledge concerning the subtleties in serum TSH concentrations in normal individuals, which have a compelling impact on clinical decisions that will especially affect patients with subclinical thyroid dysfunction. This article and another just published article (5) that was highlighted in the May issue of Clinical Thyroidology set the standard for our understanding of the subtle changes in TSH with age, which will likely change our practice.

Ernest L. Mazzaferri, MD, MACP

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