TSH Reference Limits: Emerging concepts and implications for the prevalence of subclinical hypothyroidism

The diagnosis of hypothyroidism is based on negative feedback between serum thyroid hormones and serum thyrotropin (TSH). A raised TSH with decreased free thyroxine (T_4) defines primary hypothyroidism, but when free T_4 remains within reference limits, the diagnosis is subclinical hypothyroidism. Given the high prevalence of raised TSH, particularly among older patients with normal free T_4, designation of the upper reference limit is critical.

During the past 15 years, the reported upper limit has been considered to be about 4.0 to 5.5 mIU/L, and several national reference laboratories and manufacturers of TSH assay kits provide similar limits. Analysis of TSH distribution from the National Health and Nutrition Examination Survey III (NHANES III) (1) suggested an upper limit of 4.12 mIU/L for a large reference population that was free of thyroid disease and representative of the U.S. population. Also excluded from that group were subjects who were taking thyroid medications, or other medications that might affect thyroid measurements, as well as those who had antithyroid antibodies.

This Concise Review will address two issues: First, concerns regarding the proposal to lower the upper reference limit to 2.5 to 3.0 mIU/L; and second, new data that supports use of age- and ethnic-specific reference limits in evaluation of patients with thyroid dysfunction.

TSH reference limits are determined by analyzing TSH distribution after log transformation. Distribution curves generally show a skew toward higher TSH concentrations, which has been assumed to represent individuals with undetected autoimmune thyroid disease. The National Academy of Clinical Biochemistry suggested that the upper reference limit of rigorously screened individuals without thyroid disease would likely be 2.5 mIU/L (2), and some authorities and professional societies have recommended decreasing the upper limit from 4 mIU/L to 2.5 to 3.0 mIU/L (3) for a comparable population. This recommendation is not only controversial (4), but would have enormous public health consequences since TSH exceeds 2.5 mIU/L in 10 to 20% of individuals of all ages and 35% of people who are more than 70 years of age. Such individuals could be designated hypothyroid and possibly treated with levothyroxine, unnecessarily, for the duration of their life (4).

However, several recent studies of thyroid disease-free individuals found no significant change in the TSH upper limit when patients with antithyroid antibodies (5-7) or even abnormalities on thyroid ultrasound (5,6) were excluded. Most recently, Hamilton et al. (6) studied a mainly white U.S. population (97.4%) without thyroid disease or antithyroid antibodies and found a similar 97.5th percentile whether or not those with thyroid ultrasound abnormalities were excluded. After correcting for changes in assay methods, the 97.5th percentile was 4.1 mIU/L, identical to the 97.5th percentile from NHANES III, 4.12 mIU/L (1). These findings in an iodine-sufficient North American population confirm similar observations from Europe that excluding people with antithyroid antibodies or ultrasound abnormalities did not significantly influence the 97.5 percentile (5). They provide additional evidence against an arbitrary decrease in the TSH upper limit.

The 97.5th percentile reported by Hamilton and colleagues (6) is for a population without thyroid disease. However, the 20-year follow-up of the Whickham study did show an increased rate of progression to overt hypothyroidism when TSH was >3.0 mIU/L (8), suggesting that some in this group did have underlying thyroid disease. Further analysis of these data showed that progression to hypothyroidism occurred in less than 10% of 20- to 40-year-olds and in 5 to15% of individuals 50 to 70 years of age who had TSH >3.0 mIU/L (4). The prevalence increased further in those who had antithyroid antibodies. Since nearly 80% of subjects with TSH between 3.0 and 5.0 mIU/L do not have antithyroid antibodies (4), it is likely that the large majority of people with TSH in that range have little risk of hypothyroidism.

An explanation for the skew in TSH distribution curves toward higher serum TSH was recently reported (9). In all analyses thus far, TSH distribution curves were developed from TSH measurements from people of all ages, thus representing a composite curve across the spectrum of age. When the NHANES III database was reanalyzed by development of TSH distribution curves for specific age deciles, a progressive shift in the curves to higher TSH with age was observed, rather than a skew to higher values. These findings, confirmed by analysis of a more recent NHANES survey (1998–2002), suggested that TSH distribution and reference limits increase with age, and that TSH reference limits derived from curves that are composite for all ages could lead to significant misclassification of patients with thyroid disease. For example the upper age-specific limit for people older than 80 years of age was 7.5 mIU/L and it was estimated that about 70% of such people who had TSH >4.5 mIU/L, previously considered to have raised values, were within their age-specific limits.

When an urban outpatient practice of medicine was similarly analyzed, the shift in TSH distribution and upper reference

limit with age was observed in the total population and in each major ethnic subgroup, blacks, whites, and Hispanics (10). Moreover, significant differences were observed in TSH distribution and reference limits between the individual ethnic subgroups, with blacks and Hispanics having a shift to lower TSH compared with whites. Significant misclassification of individuals with raised or decreased TSH occurred unless both ethnic- and age-specific limits were used.

SUMMARY

Recent literature provides evidence against lowering the upper limit of the TSH reference range in the United States and emphasizes the importance of using both ethnic- and age-specific reference limits in order not to misclassify patients with thyroid disease.

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