Editorial: Upper Limit of Normal Serum Thyroid-Stimulating Hormone: A Moving and Now an Aging Target?

Serum TSH measurement is the most sensitive screening test for thyroid dysfunction and for the diagnosis of subtle forms of hyper- and hypothyroidism (1). Serum TSH has a log-linear relationship with circulating thyroid hormone levels; thus a small change in peripheral thyroid hormone concentrations, even within the normal laboratory reference range, may result in an increase or decrease in serum TSH outside its normal range (2). The laboratory reference range is usually chosen by determining the 95% confidence limits of a population of individuals free of known thyroid dysfunction. By this method, 2.5% of normal individuals may have high serum TSH values. However, if unrecognized thyroid failure is present in more than 2.5% of the population, mild hypothyroidism will be underdiagnosed. Thus, it has been proposed that more strict selection criteria should be the basis for determination of normal values (3).

In interpreting serum TSH levels, one should consider physiological variations as well as occult thyroid disease. Values are highest in the early morning and lowest in the afternoon. This diurnal variation may be affected by depression, bipolar disorder, and night shift work (4–6). Serum TSH may be slightly higher in morbid obesity and may be reduced after weight loss (7). There are other causes of high TSH not associated with thyroid failure, such as heterophile antibodies (i.e., assay interference), recovery from nonthyroidal illness, thyroid hormone resistance, TSH-producing pituitary tumors, TSH molecules with lower biological activity, and certain cases of hypothalamic-pituitary disorder, when secretion of TSH with altered biological activity may occur. However, these conditions are uncommon, and most patients with persistently elevated TSH have autoimmune thyroid disease (1).

It has been suggested that when individuals with thyroid autoantibodies, goiter, or a strong family history of thyroid disease are excluded, the 95% TSH reference range shrinks to between 0.3 and 2.5 or 3.0 mIU/liter (3). It has been argued that such a “refined normal” range is a better reflection of “thyroid health” than a standard population-based reference range (3) and that values between 2.5 and 4.5 mIU/liter predict “thyroid health” better than the standard laboratory reference range (3). Consequently, it has been proposed that more strict selection criteria should be the basis for determination of normal values (3).

Moreover, it has been suggested that when individuals with thyroid autoantibodies, goiter, or a strong family history of thyroid disease are excluded, the 95% TSH reference range shrinks to between 0.3 and 2.5 or 3.0 mIU/liter (3). It has been argued that such a “refined normal” range is a better reflection of “thyroid health” than a standard population-based reference range (3) and that values between 2.5 and 4.5 mIU/liter predict “thyroid health” better than the standard laboratory reference range (3).

In contrast to the controversy about subclinical hypothyroidism and serum TSH values at the upper limit of normal, there is no controversy about TSH levels below the lower limit of normal. One reason is that the number of individuals with serum TSH between 0.3 and 0.4 mIU/liter is not very high, and there is not a skewed TSH distribution at the lower end of serum TSH distribution as there is at the high end. There is also no controversy about management of subclinical hyperthyroidism because of strong evidence for adverse effects on bone health and cardiovascular system (10).

The importance of having a consensus on the normal TSH range is that some authors have recommended routine screening for thyroid disease after age 35 (11) and other societies for women above age 50 (12). Screening of pregnant women and women anticipating pregnancy has also been proposed (13). With TSH screening and physician awareness of thyroid disorders, a large number of individuals, up to 10% of the tested population, will have serum TSH values above the level of 4.5 mIU/liter (14). A lowering of the upper limit of normal for TSH may result in a tripling of the frequency of abnormal results for persons over 50 yr old (15).

The issues of screening (12), the treatment of subclinical hypothyroidism, and normal range for serum TSH (16) are subjects of intense debate within the thyroid community (16–21). Treatment of minimally elevated TSH between 4.5 and 10 mIU/liter has been suggested by national societies (19), and yet a consensus panel has found no evidence in favor of routine therapy of patients at these levels of TSH (21). However, there is consensus for T4 treatment of patients with elevated serum TSH levels above 10 mIU/liter (22).

A common understanding among thyroidologists has been that 15–20% of older individuals have serum TSH levels above normal due to a higher prevalence of mild autoimmune thyroid disease in this age group. In this issue of the Journal, Surks and Hollowell (22) offer an alternative explanation. These authors examined the age-specific distribution of serum TSH and antithyroid antibodies in both National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES (1999–2002). The authors obtained similar results in both NHANES groups. In NHANES III, there were 16,533 disease-free individuals not reporting thyroid disease, goiter, or thyroid-related medications. After exclusion of medications such as lithium and estrogens and individuals with positive thyroid peroxidase or thyroglobulin antibodies and overt hyperthyroidism or hypothyroidism, 1344 remained and were designated reference population (23). NHANES (1999–2002) included 4392 individuals.

Surks and Hollowell (22) analyzed the data for different age groups, categorized by TSH levels: 0.4–2.5 mIU/liter (proposed normal by some national societies); 2.4 to 4.5 mIU/liter (proposed normal by some national societies); 5.1 to 10 mIU/liter (proposed normal by some national societies).
mIU/liter (4.5 is the traditionally accepted upper limit of normal); and TSH above 4.5 mIU/liter. They determined the distribution of these TSH subgroups in different decades of life in individuals aged 12 to over 80 yr. They noted that in both the disease-free population and the thyroid antibody-negative reference population, the distribution of TSH and peak frequency (most commonly occurring serum TSH level) are shifted upward from TSH levels with increasing age. In the antibody-negative reference group, the 99.5th percentile, representing the upper limit of normal, was 3.56 mIU/liter for the 20- to 29-yr-old group and progressively increased to 4.33 mIU/liter for ages 60–69, 5.9 mIU/liter for ages 70–79, and 7.49 mIU/liter for the over 80 age group. Similarly, for the disease-free population, the upper limit of TSH for the younger group starts at 4.0 and increases to 9.36 mIU/liter for the over-80 age group. The authors show that positive antithyroid antibodies in the older age group account for only 4% of the increase in TSH. They propose that the higher TSH levels in the older age groups are not entirely related to the higher frequency of thyroid failure because the TSH distribution curves of antibody-negative and disease-free groups are almost superimposable. The peak frequency of TSH also increases with advancing age. The authors did not supply data, but they indicate that the same trend was present for males and females, and changes in ethnic distribution did not account for the findings. The data show that 67% of the 40–49 age group with TSH above 4.5 mIU/liter had positive antibodies. However, although TSH levels increased with increasing age, the percentage of individuals with positive antithyroid antibodies decreased to 40% in the 80+ age group.

The authors accept the limitations of the study, namely the fact that the data may not apply to populations outside of the United States and that the older age group with higher TSH levels still may have autoimmune disease that was not detected by present assays for antithyroid antibodies. Also, the authors could not exclude the possibility that the elevated TSH levels in the older age groups may be related to medications taken for other conditions. The findings also contrast with studies showing a reduced response of TSH to thyroid failure in older compared with younger individuals. In contrast to the present study, others have shown lower TSH levels in the very old. The authors suggest that those studies included smaller numbers of cases, which may account for the discrepancy. In my opinion, the majority of the prior reports, which were from Europe, may have been influenced by the increased frequency of endemic goiter resulting in nodular disease with partial autonomy of thyroid. It would have been of interest for Surks and Hollowell to show data for serum T4 measurements in the same populations to determine the nature of the relationship between T4 and TSH within the studied populations.

How important is it to have an age-adjusted upper limit of normal for serum TSH? It all depends on clinical importance of a mildly elevated serum TSH. There is no convincing evidence for adverse effects in thyroid antibody-positive patients with TSH levels between 2.5 and 4.5 mIU/liter, except for a higher probability of progression to hypothyroidism. For TSH levels between 4.5 and 10 mIU/liter, evidence for adverse effects and benefits of therapy are controversial (22). For the important subgroup of patients with serum TSH levels under 10 mIU/liter, some studies have shown no benefit of T4 therapy for metabolic parameters and/or quality of life. In terms of adverse events, some studies have shown an association with atherosclerosis and increased cardiovascular or total mortality, whereas others have not.

Thus, the subject remains controversial, and the data upon which to base a firm conclusion are insufficient. For cardiac dysfunction, several studies have shown slowed left ventricular relaxation time, increased vascular tone at rest, and left ventricular systolic dysfunction in subclinical hypothyroidism. Some studies have shown improvement of cardiac contractility and systolic time interval with therapy. These studies may apply only to patients with serum TSH levels above 10.0 mIU/liter. Until the issue of whether elevated TSH between 4.6 and 10 mIU/liter is a risk factor for cardiovascular events is clarified, and until large-scale randomized clinical trials show benefits of therapy, mildly elevated serum TSH, especially in patients above age 70, should not necessarily be considered indicative of disease, particularly in the absence of antithyroid antibodies. Indeed, one study showed a protective survival effect of having an elevated serum TSH in individuals over age 85 yr. These observational studies and the data presented by Surks and Hollowell in this issue of the Journal speak against diagnosis of mild thyroid failure on the basis of minimally elevated serum TSH levels that may be more applicable to younger patients but not to an older age group. It should also be considered that a large number of T4-treated individuals may be at risk for inadvertent iatrogenic hyperthyroidism and overzealous T4 therapy may be harmful. Surks and Hollowell are against the proposed lowering of the upper limit of normal TSH to 2.5 or 3.0 mIU/liter, especially if it is applied to all age groups. Of interest, the proposal to lower the upper limit for TSH was heavily based upon the same NHANES III data that were also used by Surks and Hollowell. The reanalysis with categorization to age groups results in a different conclusion.

What should clinicians do when faced with unanswered questions about the upper limit of normal for TSH and about the management of patients with mildly elevated serum TSH? Until large-scale studies result in clear guidelines and recommendations, a practical approach both for diagnosis and intervention is recommended. In interpreting TSH values, the age of the patient, the presence or absence of antithyroid antibodies, the presence of symptoms, and patient preferences should be considered. Patients younger than age 60 with serum TSH levels between 2.5 and 4.5 mIU/liter with positive antibodies may be at higher risk of developing overt hypothyroidism and deserve follow-up. Any woman anticipating pregnancy with positive antibodies and serum TSH above 3.0 mIU/liter should be considered for T4 therapy. The data presented in this issue of the Journal offer strong evidence that individuals above age 70 with serum TSH levels under 7.5 mIU/liter and negative antibodies are unlikely to have thyroid failure and may be in their age-adjusted normal range. However, in the presence of immunological, clinical, and ultrasound abnormalities, patients may need to be followed every 6–12 months with TSH measurement. Also, it
is reasonable to consider a higher therapeutic TSH target for older hypothyroid patients on T₄ therapy.

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