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# Using Age-Specific Upper Limits for Normal TSH Slightly Reduces the Incidence of Subclinical Hypothyroidism in the Elderly

Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. Clin Endocrinol (Oxf). June 15, 2012 [E-pub ahead of print]. doi:10.1111/j.1365-2265.2012.04463.x

## SUMMARY

### Background

It is fairly common to find that a patient's TSH level is above normal (but below 10), yet the thyroid hormone levels are normal. What is more, TSH levels increase with age—even in elderly patients without thyroid disease—whereas $FT_4$ levels do not change (1). This raises the question of when (or whether) a high TSH should be treated in elderly patients, particularly in view of recent reports that longevity is associated with higher TSH levels in several groups of individuals, which raises the possibility that a mildly elevated TSH could somehow be beneficial in certain elderly patients. The authors of this paper determined age-specific reference ranges for the TSH assay used in their region, permitting them to estimate how raising the upper limit of normal for TSH in apparently euthyroid elderly patients would affect the number of patients given the diagnosis of subclinical hypothyroidism.

### Methods

Over 220,000 consecutive TSH screening assays were performed in 2010 in a statewide reference lab in Western Australia that uses the Siemens ADVIA Centaur assay. The majority of samples came from general practitioners' offices. Dietary iodine is sufficient in this area, where the population is predominantly of European descent. Based on information provided on pathology request forms, sera from patients with known or suspected thyroid disease were excluded, as were samples from any patients on whom $FT_4$, $FT_3$, or antithyroid antibodies had been requested. They also eliminated samples from infants and from patients who were pregnant or taking lithium, amiodarone, or anticonvulsants. Also eliminated were samples obtained after 6 p.m. or before 7 a.m. This left about 150,000 TSH determinations from unique patients for analysis. The TSH data were sorted by patient age in 5-year intervals. The authors also performed a separate study that compared the consistency of TSH determinations obtained using the Centaur assay with results from three other commonly used third-generation assays (Architect [Abbott], Modular Analytics [Roche] and Immulite [Siemens]) using 120 samples with TSH values between 0 and 10 mU/L.

### Results

For patients up to 55 years of age, the 97.5th percentile for TSH values was less than 4.0 mU/L. Above that age, the upper value for the 97.5th percentile gradually rose, reaching about 4.75 mU/L in the 11,000 patients who were between 75 and 85 years of age, and reaching 5.0 mU/L for the 2500 patients between 85 and 90.

The comparison of the four third-generation TSH assays revealed that their variability on samples with TSH values under 2 mU/L was not as striking as on samples with values above 4.0 mU/L, where the assay results could differ by more than 1 mU/L.

### Conclusions

Using age-specific reference ranges for TSH does reduce the fraction of elderly patients who would be given a diagnosis of subacute hypothyroidism, but only by 2% for patients over age 75, and by 5% for those over age 90. In addition, some third-generation TSH assays seem to have steeper TSH dose–response slopes than others, which makes it more difficult to compare TSH values between studies that have used different assays. A TSH reported as being slightly elevated on one assay could be reported to be normal on another assay.

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## ANALYSIS AND COMMENTARY

A recent reanalysis of the NHANES III data, using age-, sex- and ethnicity-specific TSH reference limits, eliminated 144 of 13,344 subjects in the "Reference Population" because they had a TSH >10 or <0.1 mU/L, leaving 4671 whites for analysis (2). The 97.5th percentile for TSH values in whites 70 to 79 years old was 5.6 mU/L, and for those over age 80 it was 6.6 mU/L. The reference population was known not to be overtly hyperthyroid or hypothyroid, was not taking medications known to affect thyroid-function tests, and was specifically known to have no detectable antithyroid antibodies, and thus is closest to the Western Australian population studied, with the exception that anyone who had had antithyroid antibodies ordered was excluded from the Australian study. In the 14,347 Australian subjects who were 70 to 79 years old, the 97.5th percentile for TSH was 4.5 mU/L; for the 8417 subjects over age 80, it was 5.0 mU/L. Thus, the increase in TSH with increasing age in Australia was not as great as that found in the reanalysis of the NHANES III data. One major difference between the two studies is the much greater sample size in the Australian study, but the differences between the TSH assays used, in geography, and in ethnic backgrounds also need consideration.

Until recently, manufacturers of TSH assays indicated that values between 0.4 to 4.0 mU/L were normal, although it is now clear that the TSH level in a healthy individual does not vary by that much. Some of the genes that contribute to the TSH set point have been identified, but as an individual ages, there could be changes in 1) TSH bioactivity, 2) thyroidal TSH responsiveness, 3) factors regulating thyroid hormone uptake and metabolism, 4) thyroid hormone receptors, and/or 5) cofactors that modulate the $T_3$-responsiveness of a given gene in a given tissue. A recent study of patients over 65 years of age who were able to function normally in a community and were not taking thyroid hormone indicates that subclinical hypothyroidism commonly persists for at least 4 years, but if a patient's TSH is below 7 mU/L (as determined by Elecsys 2010 analyzer, Roche) and the anti-TPO titer is normal, the TSH is more likely to normalize within 2 years (3). Undoubtedly, administering L-$T_4$ to elderly patients with mild subclinical hypothyroidism can alter physiological and biochemical parameters. (For example, Dr. Mestman discusses such a report in this issue of Clinical Thyroidology on patients under age 75 with subclinical hypothyroidism plus chronic kidney disease, in which giving L-$T_4$ reduced the rate of decline in renal function [4]). In general, replacement of $T_4$ in elderly patients with subclinical hypothyroidism should be gradual and monitored closely, to avoid overreplacement. Evidence that such therapy improves mortality remains meager, however, particularly in those over age 65 (5).

**— Stephen W. Spaulding, MD**

## References

1. Bremner AP, Feddema P, Leedman PJ, Brown SJ, Beilby JP, Lim EM, Wilson SG, O'Leary PC, Walsh JP. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab 2012;97:1554-62. Epub February 16, 2012.
2. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 2011;21: 5-11. Epub November 8, 2010.
3. Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study.

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J Clin Endocrinol Metab 2012;97:1962-9. Epub March 21, 2012.

4. Shin DH, Lee MJ, Kim SJ, Oh HJ, Kim HR, Han JH, Koo HM, Doh FM, Park JT, Han SH, Yoo TH, Kang SW. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab. June 20, 2012 [Epub ahead of print]. doi:10.1210/jc.2012-1663.
5. Yang LB, Jiang DQ, Qi WB, Zhang T, Feng YL, Gao L, Zhao J. Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies. Eur J Endocrinol 2012;167:75-84, Epub April 24, 2012.