Upper Limit of TSH Reference Range Debated

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Providers looking for a defined upper limit of the statistically normal reference range for serum thyroid-stimulating hormone in apparently healthy, nonpregnant individuals—a measurement beyond which a patient might be followed or worked up for hypothyroidism—will be hard pressed to find a consensus around any single number.

Whichever number is used for that cutoff could have enormous public health implications by including or excluding millions of people from being considered to have "normal" thyroid-stimulating hormone (TSH) levels. Spirited debate in the past few years continues, with providers and laboratories using different numbers at different institutions. Consider:

'You can't make a strong case either way' to treat or not treat mildly elevated TSH levels.

DR. FATEMI

- ► The Mayo Clinic, Rochester, Minn., sets the upper limit for the TSH reference range at 5 mU/L.
- ► The Southern California Kaiser Permanente Medical Group sets the upper limit at 4 mU/L.
- ► The University of Southern California, Los Angeles, recently lowered its cutoff to 3 mU/L.
- ► Some thyroid experts advocate for the upper limit to be even lower—2.5 mU/L.

What difference does a number make? Possibly quite a bit.

A study of TSH measurements in 75,882 patients without diagnoses of thyroid disease at the Mayo Clinic found that lowering the upper limit of normal from 5 mU/L to 3 mU/L would quadruple the number of patients classified as having elevated TSH concentrations, or "biochemical hypothyroidism," from 5% to 20% of the cohort, Dr. Stefan K. Grebe and associates reported (JAMA 2003; 290:3195-6).

This change could greatly increase unnecessary monitoring and treatment, as well as possible side effects from overdosing, said Dr. Grebe, director of the endocrine laboratory at the Mayo Clinic.

More appropriately, a patient with an elevated TSH measurement should be checked for thyroid antibodies and have the TSH level confirmed on a separate blood specimen drawn 1-2 months later before treatment is considered.

While there's remarkable agreement in the medical community that the lower limit of the reference range (below which someone might be evaluated for hyperthyroidism) hovers around 0.3 mIU/L, debates rages on both the appropriate upper limit and on what level of TSH elevation above that upper limit should be treated.

If you base the TSH reference range on a population that excludes anyone with a personal or family history of thyroid disease, the upper limit of normal settles around 4-5 mU/L, Dr. Grebe noted. More strenuous criteria in the National Health and Nutrition Examination Survey III (NHANES III) that also excluded anyone with a predisposition to thyroid dysfunction (evidenced by the presence of thyroid antibodies) produced a reference range upper limit of around 3.5 mU/L.

Around 20% of people with mild TSH elevations who have ultrasound evidence of occult thyroid dysfunction will have no thyroid antibodies detected, however, suggesting that the upper limit of the reference range in NHANES III is inflated by this subgroup, said Carole Spencer, Ph.D. A more appropriate upper limit probably is 2.5 mU/L, she argued in a recent analysis of the NHANES III data that was published online and accepted for print publication (J. Clin. Endocrinol. Metab. 2007 [Epub doi:10.1210/jc.2007-0287]).

"Because you've got these people with mild degrees of thyroid dysfunction contaminating the calculation, you cannot use population data to get a really clean TSH upper limit," explained Dr. Spencer, one of the most vocal proponents of setting an empirical reference range of 0.3-3 mU/L and a professor of medicine at the University of Southern California, Los Angeles.

Guidelines that have attempted to deal with the diagnosis and management of subclinical hypothyroidism have been surrounded by controversy.

The American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society sponsored an evidence-based consensus conference in 2002. Among its conclusions, the panel recommended against routine screening for subclinical thyroid dysfunction in the general population or in women who are currently or planning to be pregnant, and against routine treatment of patients with serum TSH levels of 4.5-10 mU/L because of insufficient evidence that this is beneficial (JAMA 2004;291:228-38).

The three sponsoring organizations subsequently disowned those conclusions in a statement arguing that there's no evidence for a lack of benefit either, so providers should consider individual patient factors in determining the need for TSH testing and treatment. The potential benefits of early detection and treatment of subclinical thyroid dysfunction outweigh potential side effects, the authors stated (Endocr. Pract. 2004;10:497-501).Thyroxine treatment is believed to be fairly safe, but overdosing in the elderly can increase their risk for cardiac arrythmia or osteoporosis,

Dr. Martin Surks, professor of medicine and pathology at Albert Einstein College of Medicine, New York, and lead author of the consensus conference statement, said studies suggest that around 20% of patients taking thyroid medication are overdosed. There are no studies specifically designed to show that thyroid hormone therapy is safe in people with mild TSH elevations, he said.

"There is a lot of controversy over whether these minimally raised levels of TSH affect anyone badly," Dr. Surks added. "They may even be beneficial," one published study suggests. "Nobody knows."

Three meta-analyses published this year reached divergent conclusions, with two saying mildly elevated TSH levels increased the risk of cardiac complications, and one reporting no increased risks. "That tells you the data are no good," Dr. Surks said.

He and his associates will publish a new analysis of the NHANES III data this fall concluding that a significant share of the elderly people whose TSH levels were designated as elevated were inappropriately classified.

As for setting the upper limits on TSH low, Dr. Shireen Fatemi, director of endocrinology at the Panorama City (Calif.) Kaiser Permanente Medical Center, said that it's important to treat case by case. "You can't make a strong case either way" to treat or not treat mildly elevated TSH levels, she said. "Take the whole patient into consideration." ■