TSH Range Is Not Universally Applicable

BY DIANA MAHONEY
New England Bureau

Mistaking the population reference range of thyroid-stimulating hormone for an individual's "normal" range can lead to suboptimal diagnosis and treatment of thyroid disease, according to Carole Spencer, Ph.D., professor of medicine and director of the Endocrine Services Laboratory at the University of Southern California in Los Angeles.

Population reference ranges for thyroid function tests are based on statistical averages, not on standards of biologic activity at different levels of thyroid hormones, Dr. Spencer stressed in an audioconference on the challenges of thyroid testing sponsored by the American Association of Clinical Chemistry. "Because individuals have different pathophysiologic factors that influence TSH [thyroid stimulating hormone], the combination of these variables in cohorts of individuals widen the TSH population reference range," she said.

For example, "the typical [National Health and Nutrition Examination Survey] U.S. population reference range for TSH is 0.4-4.1 mU/L, which is much wider than the annual fluctuations in TSH typical of individuals," said Dr. Spencer. "In fact, a TSH change in an individual that exceeds 0.75 mU/L, which is well within the population range, is biologically significant."

Although the TSH population reference range is a crude parameter for detecting disease in individual patients, its accuracy is considered critical "because TSH is the first abnormality to appear as disease develops," said Dr. Spencer. Additionally, "there is growing data suggesting that mild subclinical hypothyroidism can exacerbate the risk for cardiovascular disease in susceptible individuals," she said. As such, identifying patients at risk for developing this condition is important.

There has been much debate among endocrinologists over the upper reference limit for TSH in particular. Over the past 3 decades, "the reference ranges have contracted as a result of improvements in TSH assay sensitivity and specificity, coupled with more sensitive thyroid antibody tests that are used to eliminate individuals with thyroid autoimmunities from reference range calculations," said Dr. Spencer. "While the lower reference has been established as being around 0.3 mU/L, the upper reference limit has steadily declined from approximately 10 mU/L to between 4.0 and 4.5 mU/L."

Additionally, there is strong clinical rationale for adopting the even narrower TSH reference range of 0.3-3.0 mU/L recommended by the American Association of Clinical Endocrinologists in 2003, Dr. Spencer noted. "We know from a 20-year follow-up survey of the Wickham thyroid survey [a historical cohort study that provided incidence data for thyroid disease for a representative cross-sectional sample of the population] that a TSH above approximately 2.0 mU/L is a risk factor for future development of hypothyroidism, especially when thyroid peroxidase [TPO] antibody is detected." This is true "even in the absence of thyroid antibodies," she said.

The empiric lowering of the upper reference limit is further justified in light of the growing recognition that even mild subclinical thyroxine deficiency in early pregnancy is detrimental to the mother and fetus, Dr. Spencer added.

Despite the data supporting the narrower reference ranges, many U.S. laboratories have not revised their "normal range" criteria, nor have all clinicians adopted the new range for diagnostic and treatment purposes, according to Dr. Spencer. One perceived roadblock has been the lack of data on the patient management implications of making the change, she said.

"Patients with TSH outside the narrower reference range do not necessarily require treatment," said Dr. Spencer. "Rather, the degree of TSH abnormality outside the range should be viewed as a risk factor for current or future development of hyper- or hypothyroidism."

The threshold for treatment has to be adjusted for patient-specific factors, such as the degree of TSH abnormality, family history of cardiovascular disease, diabetes, insulin resistance, hypertension, smoking, age, and presenting symptoms, Dr. Spencer noted. Additionally, the presence and concentration of thyroid autoantibodies is an important factor. "The higher the thyroid peroxidase autoantibody concentration, the more rapid the progression of disease," she said.

Ultimately, the diagnosis and efficacy of treating subclinical hypothyroidism should not be based on the TSH reference range alone, "but should integrate the degree of TSH elevation with patient-specific risk factors and the concentration of TPO antibodies," Dr. Spencer said. ■

Algorithm Guides Thyroid Nodule Aspiration

BY JOYCE FRIEDEN
Senior Editor

WASHINGTON — The decision to perform fine-needle aspiration on a patient with a thyroid nodule depends on several factors, including nodule size, serum thyroid stimulating hormone level, and presenting symptoms, Dr. Erik Alexander said at a meeting jointly sponsored by the American Thyroid Association and Johns Hopkins University.

Dr. Alexander, who is with the division of endocrinology, diabetes, and hypertension at Brigham and Women's Hospital in Boston, outlined the algorithm he uses to evaluate a thyroid nodule.

Male gender, young age, and being symptomatic can increase the risk of a nodule being cancerous by about twofold, he said. But even if a nodule turns out to be cancerous, it doesn't necessarily mean that something has to be done about it.

"Do all thyroid cancers pose a danger? I think the answer likely is no," said Dr. Alexander, who is also an assistant professor of medicine at Harvard Medical School, Boston. "Nodules that are over 1 cm are really the nodules and cancers that pose risk" because of their increased likelihood of distant metastasis.

One recent 10-year study of 650 patients with well-differentiated follicular or papillary thyroid carcinoma found that with papillary thyroid carcinoma, there was essentially a zero risk of extrathyroidal growth in cancers of 10 mm or less in diameter, further validating the idea of a 1-cm cutoff, Dr. Alexander said (Cancer 2005;103:2269-73).

Ultrasound imaging can help further determine the risk of a nodule being cancerous, but cannot rule out the need for fine-needle aspiration, Dr. Alexander noted. That's because several studies have shown that ultrasound identifies only about 80% of thyroid cancers. "Would any of us be willing to have a 20% false-negative rate? I don't think so."

On the other hand, "Ultrasound is highly useful; it's most effective at assessing cancer risk," he continued.

One study done at Dr. Alexander's hospital found that a woman who presents with a solitary nodule that is found on ultrasound to be completely solid with punctate calcifications has a 33% chance of that nodule being cancerous, while a woman who presents with a multiple nodules found on ultrasound to be mixed solid and cystic with rim or coarse calcifications has a much lower risk—about 6% (J. Clin. Endocrino. Metab. 2006;91:3411-7).

Dr. Alexander's approach to assessing thyroid nodules begins with a thyroid ultrasound. If no nodules greater than 1 cm are found, no more intervention is warranted. If a nodule greater than 1 cm is found, he orders a serum TSH test. If TSH is suppressed, he orders a thyroid scan to look for a toxic adenoma; if it is normal or elevated, he considers whether the patient is symptomatic or not.

In symptomatic patients, he performs fine-needle aspiration; for asymptomatic patients, he assesses their cancer risk—as determined by gender, ultrasound results, and serum TSH—as well as their comorbidities and, in an older population, estimated longevity, before deciding whether to proceed with aspiration.

He noted that 70% of nodules evaluated by fine-needle aspiration prove benign. And although Dr. Alexander's protocol puts the question of fine-needle aspiration at the end of the evaluation, "there are some individuals in which [an earlier] fine-needle aspiration would be helpful in giving you further data," he said, adding that "fine-needle aspiration does not obligate you to further intervention," even if suspicious or intermediate lesions are found. ■

In Benign Goiter, Unilateral Excision Is Best

BY NANCY WALSH
New York Bureau

CHICAGO — Unilateral thyroidectomy is the procedure of choice for symptomatic benign multinodular goiter, Dr. Sarah Olson said at the annual meeting of the Central Surgical Association.

Multinodular goiter is the most common form of benign thyroid disease in the United States and is characterized by symptoms that include dysphagia and shortness of breath. The extent of surgery required—unilateral lobectomy or bilateral resection—is controversial, however, with many surgeons recommending total thyroidectomy for all patients.

"Bilateral surgery should be associated with a lower recurrence rate, but also may have potentially higher morbidity, so we undertook a retrospective analysis of data from an ongoing prospective endocrine database," said Dr. Olson of the University of Wisconsin, Madison.

Lobectomy is the procedure of choice, but only when significant disease is absent in the contralateral lobe.

DR. McHENRY

Between May 1994 and November 2004, 883 patients underwent thyroid surgery at the university. Of these, 237 patients underwent thyroidectomy for multinodular goiter, with the decision on unilateral or bilateral surgery being at the discretion of the individual surgeon. A total of 140 patients had unilateral lobectomy, with the remaining 97 undergoing total or subtotal thyroidectomy. The patients' mean age was 51 years, and 196 (83%) were female.

With up to 134 months of follow-up, patients who had unilateral resection had an 11% recurrence rate, whereas those in the bilateral group had a recurrence rate of 3%, a statistically significant difference.

The overall postoperative complication rate in the bilateral resection group was significantly higher, at 9%, compared with the unilateral group, at 2%. This difference in complication rate was in large part because of transient hypocalcemia, which was seen in 6% of the bilateral group but in none of the unilateral group, Dr. Olson said.

Of the 18 patients who subsequently required a second procedure for a recurrence of multinodular goiter, there was only one postoperative complication, for a complication rate of 5.5%. "This compares favorably with patients undergoing initial thyroidectomy," she said.

An audience member, Dr. Christopher R. McHenry of MetroHealth Medical Center, Cleveland, said that "lobectomy is the procedure of choice for symptomatic unilateral multinodular goiter, but only when significant disease is absent in the contralateral lobe." ■