

Management of Subclinical Hyperthyroidism

Leonard Wartofsky

Department of Medicine, Washington Hospital Center, Washington, D.C. 20010

Although much controversy continues to rage in regard to what constitutes the normal upper limit for TSH in the context of subclinical hypothyroidism, it is generally accepted that a state of mild hyperthyroidism exists when the TSH level is less than 0.3 mIU/liter. The term “subclinical” hyperthyroidism has been applied when such low TSH levels are accompanied by normal to high normal reference range values for T_4 and T_3 . The laboratory results indicating this diagnosis may have been obtained during routine physical examination or because some signs or symptoms suggested the possibility of hyperthyroidism to the physician. Because TSH may be suppressed transiently for various reasons, confirmation of the result is important. Once results are obtained with a subsequent repeat test, the clinician should deal next with a determination of the cause of the low TSH and whether or not a remedy may need to be applied (1).

Other causes of a low TSH level are excluded as we look for a cause of subclinical hyperthyroidism with a focus on disease of the thyroid gland. Thus, in the differential diagnosis for a low serum TSH level, we can exclude pituitary or hypothalamic disease, the euthyroid sick syndrome, or drugs that suppress TSH such as dobutamine, dopamine, and steroids because these entities do not reflect thyroid disease *per se* and would be associated with low or low normal serum T_4 and T_3 . The low TSH usually seen in the first trimester of pregnancy is a physiological change, although a degree of subclinical hyperthyroidism may exist with human chorionic gonadotropin stimulation of the thyroid causing augmented hormone secretion, and total T_3 and T_4 levels rising to or above the reference range enhanced by estrogen-mediated increases in thyroid hormone binding proteins. Factitial or unintentional iatrogenic TSH suppression due to excessive thyroid hormone ingestion as a cause of low TSH can also be excluded by history, and

of course its management is not rocket science, merely being dosage adjustment as required.

Having excluded these various nonthyroidal causes of a low TSH value, we are left with the likelihood of subclinical hyperthyroidism due to either transient or long-term endogenous thyroid hormone excess usually on the basis of Graves' disease or nodular goiter. The compelling imperative to make the diagnosis is based upon the consequences of long-term untreated subclinical hyperthyroidism, which may include atrial fibrillation (2–4), diastolic dysfunction (5), a suggestion of higher rates of death due to cardiovascular disease (6), and osteopenia, osteoporosis, and increased fracture rate, especially in postmenopausal women (7, 8).

Given these potential consequences of untreated subclinical hyperthyroidism, it would seem logical to implement treatment. However, the necessity for treatment may be arguable depending upon factors such as the degree of TSH suppression (<0.1 *vs.* between 0.1–0.4 mIU/liter) (9), the patient's age, and the presence of comorbid conditions. Moreover, it is possible that the TSH suppression may not be “permanent,” that the subclinical state will not progress to overt hyperthyroidism, and therefore that intervention would not be required. In this issue of the *JCEM*, Vadiveloo *et al.* (10) report epidemiological data on the prevalence, incidence, and natural history of 2024 subjects with subclinical hyperthyroidism with data up to 7 yr after diagnosis. In brief, most of the subjects continued to maintain a low TSH level over the course of follow-up, about a third had reverted to normal values by 5–7 yr, and very few (<1%) actually progressed to overt hyperthyroidism. This experience is very similar to that reported by Rosario (11), but it differs from that reported by Diez and Iglesias (12), who observed that 45% of patients progressed to overt disease during the course of follow-up.

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The results of all three of the latter studies are in agreement, however, insofar as finding that it is the patients with TSH values less than 0.1 mIU/liter who are most likely to progress, whereas a large proportion of those with TSH values greater than 0.1 mIU/liter will revert to normal. Thus, decision analysis would dictate that it is the former group of subjects that warrant the strongest consideration for therapy.

Nevertheless, whereas we should be most concerned about the fraction of subjects who go on to overt thyrotoxicosis, it is important to reflect that the above-mentioned effects on heart and bone apply to all patients with subclinical disease, although the sequelae may be more likely or most profound in those with a TSH less than 0.1 mIU/liter. Based upon a smaller series of patients reported by Woeber (13), it did not matter whether the initial TSH was less than 0.1 or between 0.1 and 0.4 mIU/liter in regard to reversion to normal when the subjects had Graves' disease. This may reflect improvement and normalization of thyroid function with time secondary to either spontaneous decline in TSH receptor antibody or to prior therapy with radioiodine. Moreover, intermittent transient episodes of hyperthyroidism may occur in previously euthyroid Graves' patients after exposure to an iodine source, with reversion to normal function as the iodine effect is dissipated.

Treatment of subclinical hyperthyroidism will depend on its cause. In the case of clinical evidence for underlying Graves' disease (goiter, ophthalmopathy, positive TSH-receptor antibodies), low-dose thiourea therapy with methimazole could be considered as well as radioiodine. In my experience, nuclear medicine departments will be reluctant to treat with ¹³¹I unless there is frank elevation of blood T₄ or T₃ levels, whereas a low TSH level alone is usually insufficient for them. How long to treat with methimazole will be rather empiric, titrating to the lowest dose required or periodically lowering the dose or discontinuing it altogether and observing for recurrent evidence of hormone excess (rising free T₄, falling TSH). The evaluation should include a thyroid ultrasound, followed by a radionuclide scan if nodules are seen on the ultrasound. Typically in the older patient, the scan will be heterogeneous with evidence of hyperfunctional ("hot") nodules. In the latter case, the patient is a good candidate for radioiodine therapy.

A decision to treat should be based upon evidence of benefit of such treatment. And indeed, benefit has been demonstrated with therapy of subclinical hyperthyroidism in the form of reversion from atrial fibrillation to normal sinus rhythm, reduced heart rate, improved vascular resistance, and improved bone mineral density (1). Although studies examining the effect of subclinical hyperthyroidism on quality of life and symptoms have been less compelling, one study did show significant improvement

with intervention (14). Stronger consideration for treatment should be given to those patients who have presented with atrial fibrillation, who are above age 60, or who have documented evidence of osteopenia or osteoporosis. These recommendations most appropriately apply to the patient with a TSH of less than 0.1 mIU/liter. Randomized controlled clinical trials will be required to assess benefit of therapy in the population of patients with TSH levels between 0.1 and 0.4 mIU/liter to determine potential benefit. In the interim, if not placed under treatment and closer observation, the latter should have their thyroid function rechecked on an every 3- to 6-month basis. Thyroid cancer patients and some goiter patients who are being administered thyroid hormone for TSH suppression, who have TSH levels between 0.1 and 0.4 mIU/liter, and who are symptomatic (tachycardia, palpitations, anxiety) may benefit from adjunctive β -adrenergic blockade, and those with marginal bone mineral density should be considered for bone enhancement therapy such as with bisphosphonates. Patients with euthyroid Graves' disease or subclinical hyperthyroidism due to single or multiple autonomous thyroid nodules should avoid exposure to high doses of iodine as are contained in radiological contrast dyes and certain organic food and vitamin supplements.

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Address all correspondence and requests for reprints to: Dr. Leonard Wartofsky, *JCEM* Editor in Chief, Washington Hospital Center, Department of Medicine, 110 Irving Street N.W., Washington, D.C. 20010-2975. E-mail: leonard.wartofsky@medstar.net.

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