What causes a low TSH level with a normal free T4 level?

EVIDENCE-BASED ANSWER
Subclinical hyperthyroidism (SCH) is defined as a low thyroid-stimulating hormone (TSH) level with normal free T4 and free T3 levels in patients without specific symptoms of hyperthyroidism. There is no evidence that treating SCH results in improved cardiovascular outcomes and evidence is insufficient that it improves neuropsychiatric outcomes (strength of recommendation [SOR]: C).

Bone mineral density may be increased with treatment of SCH (SOR: B, based on one randomized clinical trial).

CLINICAL COMMENTARY
Early detection and management of SCH is important
SCH is one of those subclinical diseases commonly encountered in primary care; it is more common in women than men, in blacks than whites, and in the elderly. It is less common, however, than subclinical hypothyroidism. Early detection and management of SCH is important for several reasons. First of all, with careful history taking and a thorough laboratory follow-up, other hidden thyroid diseases and medication problems may be found and prevented. Second, the cardiovascular abnormalities related to this disease may precede the onset of a more severe cardiovascular disease. Third, it is becoming apparent that this disease may accelerate the development of osteoporosis, particularly in postmenopausal women. Finally, as I have learned from my clinical experience, if patient and family are not counseled properly, they may become confused and abandon follow-up or treatment.

Jae Ho Lee, MD
Department of Family and Community Medicine,
Baylor College of Medicine, Houston, Tex;
Catholic University Medical College of Korea

Evidence summary
The decreased TSH level seen in SCH results from the pituitary's response to minor elevations in serum or tissue T4 and T3 levels. Although these levels remain within the normal range, the increases are sufficient to decrease the serum TSH level. The prevalence of SCH depends on the level of TSH used as a threshold. When the lower limit of TSH is set at 0.4 mIU/L, the prevalence was 3.2%. When followed up at 1 year, 40% to 60% of subjects with suppressed TSH levels will have normal TSH values. Progression to overt hyperthyroidism is uncommon, occurring in 4.3% of subjects at 4 years. It is worth noting that individuals treated with levothyroxine have a prevalence of iatrogenic SCH from 14% to 21%.

In patients with SCH aged >60 years,
the cumulative incidence of atrial fibrillation after 10 years varied with the serum TSH level: it was 28% in those with serum TSH <0.1 mIU/L; 16% in those with values between 0.1 and 0.4 mIU/L; and 11% in those with normal values.\(^6\) Patients with SCH have been reported to have increased heart rate, contractility, left ventricular mass, and increased risk of diastolic dysfunction and atrial arrhythmias.\(^7\) Patients aged >60 years with at least 1 suppressed TSH value have an increase in mortality over 5 years (standardized mortality ratio [SMR]=1.8; 95% confidence interval [CI], 1.2–2.7). At 10 years, the SMR was 1.2 (95% CI, 0.9–1.7). It appears that this is primarily related to cardiovascular mortality.\(^8\)

There are little data on the effects of treating SCH. One study of postmenopausal women with endogenous SCH (defined as TSH <0.1 mIU/L) randomly assigned women to take methimazole (Tapazole) or placebo. Both groups were followed for 2 years and none received any medication with known effects on bone metabolism in the past or during the study period. The untreated patients with SCH had significantly higher bone mineral density loss (>5%) at both 18 and 24 months.\(^9\)

**Recommendations from others**

A systematic review suggests the following regarding the evaluation and treatment of SCH.\(^10\)

1. Exclude other causes of subnormal serum TSH concentration (TABLE)  
2. Retest patients. Patients with atrial fibrillation, and cardiac disease, or a TSH <0.1 mIU/L should be retested in 2 to 4 weeks. Other patients can be retested in 3 months.  
3. Patients whose TSH remains <0.1 mIU/L should undergo a radioactive iodine uptake scan. If the uptake is high (consistent with Graves’s disease or a focal nodule), treat as appropriate for that disease.  
Younger patients (<60 years), with mild TSH suppression (0.1–0.45 mIU/L) or low radioactive iodine uptake can be followed with serial TSH testing at 3- to 12-month intervals. However, for these patients who also have cardiac disease, decreased bone mineral density, or symptoms suggestive of hyperthyroidism, thyroid suppression is recommended.

In patients aged >60 years with TSH <0.1 mIU/L, antithyroid treatment should be considered to decrease cardiac and bone loss complications.

Patients receiving thyroid replacement therapy should have their dose adjusted to maintain a normal serum TSH concentration. However, when thyroid hormone therapy is used for TSH suppression to prevent or reduce goiter growth or prevent recurrence of thyroid cancer, then a lower TSH may be unavoidable. The adverse effects can be minimized by treatment with the least level of suppression necessary to meet the desired goal.

**REFERENCES**

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11. Shrier DK, Burman KD. Subclinical hyperthyroidism: con-