



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Is a serum TSH measurement sufficient to monitor the treatment of primary hypothyroidism?

A 28-YEAR-OLD WOMAN returns for follow-up of her hypothyroidism. She was diagnosed 4 years ago when she presented with fatigue, “foggy” thinking, poor concentration, cold intolerance, and constipation. Her thyroid-stimulating hormone (TSH) level at that time was elevated at 15 mIU/L (reference range 0.4–4). She was started on 50 µg of levothyroxine daily, which helped her symptoms, but she continued to complain of tiredness and the inability to lose weight. She has been on 100 µg of levothyroxine daily since her last visit 1 year ago.

On examination, she has a small, diffuse, and firm goiter; she has no Cushing-like features, visual field abnormalities, or signs of hypothyroidism.

Her TSH level today is 1.2 mIU/L. Based on this, you recommend no change in her daily levothyroxine dose. She expresses dissatisfaction that you had ordered only a TSH, and she asks you to order thyroxine (T_4) and triiodothyronine (T_3) measurements because she read on the Internet that those were needed to determine the appropriateness of the levothyroxine dose.

Should T_4 or T_3 be routinely measured when adjusting thyroid replacement therapy?

■ IN PRIMARY HYPOTHYROIDISM, TSH IS ENOUGH

In a patient with primary hypothyroidism and no suspicion of pituitary abnormality, a serum TSH is sufficient for monitoring thyroid status and adjusting the dose of thyroid hormone.

Hypothyroidism is one of the most common endocrine disorders, affecting about 4% of the adult US population.¹ In areas of iodine sufficiency, primary hypothyroidism is due predominantly to Hashimoto thyroiditis.

doi:10.3949/ccjm.83a.15165

The role of the lack of thyroid hormone in the pathogenesis of myxedema was recognized in the late 19th century through the observation of a “cretinoid” state occurring in middle-aged women, associated with atrophy of the thyroid gland and a similar severe state noted after total thyroidectomy.²

In 1891, George R. Murray was able to “cure” myxedema in a patient by injecting sheep thyroid extract subcutaneously. Thyroid extracts continued to be the only treatment for hypothyroidism until 1950, when levothyroxine was introduced and later became the main treatment. Around that time, T_3 was discovered and was described as being the physiologically active thyroid hormone. Later, it was noted that 80% to 90% of circulating T_3 is generated through peripheral deiodination of T_4 , the latter being considered a prohormone.²

The pituitary-thyroid axis is regulated through negative feedback. At concentrations of free T_4 below normal, plasma TSH rises rapidly with small decrements in T_4 levels.³ The opposite phenomenon occurs with free T_4 concentrations above normal. Since T_4 has a long disappearance half-time—about 7 days—a normal TSH tends to stay relatively stable in the same individual.⁴ The relationship between TSH and T_4 was long thought to be inverse log-linear, but Hadlow et al⁵ found that it is complex and nonlinear and differs by age and sex. TSH and T_4 concentrations have narrower within-individual variability than inter-individual variability. Although environmental factors may affect this hypothalamic-pituitary set-point, there is evidence

With primary hypothyroidism, TSH is enough to monitor thyroid status and to adjust the dose of thyroid hormone

that heritability is a major determinant of individual variability.⁶

■ GUIDELINES AND CHOOSING WISELY

In 2014, the American Thyroid Association published comprehensive, evidence-based guidelines for the treatment of hypothyroidism.⁷ The guidelines state that the goal of thyroid hormone replacement is to achieve clinical and biochemical euthyroidism.⁷ TSH continues to be the most reliable marker of adequacy of thyroid hormone replacement in primary hypothyroidism. The guidelines recommend aiming for a TSH in the normal range (generally 0.4–4 mIU/L).

Most studies of the risks associated with hypothyroidism or thyrotoxicosis have looked at TSH levels. Significantly increased risk of cardiovascular mortality and morbidity is seen in individuals with TSH levels higher than 10 mIU/L.⁸ On the other hand, excess thyroid hormone leading to a TSH level lower than 0.1 mIU/L has been associated with an increased risk of atrial fibrillation in older persons and osteoporosis in postmenopausal women.

The classic symptoms and signs of hypothyroidism correlate with biochemical hypothyroidism and usually improve with the restoration of euthyroidism. Some of these symptoms, however, lack sensitivity and specificity, especially with modest degrees of hypothyroidism.⁷ A randomized controlled trial showed that patients were unable to detect any difference in symptoms when the levothyroxine dose was changed by about 20%.⁹

■ HARMS ASSOCIATED WITH ORDERING T₄ AND T₃

Other than the financial burden to the patient and society, there is no major morbidity caused by obtaining T₄ or T₃ levels, or both. However, knowing the T₄ or T₃ level does not help with management beyond the information offered by the TSH value. Hypothyroid patients treated with levothyroxine to maintain a normal TSH generally have higher free T₄ levels and lower free T₃ levels than euthyroid patients with similar TSH values.¹⁰ Therefore, reacting to a high T₄ level or a low T₃ level in a treated hypothyroid patient with a normal TSH may lead to inappropriate dose

adjustment. On the other hand, increasing the dose of thyroid hormone in a patient with a low TSH whose T₃ level is low-normal may lead to morbidity.

■ SPECIAL SCENARIO: PITUITARY COMPROMISE

We assume that the patient described above has primary hypothyroidism and that her pituitary-thyroid axis is intact. Primary hypothyroidism is diagnosed by a high TSH along with a low or low-normal T₄. In this typical case, TSH can be used to guide therapy without the need for other tests.

However, when there is pituitary compromise (hypopituitarism, congenital central hypothyroidism), the TSH will not be reliable to monitor the adequacy of thyroid hormone replacement therapy. The aim of levothyroxine management in these patients is to maintain a free T₄ concentration in the upper half of the normal range. If the free T₃ concentration is followed and is found to be elevated, the dose of levothyroxine should be reduced.¹¹

■ CLINICAL BOTTOM LINE

Since our patient's dose of levothyroxine has been stable and her TSH is not elevated, measuring serum levels of T₄ and T₃ would not contribute to her management. For such a patient, if the TSH were less than 3 mIU/L, increasing the dose would be unlikely to offer clinical benefit.

On the other hand, if her TSH was higher than 4 mIU/L, then it would be legitimate to tweak the dose upward and reassess her thyroid state clinically and biochemically 6 to 8 weeks later. One would need to be careful not to induce thyrotoxicosis through such an intervention because of the potential morbidity.

The TSH level is typically monitored every 6 to 12 months when the patient is clinically stable. It should be measured sooner in circumstances that include the following:

- Symptoms of hypothyroidism or thyrotoxicosis
- Starting a new medication known to affect thyroid hormone levels
- Significant weight change
- Hospitalization
- Pregnancy.

**TSH rises
as T₄ falls,
and vice versa**

REFERENCES

1. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid* 2007; 17:1211–1223.
2. Kopp PE. Commentary on: guidelines for the treatment of hypothyroidism. *Thyroid* 2014; 24:1667–1669.
3. Reichlin S, Utiger RD. Regulation of the pituitary-thyroid axis in man: relationship of TSH concentration to concentration of free and total thyroxine in plasma. *J Clin Endocrinol Metab* 1967; 27:251–255.
4. Azukizawa M, Pekary AE, Hershman JM, Parker DC. Plasma thyrotropin, thyroxine, and triiodothyronine relationships in man. *J Clin Endocrinol Metab* 1976; 43:533–542.
5. Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Mun Lim E, Walsh JP. The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. *J Clin Endocrinol Metab* 2013; 98:2936–2943.
6. Clark PM, Holder RL, Haque SM, Hobbs FDR, Roberts LM, Franklyn JA. The relationship between serum TSH and free T4 in older people. *J Clin Pathol* 2012; 65:463–465.
7. Jonklaas J, Bianco AC, Bauer AJ, et al; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism. *Thyroid* 2014; 24:1670–1751.
8. Rodondi N, den Elzen WP, Bauer DC, et al; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; 304:1365–1374.
9. Walsh JP, Ward LC, Burke V, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. *J Clin Endocrinol Metab* 2006; 91:2624–2630.
10. Woeber KA. Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. *J Endocrinol Invest* 2002; 25:106–109.
11. Grunenwald S, Caron P. Central hypothyroidism in adults: better understanding for better care. *Pituitary* 2015; 18:169–175.

ADDRESS: Christian Nasr, MD, Endocrinology and Metabolism Institute, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; nasrc@ccf.org



Fundamental to Advanced Echocardiography in 2016

September 16 – 18, 2016

Global Center for Health Innovation | Cleveland, OH

Register Today! ccfcme.org/AttendEchoCardio