



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: What is the target TSH level in thyroid hormone replacement for primary hypothyroidism?

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A: Based on a number of studies, my goal in giving levothyroxine to healthy patients with primary (autoimmune) hypothyroidism is a thyroid-stimulating hormone (TSH) level between 0.4 and 3 mU/L, at the lower end of the normal range (0.4–5.5 mU/L) used at The Cleveland Clinic.

If after 6 to 12 weeks of levothyroxine a patient has a TSH in the normal range and no symptoms of hypothyroidism, I maintain the dose and check the TSH once a year to make sure further adjustment is not necessary.

■ FINE-TUNE THE DOSE

If a patient still has symptoms of hypothyroidism after 6 to 12 weeks of thyroid hormone replacement, I increase the dose to depress TSH levels further (but still in the low-normal range). If on the other hand the patient develops palpitations or anxiety, I reduce the dose in order to allow TSH levels to rise into the high-normal range.

■ AVOID SUBCLINICAL HYPERTHYROIDISM

We must avoid driving TSH levels too low, since this can produce subclinical hyperthyroidism, a condition associated with cardiac arrhythmias.^{1–8} In addition, studies^{9–11} have shown a decrease in bone mineral density—and therefore an increased risk of osteoporosis—in patients with subclinical hyperthyroidism. Because osteoporosis, cardiac arrhythmias, and diastolic dysfunction can increase mortality, thyroid hormone replacement should aim for TSH levels at or above the low-normal range.

Subclinical hyperthyroidism is usually defined as a low serum TSH level coupled with normal serum thyroxine (T₄) and triiodothyronine (T₃) concentrations.¹²

Atrial fibrillation

The risk of atrial fibrillation is increased in patients with subclinical hyperthyroidism.

Sawin et al¹ found that, in 200 patients age 60 or older followed for 10 years, the cumulative incidence of atrial fibrillation was 28% in those with TSH levels 0.1 mU/L or lower, 16% in those with TSH levels between 0.1 and 0.4 mU/L, and 11% in those with normal TSH levels.

Tenerz et al² found that atrial fibrillation was twice as common in patients with subclinical hyperthyroidism vs controls.³

Monreal et al³ found that, of 126 consecutive patients presenting to an emergency room with atrial fibrillation, 2 (2%) had overt hyperthyroidism, and 13 (10%) had subclinical hyperthyroidism.

Additional cardiac effects

Subclinical hyperthyroidism is associated with an increased heart rate and an increase in atrial premature beats,^{4,5} impaired left ventricular diastolic filling,⁶ increased left ventricular mass index,⁵ and decreased systolic time intervals.^{7,8} Impaired left ventricular diastolic filling is associated with reduced exercise capacity.

Treatment lowers cholesterol

A higher prevalence of heart disease is associated with TSH levels over 4.0 mU/L.¹³ This may in part be due to the effects of thyroxine on cholesterol levels. In another study,¹⁴ giving levothyroxine to patients with TSH 2 to 4 mU/L lowered cholesterol, but not if initial TSH levels were in the range of 0.4 to 1.99 mU/L.

Driving TSH levels too low risks causing cardiac arrhythmias



May worsen angina

In patients with hypothyroidism, treatment with levothyroxine results in development of angina in 2%. In patients with pre-existing angina, 38% improve, 46% have no change, and 16% worsen with levothyroxine therapy.¹⁵ If cardiac disease is present or suspected, levothyroxine treatment can be delayed until evaluation and treatment of the cardiac disease.¹⁶ Dosing in the elderly and in patients with coronary artery disease should begin at 25 to 50 µg. If normalizing TSH results in worsening of cardiac symptoms, treatment should aim for the lowest TSH level that avoids cardiac symptoms and may necessitate allowing TSH levels to be above the normal range.

■ WHAT IS 'NORMAL'?

The main reason we need to aim for TSH levels in the lower normal range in patients taking levothyroxine is that the current normal range is wider than it ought to be. Several studies indicate that the number

of patients with primary hypothyroidism may be much larger than previously thought.¹⁷⁻¹⁹ The normal range is based on data for people with no diagnosis of primary hypothyroidism.¹⁷ However, the Whickham survey,¹⁸ a 2-year longitudinal study, indicated that patients with TSH levels greater than 2.0 mU/L have increased risk of developing overt hypothyroidism over the next 20 years, and Dayan¹⁹ found that up to 40% of healthy women have lymphocytic infiltration of the thyroid and 15% have antithyroid antibodies. This makes subclinical hypothyroidism so common that the reference ranges developed from testing apparently healthy subjects could be contaminated by diseased individuals.

Bjoro et al²⁰ studied a population with no thyroperoxidase antibodies and no personal history of thyroid disease. He found that 95% of TSH values lay within 0.48 to 3.6 mU/L (much smaller than the current normal range of 0.4 to 5.5 mU/L). Indeed, three studies^{13,14,20} demonstrated an increased rate of thyroperoxidase antibodies in patients outside the test range of 0.2 to 1.9 mU/L. ■

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