



THYROID HORMONE TESTS

Determination of optimal TSH ranges for reflex Free T₄ testing

BACKGROUND

TSH measurement is generally regarded as the most sensitive initial laboratory test for screening individuals for thyroid hormone abnormalities. This is due to the fact that small changes in Free T₄ levels result in larger changes in TSH values. Many clinicians and laboratories check TSH alone as the initial test for thyroid problems and then only add a Free T₄ measurement if the TSH is abnormal (outside the laboratory normal reference range). When the laboratory adds the Free T₄ test to the blood sample automatically based on an abnormal TSH result, it referred to as “reflex” testing. Although laboratories vary, most report a normal TSH reference range between 0.4-0.5 mU/L on the lower end and 4-5.5 mU/L on the upper end of the range. The goal of this study was to evaluate different TSH cutoffs leading to reflex Free T₄ testing, with the purpose to determine whether a widened normal range could decrease the need for additional Free T₄ testing and not lead to missing cases of thyroid problems.

THE FULL ARTICLE TITLE

Henze M et al. Rationalizing thyroid function testing: Which TSH cutoffs are optimal for testing Free T₄? J. Clin Endocrinol. Metab. 2017. 102 (11): 4235-4241.

SUMMARY OF THE STUDY

These investigators evaluated TSH and Free T₄ measurements in two populations. One group of 120,403 individuals (named the clinical group) had thyroid tests performed in a single laboratory in Western Australia over a 12 year period of time. This group was compared to community group of 4568 individuals participating in the Busselton Health Study. All individuals had both TSH and Free T₄ measured. They excluded people with known pituitary disease, thyroid disease and other factors known to affect thyroid function tests. These investigators quantified the number of individuals at different TSH values that had high, low or normal Free T₄ levels. They measured the effect of changing the TSH reference range cutoffs on the number of reflex Free T₄ tests. They determined how many times an abnormally high or low Free T₄ would have gone undetected if the TSH cutoffs for reflex testing had been changed. The normal reference

range for the TSH was 0.4-4 mU/L in this study. They found in the clinical group that if the TSH normal range that led to reflex Free T₄ testing was changed to from 0.4-4 mU/L to 0.3-5 mU/L, this would have led to a 22% reduction in the number of Free T₄ tests performed. As expected, if the TSH normal reference range was widened even more to 0.2-6 mU/L, even fewer reflex Free T₄ tests would have been done. They then examined how many of those Free T₄ levels that would not have been done were abnormal. When the TSH lower limit was reduced from 0.4 to 0.2 mU/L, a high Free T₄ would have been missed in 4.2% of people who had a TSH between 0.2 and 0.4 mU/L. When the TSH upper limit was raised from 4 to 6 mU/L, a low Free T₄ would have been missed in 2.5% of the people who had a TSH between 4 and 6 mU/L.

The authors noted that this was a relatively small number of people that would have been missed and that the majority had only very slight abnormalities of Free T₄. They suggested that these mild abnormalities were unlikely to be associated with clinically important overt hyper- or hypothyroidism. The vast majority of people (97%) with a TSH in the normal range of 0.4-4 mU/L also had normal Free T₄ values. The findings were similar but of lesser magnitude in the smaller community group of patients. The authors concluded that the TSH reference range leading to reflex Free T₄ testing could likely be widened to decrease the number of unnecessary Free T₄ measurements performed. This would reduce overall costs to the medical system without likely causing negative consequences in terms of missing the detection of people with thyroid hormone abnormalities.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

These results indicate that by widening the normal reference range for TSH, the need for additional reflex testing for Free T₄ values could be reduced. The authors suggested that fewer unnecessary Free T₄ measurements would be performed and thus these changes would be cost saving for the health care system. The results indicated that the TSH normal reference range could be altered with minimal clinical effects. In other words, few cases of overt





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hyper- or hypothyroidism would go undetected if the TSH cutoffs leading to reflex Free T₄ testing were only slightly changed. It is important to note, that this study refers to the finding of overt thyroid disease and does not address the concept of “subclinical” or mild thyroid disorders. Additionally it is important to remember that TSH testing alone is inadequate or misleading in some conditions (such as central hypothyroidism or other abnormal thyroid

conditions). This study primarily addresses the utility of isolated TSH measurements when screening people for new thyroid disease. When screening the general population for thyroid disease, the majority of people with a TSH in the normal reference range will also have a normal Free T₄, making the new diagnosis of a thyroid disorder unlikely when a person has a normal TSH.

— Whitney W. Woodmansee MD

ATA THYROID BROCHURE LINKS

Thyroid Function Tests: <https://www.thyroid.org/thyroid-function-tests/>

Hypothyroidism (Underactive): <https://www.thyroid.org/hypothyroidism/>

Hyperthyroidism (Overactive): <https://www.thyroid.org/hyperthyroidism/>

ABBREVIATIONS & DEFINITIONS

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Thyroxine (T₄): the major hormone produced by the thyroid gland. T₄ gets converted to the active hormone T₃ in various tissues in the body.

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

Subclinical Hypothyroidism: a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

Overt Hypothyroidism: clear hypothyroidism an increased TSH and a decreased T₄ level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Subclinical Hyperthyroidism: a mild form of hyperthyroidism where the only abnormal hormone level is a decreased TSH.

