



Trust the thyroid thermostat

Primary hypothyroidism is common. Most patients acquire it when the thyroid gland is damaged by autoimmune inflammation. It is readily and reliably treated with the orally administered synthetic hormone levothyroxine, or less reliably with thyroid gland extracts. Absorption of either medication is significantly influenced by food, so patients need to pay attention to the timing of ingestion. But occasional blood testing can be used to easily monitor the sufficiency of replacement therapy.

The predominant active thyroid hormone is triiodothyronine (T3), most of which is converted from thyroxine (T4) by deiodination outside of the thyroid gland. Circulating thyroid-binding globulins tie up significant amounts of these hormones in the blood, and this protein binding is affected by a number of factors. Free T3 and T4—not bound—are the substances that exert physiologic effects on target organs and also give feedback information to the pituitary gland which, completing the loop, releases thyroid-stimulating hormone (TSH) and ultimately controls the healthy thyroid gland's production and release of its hormones. Hence, the total circulating thyroid hormone levels are not as biologically relevant as the free T3 and T4 levels. Even in the absence of a functioning thyroid gland, the TSH level reliably reflects the bioactivity of circulating thyroid hormones so long as the pituitary gland is functioning normally.

Routine tracking of the biologic effects of thyroid hormone, such as the metabolic rate, is unreasonable, and other biologic effects such as the cholesterol level are influenced by so many factors in addition to T3 as to be unreliable indicators of thyroid hormone levels. Assuming the patient's hypothalamic-pituitary axis is normal, the most reasonable and reliable way to track the biologic effect of thyroid hormone is to follow the TSH level. Although the exact relationship between free thyroid hormone and TSH levels is slightly different between patients with normal thyroid glands and those with damaged glands receiving replacement therapy, TSH measurement is an excellent indicator of the level that the brain wants thyroid function to be. Other than in specific nonhomeostatic circumstances, the pituitary gland is usually a superb thermostat for thyroid hormone activity.

In this issue of the *Journal* (page 571), Dr. Christian Nasr discusses the rationale for routinely using TSH measurement alone to direct exogenous thyroid replacement, explaining why it is cost-effective and clinically appropriate.

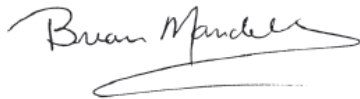
While following T3 and T4 may occasionally be useful in a few patients, the wealth of clinical data does not support this practice. As a routine practice it is certainly financially wasteful, and may lead to inappropriate clinical decisions.

Why, then, do some physicians persist in regularly following T3 and T4 levels in addition to TSH? There is no single answer. Although some patients may feel "better" if they take a little more rather than a little less levothyroxine, whether this benefit outweighs the metabolic price in the long run is not at all clear. Plus, in the published experience with treating subclinical hypothyroidism,¹ patients did not generally feel better or experience desired weight loss when they received slightly more exogenous

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thyroid hormone. Somewhat analogously, if the TSH level is already normal, increasing thyroid replacement to attain a free T3 or T4 level in the high-normal range is unlikely to improve clinical outcomes in a meaningful way and may well be detrimental in the long term.

Despite a lot of chatter on Internet blogs regarding the multiple benefits of selective T3 replacement and higher T3 levels, akin to testosterone supplementation above what the (normal functioning) hypothalamic-pituitary axis has determined to be biologically appropriate, there is limited clinical evidence to support this practice. When replacing the output of a diseased or absent thyroid gland, it is reasonable clinical practice to trust the pituitary readings of the thyroid thermostat.



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1. **Rugge JB, Bougatsos C, Chou R.** Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015; 162:35–45.