There is more to the TSH than a number

In a previous issue of the *Journal*, an article[1] and commentary[2] discussed the efficiency and sufficiency of using only the thyroid-stimulating hormone (TSH) level to monitor the dosing of thyroid replacement therapy in patients with primary hypothyroidism. The validity of the TSH measurement in that setting was emphasized. Yet in the current issue of the *Journal*, Azim and Nasr (page 101) summarize some of the controversies in managing subclinical hypothyroidism (an elevated TSH in the setting of a normal level of endogenous free thyroxine, T_4), and some of the controversies relate to foibles in interpreting the measured level of TSH.

At a quick read, the messages from these articles may seem contradictory. But the biology is more complex in the setting of endogenous production of T_4 by the thyroid gland, which is regulated by TSH, which in turn is regulated in a feedback loop by the thyroid-produced T_4. In the setting of a fixed replacement dose of exogenous levothyroxine, the provided hormone affects the pituitary production of TSH, which likely will have no significant subsequent effect on the T_4 level. Thus, the feedback control loop is far simpler.

There has not been a definitive study demonstrating that thyroxine supplementation in patients with subclinical hypothyroidism results in a superior clinical outcome. There are hints that this may be the case, and Azim and Nasr cite some of these studies. Recognizing a few markedly different physiologic reasons why the TSH can be slightly elevated and the T_4 normal helps explain the lack of uniform clinical success with supplementation therapy and provides rationales for some management strategies.

Any biological variability in the responsiveness of the thyroid gland to TSH may affect the relationship between the levels of TSH and thyroid gland-released T_4. In theory, if the thyroid receptor has decreased affinity for TSH, a higher TSH concentration will be needed to get the thyroid gland to secrete the level of T_4 that the pituitary sensing mechanism deems normal for that individual. If the receptor affinity was decreased due to a gene polymorphism, this relationship between TSH and T_4 may be stable, and providing exogenous T_4 will result in a lower, "normalized" TSH level but may disrupt the thyroid-pituitary crosstalk and may even produce clinical hyperthyroidism.

A similar scenario exists in the setting of early thyroid gland failure, such as in Hashimoto thyroiditis. But in the latter scenario, the TSH-to-T_4 production relationship may be unstable over time, for as additional thyroid gland is destroyed, T_4 production will continue to decrease, the TSH will increase, and the thyroid gland may ultimately fail and hypothyroidism will occur. Hence the recommendation that in the setting of subclinical hypothyroidism *and* antiperoxidase antibodies, T_4 and TSH levels should be monitored regularly in order to detect early true thyroid gland failure when the T_4 level can no longer be maintained despite the increased stimulation of the gland by the elevated TSH. Analogous to this may be subclinical hypothyroid-

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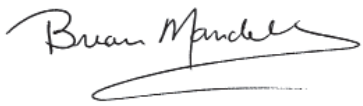
ism in the elderly, in whom thyroid gland failure may develop, despite an increased TSH, from senescence rather than autoimmunity. What I am suggesting is that the natural history of all patients with subclinical hypothyroidism is not alike, and it thus should not be surprising that there does not seem to be a one-size-fits-all approach to management.

Symptoms in patients with subclinical hypothyroidism have not uniformly improved with T_4 treatment compared with placebo. Notably, most patients with subclinical hypothyroidism experience no symptoms. But consider the extremely common symptom of fatigue, which can be present for a myriad of defined and undefined reasons. This symptom may often lead physicians to check the TSH and, if that is even slightly elevated, to also check the T_4. It may also lead some physicians to routinely check the T_4. Subclinical hypothyroidism is also quite common; thus, by chance alone or because of the circadian timing of checking the TSH, a slightly elevated TSH and fatigue may coexist and yet be unrelated.

Additionally, a positive biochemical response to thyroxine supplementation, such as a lowering of cholesterol, does not prove that the patient was clinically hypothyroid prior to supplementation, any more than lowering a patient's blood glucose with insulin proves that the patient was diabetic. The management of subclinical hypothyroidism should be nuanced and based on both clinical and laboratory parameters.



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2. **Mandell BF**. Trust the thyroid thermostat. Cleve Clin J Med 2016; 83(8):552–553. doi:10.3949/ccjm.83b.08016