EDITORIAL

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Low TSH? It Might Not Be Thyrotoxicosis

This editorial could have quite a negative impact on my fellow endocrinologists. That's because it could result in a significant reduction in the number of referrals to endocrinologists for patients with low thyroid-stimulating hormone (TSH) levels, at least that's a best-case scenario. Despite the potentially negative impact on endocrine referrals, I feel compelled to suggest that you may be overreacting to low TSH levels in many of your patients.

You know what I mean—you see moderately suppressed TSH levels all of the time in day-to-day clinical practice. And of course, as a faithful provider, you harken back to your training days and remember the basics of the thyroid-pituitary axis. Theoretically at least, the pituitary gland secretes TSH in proportion to the need for the thyroid gland to put out more thyroid hormone. If the thyroid gland starts to fail for any reason (Hashimoto's thyroiditis, an autoimmune disease, is by far the most common cause), the pituitary will detect that there is an insufficient amount of thyroid hormone floating around and will secrete more TSH to try to stimulate the thyroid to pump out more hormone.

Conversely, if the thyroid gland becomes overactive for any reason (Graves' disease, another autoimmune phenomenon, is the most common cause here), then the secretion of TSH will be suppressed by the excess thyroid hormone. It is seemingly straightforward: An elevated TSH means hypothyroidism, and a suppressed TSH means an overactive thyroid gland.

Alas, dear reader, if only it were so simple! It turns out that a very large fraction of the low TSH levels seen in clinical practice are not related at all to an overactive thyroid gland, and no therapeutic intervention of any sort is indicated. In light of the intricate feedback loop, which controls the delicate balance between the secretion of thyroid hormone on the one hand and that of TSH on the other, how can that possibly be true?

The answer is that the feedback loop is nowhere near as simple and straightforward as you were taught as an eager student of human physiology. The thyrotroph cells in the pituitary, the ones that secrete TSH, do indeed respond rather exquisitely to the ambient levels of circulating thyroid hormones. But they are also very susceptible to a number of other circulating compounds that are quite capable of suppressing their output of TSH every bit as effectively as thyroid hormones.

The classic setting in which TSH levels are suppressed in the absence of true thyrotoxicosis is euthyroid sick syndrome (ESS). I always tell my trainees that the surest way to find patients with ESS is simply to ask for directions to the intensive care unit (ICU). Assuming that the patients in the ICU truly need to be there, every single one of them will display thyroid hormone changes consistent with ESS. It's still not clear whether or not ESS is an adaptive or protective mechanism, but it occurs in virtually all patients who are sufficiently sick.

The first manifestation of ESS is low T3 syndrome, wherein the conversion of T4 to the more metabolically potent T3 is markedly reduced. Since T3 is by far the more physiologically active of these 2 thyroid hormones, the net effect of the block in conversion to T3 is a down-regulation of the thyroid axis. The dialing back of thyroid effect may well be a protective physiologic mechanism so the body can focus on defending against whatever severe physiologic insult set the whole process in motion in the first place. It may represent a turning down of the metabolic thermometer or burn rate.

If the underlying illness persists or worsens, usually the next manifestations of ESS are a suppression of TSH, and then a concomitant suppression of the production of T4 from the thyroid gland. So most truly ill individuals experience an uncoupling of the usual relationship between TSH levels and thyroid hormone levels. The suppression of the TSH levels in ESS is generally attributed to the circulating presence of abnormally high levels of cytokines associated with severe illness, including interleukins and a number of other potent mediators of inflammation.

It also turns out that less ill patients can also experience a suppression of TSH levels due to a number of circulating compounds, prominent among them are corticosteroids, catecholamines, and opi-

oids. Thus, many patients who have chronically elevated levels of corticosteroids, catecholamines, or opioids will also have relatively suppressed levels of TSH without a hint that they are suffering from thyrotoxicosis.

Any endocrinologist who has been reading this is probably bored, but hopefully the rest of you have gained just a small bit of insight into the multiplicity of factors that can lead to low levels of TSH. In a perfectly healthy person with no reason to have elevated levels of corticosteroids or catecholamines, a low TSH level does indeed raise the concern for thyrotoxicosis, especially if the TSH is not measurable, as it usually is with true thyrotoxicosis. But in patients who are ill, all bets are off. A low TSH level is very probably not an indicator of excess circulating thyroid hormone.

It is hoped my fellow endocrinologists will now receive fewer consults for low TSH levels, and they can concentrate on something more important, such as trying to tame those pesky glucose levels in our ever-increasing glut of diabetic patients. ●

Author disclosures

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