EDITORIAL

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Subclinical hypothyroidism: What's in a name?

In primary hypothyroidism, there is a decline of thyroid hormone production by the thyroid, leading to compensatory up-regulation of thyrotropin (thyroid-stimulating hormone [TSH]) production by the pituitary in an effort to maintain thyroid hormone levels. Primary gland failure is frequently a gradual process, occurring over years, with a long preclinical phase during which regulatory feedback mechanisms are able to maintain homeostasis.

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With the advent of sensitive assays to measure TSH, the diagnosis of hypothyroidism moved from the detection of only severe cases based on the metabolic consequences of hypothyroidism, to simple blood tests that can detect altered regulatory feedback in the hypothalamic-pituitary-thyroid (HPT) axis, which can represent the early stages of gland failure. In more advanced cases, TSH is elevated and thyroxine (T4) levels are low, and primary hypothyroidism may be comfortably diagnosed. The concept of *subclinical hypothyroidism* was developed for those with elevated TSH and a compensated free T4 level within the reference range, opening the debate about whether to treat these patients, and at what threshold of TSH elevation, as discussed in detail by Xu et al[1] in this issue of the *Journal*.

Isolated elevated serum TSH in older adults

But there is an earlier question that is especially relevant in older adults, which is whether all individuals with an isolated elevated serum TSH level and reference-range T4 level should be grouped together using a single unified name. By definition, this group comprises 2.5% of the reference population, but a study of data from the third National Health and Nutrition Examination Survey found that the rates are much higher for some subgroups, with about 10% of 80-year-olds otherwise thought to be without thyroid disease meeting the standard definition of subclinical hypothyroidism.[2] Thus, before we debate whether to treat subclinical hypothyroidism, we need to know whether the laboratory findings actually uniquely signify emerging primary thyroid disease in this subpopulation—or is there some other explanation that we are missing? That is, we need to know whether all older adults with an elevated TSH actually have subclinical hypothyroidism, or whether the name is misleading us.

Several different groups in the past 20 years have made interesting observations about the dynamics of and associations with isolated elevated serum TSH levels in older adults. A provocative early study from the Netherlands found that 85-year-olds with higher TSH levels had better survival than those with normal or low levels,[3] although more heterogenous studies have not been able to replicate the findings.

A second important observation is that elevations in serum TSH levels are frequently transient, especially when the elevation is less than 10 mIU/L and antithyroid antibodies are negative. For example, in a cohort study, 35% of participants with an initial diagnosis of "subclinical hypothyroidism" had normal TSH levels at follow-up 2 years later, and of these, 48% had normal levels at the 4-year follow-up.[4] Similarly, a large, multicenter randomized trial of treatment for subclinical hypothyroidism in older adults that required 2 elevated TSH values 3 months apart to enroll failed to reach its recruitment targets and power for cardiac end points because of high rates of reversion to reference-range TSH levels on repeat testing.[5]

Finally, especially for TSH less than 10 mIU/L, it is not clear that not treating results in harm or that treating leads to benefits, while overtreatment is associated with risks, as highlighted in Xu et al.[1] For example, a randomized controlled trial of levothyroxine treatment in more than 700 patients (Thyroid Hormone

doi:10.3949/ccjm.92a.25028

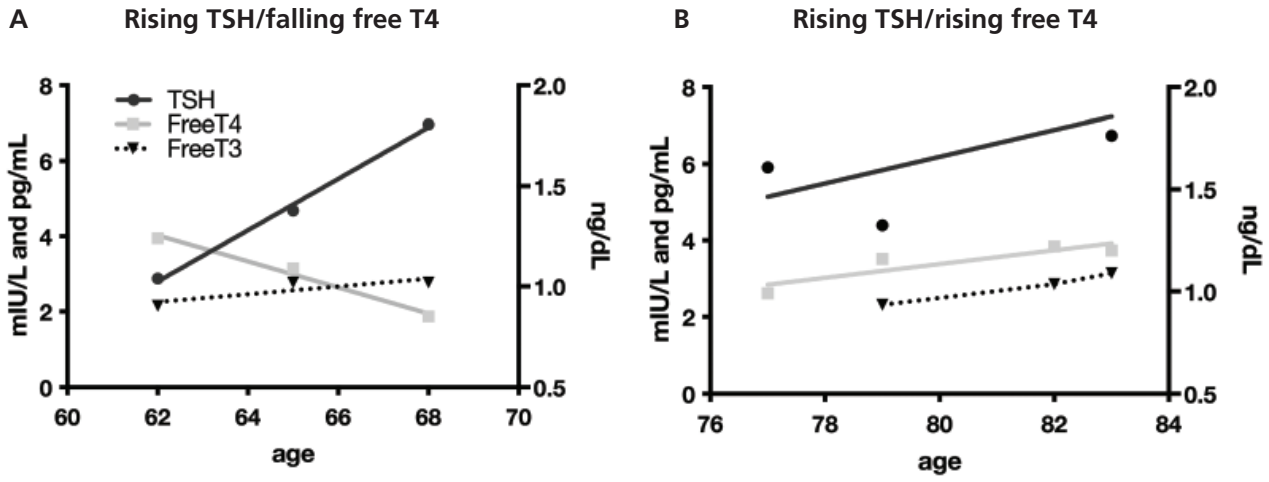

Figure 1. Varied patterns of hypothalamic-pituitary-thyroid axis hormone changes during aging in the Baltimore Longitudinal Study of Aging, with (A) a rising thyroid-stimulating hormone (TSH) accompanied by a falling free thyroxine (T4) level and (B) a rising TSH accompanied by a rising free T4 level.

T3 = triiodothyronine

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Replacement for Untreated Older Adults With Subclinical Hypothyroidism [TRUST]) did not find any effects of therapy on symptoms or cognitive function.[5]

Heterogeneity of aging-related HPT axis changes

To examine the heterogeneity of HPT axis changes in aging, we analyzed the individual trajectories for TSH and thyroid hormone together for 640 participants in the Baltimore Longitudinal Study of Aging with 3 or more measurements over an average 7 years of follow-up.[6] We found that individuals with a similarly elevated TSH at their most recent study visit can have very different hormonal feedback histories (**Figure 1**).[6] A more rapidly rising TSH has been accompanied over time by a falling free T4 (**Figure 1, panel A**), a pattern that would be consistent with developing hypothyroidism and a current diagnosis of subclinical hypothyroidism. However, the more gently rising TSH is accompanied by a slightly rising free T4 (**Figure 1, panel B**) and suggests a distinctly different phenotype.

Many alternative mechanisms could underlie the heterogeneity in the biology of serum TSH elevations in older adults. Interesting hypotheses include decreased biological activity of TSH itself due to altered glycosylation; there could be an acquired central thyroid hormone resistance as a result, perhaps, of changes in pituitary expression of thyroid hormone transporters or response to thyroid hormone receptor activation; or there could be decreased peripheral deiodinase activity in the setting of chronic inflammation and stress, similar to the changes that occur during acute nonthyroidal illness.

Most important, the presence of this heterogeneity reminds us that the HPT axis does not operate in isolation. Central regulation is located not in the pituitary but in the hypothalamus, where things like energy balance and nutrition, inflammation, and circadian rhythm are integrated to ensure that thyroid hormones, which are catabolic, are at levels appropriate for the homeostatic needs of the whole person. If individuals with elevated TSH due to an alternative mechanism are treated with thyroid hormone, it is plausible that a decrease in serum TSH levels to "euthyroid" ranges would represent an inappropriate overriding of these potentially stress-related compensations.

Unfortunately, because we do not have a robust means of clinically phenotyping this heterogeneity, the goal of a personalized medicine approach that tailors use of thyroid hormone therapy in older adults based on their individual diagnosis remains unfulfilled for now. However, this uncertainty is yet another reason for caution when considering therapy, in addition to those highlighted in Xu et al[1]: the relative lack of harm associated with isolated serum TSH elevations less than

10 mIU/L,[7] lack of demonstrated benefit in those who are treated,[5] and possible harm associated with overtreatment.[8] Among those thought to have "subclinical hypothyroidism" are individuals who do not truly have that condition. These individuals might be at greater risk from treatment than those with the condition (in whom evidence suggests treatment is unnecessary) if the treatment overrides a change in the HPT axis function that is, in fact, adaptive or working to compensate for aging-related changes in function. Clinicians should remain thoughtful about the variability in aging biology and not be blinded by a name.

DISCLOSURES

Dr. Mammen has disclosed serving as a research principal investigator for Interpace Diagnostics.

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