The Thyrotropin Reference Range Should Be Changed in Older Patients

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In endocrinology and many other disciplines, laboratory test results discriminate between patients who require treatment and those who do not. The reference range provided with the laboratory test result should align with the threshold for additional clinical action. When the reference range denoting a normal result is not aligned with the reference range needed for optimal health, confusion arises. Patients interpret the reference range as a normal range and question why abnormal test results are being ignored. Clinicians looking for an explanation for a patient's symptoms may incorrectly focus on a result outside of the reference range. Accurate laboratory reference ranges are essential for good clinical care.

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Subclinical hypothyroidism is a laboratory test–defined condition that involves a thyrotropin level above the reference range concomitant with free thyroxine levels within the reference range.[1] The current thyrotropin reference range is based on the 95% CI of the distribution of levels in a population without known thyroid disease; individuals with thyrotropin values in the lowest and highest 2.5% of this distribution are outside the range, and these values are considered abnormal. Despite the therapeutic implications, the upper and lower limits of the thyrotropin reference range are not derived from data demonstrating benefit from treatment at these thresholds. Furthermore, the distribution of thyrotropin levels in the population differs by age, with a shift toward higher levels with increasing age.[2] There are 2 implications from this finding. First, the shape of the thyrotropin distribution suggests an age-related population shift rather than increased incidence of hypothyroidism at older ages. Second, subclinical hypothyroidism is more likely to be detected in older individuals, and is present in 14.5% of individuals aged 80 years and older, compared with the expected 2.5% of individuals aged 20 to 29 years.[2] Levothyroxine is a medication with a narrow therapeutic window, and overreplacement is common in older individuals.[3] Understanding the consequences of a diagnosis of subclinical hypothyroidism, including the risks and benefits of levothyroxine treatment, is particularly important in older patients.

The study by Mooijaart et al[4] published in this issue of *JAMA* is a preplanned, pooled analysis of data from 251 participants aged 80 years and older with subclinical hypothyroidism who were included in 1 of 2 randomized double-blind, placebo-controlled trials of levothyroxine therapy that were conducted in parallel. The first trial included participants aged 80 years and older and the second trial included individuals aged 65 years and older,[5] with inclusion of data from participants aged 80 years and older in the analysis. There was no difference between levothyroxine treatment (n = 112) and placebo (n = 139) in the co-primary outcomes of hypothyroid symptoms or tiredness at 12 months, as assessed by the Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire at 12 months (range, 0-100; higher scores indicate worse quality of life; minimal clinically important difference, 9). The hypothyroid symptoms score decreased from 21.7 at baseline to 19.3 at 12-month follow-up in the levothyroxine group and from 19.8 to 17.4 in the placebo group (adjusted between-group difference, 1.3 [95% CI, −2.7 to 5.2]). The tiredness score increased from 25.5 to 28.2 in the levothyroxine group and from 25.1 to 28.7 in the placebo group (adjusted between-group difference, −0.1 [95% CI, −4.5 to 4.3]). There were also no significant differences in secondary outcomes, including quality of life, physical function, and blood pressure, at 12 months or in activities of daily living or executive cognitive function at a mean end-of-study follow-up of 17 months. The only statistically significant differences were small increases in body mass index and waist circumference in the levothyroxine group compared with the placebo group at 12 months. Adverse events did not differ between groups.

This study provides information that should change clinical practice. The key in interpreting how these findings should change practice lies in understanding to whom these data can be generalized. Study participants were aged 80 years and older, had a median (interquartile range) baseline thyrotropin level of 5.8 mIU/L (5.1-7.2) in the levothyroxine group and 5.7 mIU/L (5.2-6.6) in the placebo group, and had a low thyroid symptom burden.[4] The study population was nearly equally men and women, which differs from the female predominance of thyroid disease. Participants were required to have persistent subclinical hypothyroidism. Specifically, they had to have an elevated thyrotropin with free thyroxine levels in the reference range on 2 occasions measured between 3 months and 3 years apart. The mean levothyroxine dose was small, and the resulting decrease in the mean thyrotropin level in the levothyroxine group was small, from a baseline mean of 6.50 mIU/L to 3.69 mIU/L at 12 months.

One valuable message from this study is that subclinical hypothyroidism is frequently transient. On repeat testing, thyrotropin levels reverted to levels within the euthyroid range in 61% of participants, disqualifying them from study inclusion. Subclinical hypothyroidism that resolves without intervention does not need treatment. Patients with subclinical hypothyroidism should have thyroid function testing repeated, without initiating treatment, at least 1 month after initial testing to confirm persistent subclinical hypothyroidism.

The most consequential implication of this study is that the upper limit of the thyrotropin range should be raised to 7 mIU/L among individuals aged 80 years and older. Observational data have shown no increase in risk of cardiovascular, musculoskeletal, or neurocognitive events in individuals with subclinical hypothyroidism and thyrotropin levels of 4.5 to 6.9 mIU/L who are followed up without treatment.[1]

These data from randomized trials showed no benefit from levothyroxine treatment in a study in which more than 75% of participants had baseline thyrotropin levels in this range. Is a thyrotropin level of 4, 5, or 6 mIU/L abnormal if there is no known risk to leaving the patient untreated and no signal of detectable benefit with treatment?

If the reference range were changed for individuals aged 80 years and older, it would eliminate the need for clinicians to explain why a test result that is outside the reference range can be ignored without additional follow-up. It would help protect against polypharmacy in a vulnerable population. However, it would also influence target thyrotropin ranges among individuals who are already prescribed levothyroxine replacement. Although not directly assessed in this study,[4] increasing the dose of levothyroxine in an existing user should not have different physiologic consequences than initiating levothyroxine. In addition, the amount of additional levothyroxine would likely be less than the 50-µg dose initially prescribed in this study.[6]

Should the data from the study by Mooijaart et al[4] be generalized to all individuals in this age group with subclinical hypothyroidism? Observational data support increased cardiovascular risk in individuals with thyrotropin concentrations of 7 mIU/L or higher,[1] but few participants in this study had a thyrotropin value of 7 mIU/L or higher. It is unlikely that adequately powered clinical trials will be performed in this subgroup in light of the major effort required to recruit sufficient numbers of study participants. At this juncture, it seems more prudent to allow physician discretion in the treatment of patients with subclinical hypothyroidism with thyrotropin levels that are persistently 7 mIU/L or higher. In addition, the magnitude of thyrotropin lowering in this study was small, perhaps missing a benefit due to suboptimal levothyroxine administration. However, there is consensus among thyroid guidelines that thyrotropin levels do not need to be reduced to the lower portion of the reference range for individuals aged 80 years and older,[7-9] rendering this concern less relevant in this age group. Participants in the study by Mooijaart et al[4] had few symptoms of hypothyroidism. Even when overt hypothyroidism is present, the frequency of symptoms in patients aged 70 years and older does not differ from age-matched euthyroid control individuals,[10] suggesting that symptoms alone should not guide treatment decisions for subclinical hypothyroidism in older individuals.

The study by Mooijaart et al[4] provides the essential piece of data needed to redefine a laboratory test–defined disease affecting a large proportion of older patients. In 2017, 122 million prescriptions for levothyroxine were dispensed in the United States, the highest number of any prescription drug.[11] Medicare spending was $484 million for thyrotropin testing in 2017, higher than Medicare spending for any other laboratory test.[12] It is time to make a simple extension of the upper limit of the thyrotropin reference range to 7 mIU/L for patients aged 80 years and older. This change will reduce confusion about thyrotropin interpretation and lead to a data-driven reduction in unnecessary levothyroxine prescriptions and thyrotropin monitoring.

ARTICLE INFORMATION

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