

Optimizing management of subclinical hypothyroidism

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Story from the Front Lines:

A woman in her 70s with a history of hypothyroidism on long-term levothyroxine therapy presented to clinic. She had one mildly elevated TSH level several years ago and since, persistently suppressed TSH levels below normal levels with normal free T4 levels. She has been reluctant to decrease her levothyroxine dose despite recommendations to do so.

Teachable Moment:

Thyroid disease and replacement recommendations in elderly patients differs from younger patients, both in overt hypothyroidism as well as in subclinical hypothyroidism, which is defined as an elevated TSH with a normal free T4. The prevalence of subclinical hypothyroidism in the general population is between 3 and 15%, and rises to between 8 and 18% in patients over 65 years of age. There is a small risk of progression to overt hypothyroidism between 2 and 6%, with increased incidence in females, those with higher TSH levels, and those with TPO antibodies. Elevated TSH levels have been associated with cardiovascular disease including fatal and nonfatal events of coronary heart disease, congestive heart failure, and fatal stroke. However, other evidence suggests that a suppressed TSH is associated with atrial fibrillation, osteoporosis, and fractures, especially in patients over 60 years old. Guidelines have not been clear about the ideal treatment goal for these patients.

A recent double blinded, randomized, placebo controlled, parallel group trial was conducted to evaluate the benefits of treating subclinical hypothyroidism in patients over 65 years old. Patients treated with levothyroxine were treated with a goal TSH 0.40 to 4.59. After 12 months, there was no difference in thyroid related quality of life, tiredness score, fatal or nonfatal cardiovascular events, death, or several other measures. In addition, there was no significant difference in serious adverse events or specific adverse events including new onset atrial fibrillation, congestive heart failure, fracture, and newly diagnosed osteoporosis. As a result, the authors concluded there was no benefit to treating elderly patients with subclinical hypothyroidism, although there was also no evidence of increased adverse events in treating these patients with thyroid replacement.

Other trials have evaluated the risk of cardiovascular disease including dysrhythmia and fractures in patients on long term levothyroxine therapy. Flynn et al. conducted a retrospective, observational study of nearly 18,000 patients on levothyroxine for hypothyroidism, followed for 4.5 years. The studied patients were classified into four groups based on TSH – suppressed (≤ 0.03 mU/L), low (0.04 – 0.4 mU/L), normal (0.4 – 4.0 mU/L), and high (> 4.0 mU/L). Suppressed TSH was associated with an increase in cardiovascular morbidity and mortality when compared to patients with a normal TSH, with an adjusted hazard ratio of 1.37 (95% confidence interval 1.17 – 1.60). Suppressed TSH was also shown to be associated with a significantly increased risk of dysrhythmia (HR 1.60, 95% CI 1.10 – 2.33) and osteoporotic fractures (HR 2.02, 95% CI 1.55 – 2.62). In this study, having a low TSH was associated with a trend towards increased cardiovascular disease, dysrhythmia, and osteoporotic fractures when compared to patients with a normal TSH but the results are not statistically significant. Lastly, patients with a high TSH were found to be at increased risk of cardiovascular disease (HR 1.95, 95% CI 1.73 –

2.21), dysrhythmia (HR 1.80, 95% CI 1.33 – 2.44), and osteoporotic fractures (HR 2.02, 95% CI 1.55 – 2.62).

The results of these trials can help guide treatment of elderly patients on thyroid replacement. There may be increased risk of harm treating hypothyroidism with doses of levothyroxine that result in below normal TSH levels. Notable associations on the basis of observational data have included cardiovascular disease, dysrhythmia (primarily atrial fibrillation), and osteoporotic fractures. At the same time, in elderly patients with mildly elevated TSH levels and normal free T4 levels, there is no clear benefit to treating these patients with thyroid replacement, neither in regards to cardiovascular disease nor in terms of quality of life. Taken together, these results suggest that in our patient, by prescribing doses of levothyroxine that result in below normal TSH levels, she is not gaining any therapeutic benefit while increasing her risk of cardiovascular disease, dysrhythmia, and osteoporosis and fractures.

References:

Flynn RW, et al. Serum Thyroid-Stimulating Hormone Concentration and Morbidity from Cardiovascular Disease and Fractures in Patients on Long-Term Thyroxine Therapy. *J Clin Endocrinol Metab.* 2010;95(1):186-93.

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