

Screening and Treating Subclinical Thyroid Disease: Getting Past the Impasse

Thyroid dysfunction is common, and both insufficient and excess thyroid hormone can cause myriad systemic effects resulting in symptoms and, in extreme cases, serious illness and even death. There are sensitive and specific blood tests to diagnose thyroid dysfunction and readily available therapies to treat it. This supports the potential utility of screening.

In this issue, the U.S. Preventive Services Task Force (USPSTF) presents its findings on screening for thyroid dysfunction (1). Not surprisingly, the USPSTF concluded that evidence is insufficient to assess the balance of potential benefits and harms of screening nonpregnant adults. This conclusion is based on the absence of large prospective randomized, controlled trials (RCTs) demonstrating a benefit of treatment of subclinical hypothyroidism or subclinical hyperthyroidism (2). Indeed, the recommendation is similar to the one made by the USPSTF in 2004 (3), and it is disheartening to see that so little progress seems to have been made in trying to address this important clinical problem.

This leaves the health care provider and the patient in a familiar vacuum of management using the imperfect data available. The current USPSTF statement provides a useful summary of the few short-term clinical trials and highlights the disappointingly small number of new RCTs since the last report, with no trials conducted in the United States. However, it fails to acknowledge the publication in the intervening period of 3 individual-patient data meta-analyses of observational studies (4–6). These meta-analyses provide important information about potential risks from untreated subclinical thyroid dysfunction and support a dose-response relationship between thyroid-stimulating hormone (TSH) concentrations at either extreme and an increased risk for cardiovascular events and death. They also support potential serum TSH thresholds for increased risk of less than 0.45 and greater than 7 mIU/L and more confident thresholds of less than 0.1 and greater than 10 mIU/L, although the benefits and harms of treatment at these thresholds have not been defined in RCTs.

We agree that the first step in moving from a recommendation of “insufficient evidence” to a more clinically useful recommendation requires data from RCTs with hard end points. Although an effort to fund a U.S. trial in subclinical hypothyroidism was unsuccessful, the European TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) study is currently under way (www.clinicaltrials.gov/ct2/show/NCT01660126?term=TRUST+trial&rank=1). Two European trials designed to examine treatment of subclinical hyperthyroidism failed to complete recruitment due to the lower prevalence of the condition and were terminated. Therefore,

there is little hope of data on the risks and benefits of treating this condition. Subclinical hyperthyroidism is associated with atrial fibrillation, congestive heart failure, and osteoporosis in older persons and postmenopausal women (7). These are precisely the unfavorable health effects seen in older persons with overt hyperthyroidism, which is why professional groups recommend treating subclinical hyperthyroidism in these vulnerable populations, especially those with serum TSH concentrations less than 0.1 mIU/L (8).

As practicing endocrinologists, we find 2 themes in the USPSTF statement troublesome. The first is the reference to “measurement variability” of serum TSH. This variability is not due to poor assay performance but to inherent biological variability related to the exquisite sensitivity of the hypothalamic-pituitary-thyroid axis to even minimal perturbations in thyroid secretion. Superimposed on these clinically insignificant changes are potential episodes of silent thyroiditis and systemic illness. This is the reason for confirming the persistence of a serum TSH abnormality with a single repeated measurement several months later. The rationale in the USPSTF statement for “[m]ultiple tests . . . over a 3- to 6-month interval” is neither biologically relevant nor supported by data.

The second disturbing issue in the USPSTF statement is the use of the term “asymptomatic” in the context of thyroid dysfunction. By definition, a patient with symptoms of fatigue, hair loss, or palpitations who has a TSH test done is undergoing “case finding,” not screening. It is hard to justify withholding TSH testing in a patient who does not have an obvious alternative cause for any of these symptoms. The clinical conundrum arises when a patient with any of the nonspecific symptoms of thyroid dysfunction has test results consistent with subclinical thyroid dysfunction. Were the patient's symptoms due to a mild thyroid problem, or is there an unrelated biochemical abnormality that may or may not be clinically significant? The effectiveness of treatment of either type of subclinical thyroid dysfunction in reversing the symptoms that triggered testing has never been evaluated in placebo-controlled trials. Therefore, it is not clear that the management of a symptomatic patient with subclinical thyroid dysfunction should differ from that of an asymptomatic patient, given the potential for beneficial effects on cardiovascular outcomes and bone health, which might occur with therapy even in asymptomatic persons.

We also reiterate concerns expressed in the public comment section of the USPSTF statement about not treating asymptomatic *overt* thyroid disease (defined by serum concentrations of free thyroxine or triiodothyronine that are outside their reference ranges), as would occur in the placebo group of an RCT. The im-

PLICIT suggestion that there would only be benefit to treating symptomatic overt thyroid disease shows how far astray one can go in pursuit of the “holy grail” of the RCT. This is particularly concerning in elderly adults, in whom symptoms are often absent and atypical symptoms may prevail (9). We strongly disagree with the proposal to conduct treatment trials of asymptomatic overt thyroid dysfunction. In the case of overt hypothyroidism, treatment with levothyroxine is recommended, and patients with overt hyperthyroidism are treated with antithyroid medications, radioiodine, or surgery, depending on the clinical circumstances and patient preference. There should be no debate about this.

We hope that when the USPSTF evaluates screening for thyroid dysfunction in another 10 years, there will be additional RCT data to provide guidance. We agree that these data are urgently needed and call on researchers and funding agencies to partner to make this happen. However, without definitive information—and this is highly probable for subclinical hyperthyroidism—we will need to continue to rely on lower-quality evidence to make important clinical decisions that, admittedly, have the potential to both help and harm patients. The decades-long impasse only enhances the importance of evidence-based clinical practice guidelines designed to assist clinicians in making the best decisions for their patients (8, 10).

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