Thyroid Hormone Suppression Therapy

Bernadette Biondi, MD[a], David S. Cooper, MD[b,*]

KEYWORDS

• Thyroid cancer • Levothyroxine • Thyrotropin • Cardiovascular system • Bone • Mortality

KEY POINTS

- Thyroid hormone suppression therapy is a strategy to lower serum thyroid-stimulating hormone (TSH) levels in patients with differentiated thyroid cancer in the hope that it will improve outcomes.
- Evidence for improved outcomes with TSH suppression is lacking, except in patients with the most advanced disease.
- Iatrogenic hyperthyroidism produced by thyroid hormone suppression therapy can lead to adverse outcomes such as osteoporosis, fractures, and cardiovascular disease, including atrial fibrillation.
- The use of thyroid hormone suppression should be based on initial risk of disease and ongoing risk assessment of disease status. The lowest amount of thyroid hormone should be used whenever possible.

INTRODUCTION

The rationale behind thyroid hormone suppression therapy is the knowledge that thyroid-stimulating hormone (TSH), secreted by the pituitary, affects growth and proliferation of thyroid cancer cells.[1] Several epidemiologic studies suggest that higher serum TSH levels, even within the normal range, are associated with an increase in the frequency of differentiated thyroid cancer (DTC) in patients with thyroid nodules, as well as a more aggressive course in those patients with a thyroid cancer diagnosis.[2–5] This theory is supported by a mutant mouse model in which there is altered thyroid hormone receptor signaling, resulting in chronically elevated serum TSH levels, with such mice developing a high frequency of metastatic thyroid cancer.[6] In another mouse model, in which thyroid cancer was induced by knock-in of the oncogenic

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[a] Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, Naples 80131, Italy; [b] Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 333, Baltimore, MD 21287, USA
* Corresponding author.
E-mail address: dscooper@jhmi.edu

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V600E BRAF mutation, the development of thyroid cancer was slowed considerably in mice whose genome had the TSH receptor gene knocked out.[7] Because of absence of TSH receptor expression, these animals also have very high serum TSH levels. Although thyroid cancer occurred, it was less aggressive than in animals that expressed the wild-type TSH receptor. This suggests that, although TSH may not be necessary for the initiation of thyroid cancer, TSH signaling is important for its maintenance and progression. On the other hand, suppression of TSH levels in animals with the V600E mutation did not prevent the spread of thyroid cancer after it had been established, possibly due to subsequent tumor-related alterations in TSH receptor expression.[8] This observation may support the idea that TSH suppression may be of limited value in patients with more advanced thyroid cancer (see later discussion).

CLINICAL STUDIES

All patients undergoing total thyroidectomy, as well as the very few patients who undergo lobectomy, require thyroid hormone therapy to maintain normal serum TSH levels. In contrast, the concept behind TSH suppressive therapy is that, at least theoretically, a subnormal serum TSH may lead to slower growth and spread of existing DTC. In support of this idea, a 2002 meta-analysis of 10 studies published from the 1970s to the 1990s concluded that thyroid hormone suppression therapy was efficacious in decreasing thyroid cancer morbidity and mortality (relative risk 0.71, $P<.05$) for adverse events (combined disease progression/recurrence and death).[9] However, these older studies did not necessarily distinguish replacement from suppression therapy, and lacked modern technology (eg, ultrasound and thyroglobulin measurement) to adequately detect small-volume recurrences. However, 2 subsequent studies published more recently[10,11] also concluded that aggressive serum TSH suppression led to a survival benefit in patients with distant metastases, although the difference in cause-specific survival did not reach statistical significance in 1 of the studies.[10] Importantly, in the other study,[11] no further survival benefit was noted in patients with metastatic disease with serum TSH levels that were fully suppressed (<0.03 mU/L) compared with patients with serum TSH levels that were only suppressed to less than 0.1 mU/L.

Studies from the National Thyroid Cancer Treatment Cooperative Study Group, a thyroid cancer registry consortium in the United States, have concluded that the most aggressive TSH suppression therapy was of no value in patients at low risk for recurrence but was of benefit in high-risk patients.[12,13] In the most recent analysis from this prospective cohort involving almost 5000 subjects followed for a median of 6 years, moderate degrees of TSH suppression, meaning serum TSH levels that were consistently maintained in the subnormal (0.1–0.4 mU/L) to normal ranges (0.4–4 mU/L) led to better outcomes in patients at all stages of disease, compared with subjects whose serum TSH levels were in the normal to elevated ranges.[14] However, benefits of TSH suppression were no longer observed after 5 years of follow-up. This is consistent with an earlier Dutch study showing very low recurrence and mortality rates in subjects whose serum TSH levels were maintained at a median of less than 2 mU/l over a 9 year follow-up compared with subjects whose median serum TSH levels were greater than 2 mU/L.[15] In the only randomized prospective study of TSH suppression in thyroid cancer, 400 Japanese subjects were randomized to receive levothyroxine (L-T4) therapy to maintain serum TSH levels within the reference range versus serum TSH levels less than 0.01 mU/L.[16] After a mean follow-up of almost 7 years, there were no differences in disease-free survival between the 2 groups, even when high-risk subjects were analyzed separately.[16]

Recent American Thyroid Association (ATA) Guidelines recommend either total thyroidectomy or lobectomy for low-risk patients with DTC.[17] Many patients undergoing lobectomy will not require thyroid hormone replacement therapy to maintain serum TSH levels within the reference range. A recent retrospective analysis by Park and colleagues[18] of subjects with thyroid cancer who had undergone lobectomy showed that the use of thyroid hormone to maintain serum TSH levels less than or equal to 2.0 mU/L was of no benefit in terms of recurrence-free survival. Furthermore, even in those subjects who did not receive L-T4 therapy, there was no difference in recurrence-free survival in those subjects whose TSH levels were less than 2 mU/L compared with subjects whose serum TSH levels were between 2 and 4.5 mU/L. However, there were differences in dynamic risk stratification, with more subjects not receiving thyroid hormone having biochemically indeterminate responses compared with those lobectomized subjects who were receiving thyroid hormone treatment to maintain their TSH levels at less than 2 mU/L (17.2% vs 9.4%).[18] The study should be interpreted with caution, however, because all subjects who underwent lobectomy also underwent prophylactic ipsilateral central neck dissections, a procedure not generally performed in the United States.

In general, daily L-T4 doses of 1.6 to 1.8 μg/kg are required to achieve a normal TSH level in athyreotic individuals, whereas doses of 2.0 to 2.2 μg/kg are needed to suppress the serum TSH. However, the dose requirements in individual patients are highly variable and depend on multiple factors, including body mass index, the use of concomitant medications, and drug bioavailability, among others.

ADVERSE EFFECTS OF THYROID-STIMULATING HORMONE-SUPPRESSIVE THERAPY WITH LEVOTHYROXINE

For many years, all patients with DTC likely received excessive L-T4 doses after thyroid surgery and radioiodine (RAI) ablation to intentionally suppress serum TSH at undetectable levels (TSH levels <0.01 mU/L with a third-generation sensitive assay).[19,20] In these patients, serum free thyroxine (FT4) concentrations were often at the upper limit of the reference range or frankly elevated.[21–23] This condition, termed exogenous (Exo) subclinical hyperthyroidism (SHyper), may be associated with symptoms and signs of hyperthyroidism; impaired psychological, social, and physical quality of life[20,24–28]; and adverse effects on the heart and skeleton, including increased cardiovascular (CV) morbidity and mortality, and increased risk of osteoporosis and fractures.[19]

CARDIOVASCULAR MORBIDITY AND MORTALITY

Several retrospective studies reported that long-term TSH-suppressive therapy increases heart rate and left ventricular mass (LVM)[20,29–31]; leads to myocardial strain[30] and impaired diastolic function[32–34]; and reduces arterial elasticity,[35] cardiac reserve, and exercise capacity.[36,37] Although none of these studies stratified the assessment of CV morphology and function according to the level of TSH suppression, the increase in LVM was related to the duration of TSH suppression more than to the thyroid hormone levels in the circulation. These results suggest that the chronic hemodynamic overload and persistent hyperkinetic CV state due to the slight thyroid hormone excess was the main determinant of this concentric cardiac remodeling.[19,38] The negative alterations in CV morphology and function were reversible after beta-blockade[30,39] or the restoration of euthyroidism.[38] Atrial fibrillation (AF) and a prothrombotic state were the most important adverse events in DTC patients with Exo SHyper and were responsible for the greater risk of hospitalization for CV disease

(CVD).[40] One population-based study in subjects receiving long-term TSH-suppressive therapy reported that the risk of CVD and dysrhythmias increased with age.[41] Similarly, in 2 retrospective studies among 136[42] and 518[43] DTC subjects, a higher prevalence of AF was found in the older group (18% vs 8% older than the age of 60 years vs younger than 60 years).[42] The risk of AF was 17.5%, significantly higher that the predicted sex-and age adjusted risks.[42]

In contrast, a prospective study reported that the risk of AF was comparable in 756 subjects with low risk and intermediate risk when serum TSH levels were less than or equal to 0.4 mU/L or greater than 0.4 mU/L.[44] Similarly, no correlation was found between the level of TSH and the occurrence of AF in 2 other studies.[43,44] Interestingly, the risk of AF was independent from the traditional risk factors,[43] whereas it was correlated with the cumulative dose of RAI.[43] These data suggest a potential role of RAI on cardiac inflammation, oxidative stress, or fibrosis because the sodium-iodine symporter gene is expressed in cardiac tissue.[45] All of these data could suggest that advanced age, duration of TSH suppression, and coexistence of associated morbidities are probably the main factors correlated with the negative CV prognosis of patients with Exo SHyper.

There are conflicting data on CV and all-cause mortality in DTC patients.[40,46–49] In 1 large retrospective study, the risk of CV mortality increased 3.3-fold and the risk of all-cause mortality increased 4.4-fold in subjects with DTC compared with controls.[46] These risks were independent of age, sex, and CV risk factors. For each fold decrease in geometric mean, TSH was independently linked with a 3.1-fold increased risk of CV mortality.[46] Regarding RAI therapy, no correlation with the cumulative RAI dose was observed for the risk of all-cause mortality in patients treated with RAI ablation (cumulative RAI dose 100 MCi), despite an increased risk of CVD morbidity compared with the control group and to untreated patients.[40] Therefore, the potential role of a different degree of TSH suppression and the effects of RAI therapy on CV morbidity and mortality remain to be established.

RISK OF OSTEOPOROSIS

Thyroid hormone excess exerts important effects on bone remodeling by shortening bone remodeling cycle and accelerating bone turnover.[50] On the other hand, TSH is a negative regulator of bone turnover and has a specific inhibitory effect on bone resorption.[51,52] Cross-sectional and longitudinal studies report conflicting findings on the effects of Exo SHyper on bone turnover. Two overviews assessing the effects of TSH suppressive therapy on bone mineral density (BMD) in patients with DTC suggested that TSH suppression did not affect BMD in men or in premenopausal women, whereas postmenopausal women were at risk of bone loss.[53,54]

Similarly, 2 meta-analyses[55,56] on postmenopausal women with Exo SHyper found a decrease in BMD with an annual bone mass loss of 0.91%.[55] Some studies reported that TSH suppressive therapy can affect trabecular bone microstructure as detected by trabecular bone score measurement,[57] peripheral high-resolution quantitative computed tomography,[58,59] or radiological vertebral fractures,[60] which were found in about one-third of women with DTC and was linked with the duration of treatment, degree of TSH suppression, and age of patient.[60]

A prospective study in DTC subjects with low or intermediate risk suggested that subjects with TSH suppression less than 0.4 mU/L had a higher incidence of osteoporosis compared with nonsuppressed subjects (hazard ratio 2.1, $P = .05$), and that prolonged TSH suppression with L-T4 increased the risk of postoperative osteoporosis in DTC subjects.[44] The duration of TSH suppression is an important factor to be

considered. A randomized controlled trial in female subjects randomly assigned to receive TSH suppressive or no therapy reported that subjects with TSH suppressive therapy had a significant deterioration in BMD from 1 year after surgery. Moreover, a significant decrease in BMD was observed in older subjects (>50 years) but not in younger subjects (<50 years). A marked deterioration in BMD was reported in subjects who continued TSH suppression for 5 years, especially in those with older age and lower preoperative BMD.[61] Subjects who did not receive TSH suppression did not show any significant decrease in T-score until 5 years postoperatively.[61] All of these results suggest that a long-term TSH suppressive therapy is associated with bone loss, especially in elderly patients and postmenopausal women.

FRACTURE RISK

Postmenopausal women with serum TSH levels lower than 0.1 mU/L during L-T4 treatment had a 2-fold to 4-fold greater risk of osteoporotic fracture compared with the general population. The risk of fracture was associated with a strong dose-response relation among adults aged 70 years or more.[62] Several studies and meta-analyses, including prospective studies, have confirmed the association between subclinical thyroid hormone excess and the risk of fractures, mainly in postmenopausal women.[41,62–68] Most of these studies confirmed the associated between duration of TSH suppression and increased fracture risk. The negative effects of the slight thyroid hormone excess in SHyper on muscle strength, weight, and lean body mass loss, as well as the possible association with a cognitive decline in elderly patients, could contribute to the increased risk of fractures in patients during TSH suppressive therapy.[69]

EFFECTS OF HIGHER FREE THYROXINE LEVELS AND CARDIOVASCULAR RISK

Total T3 or FT3 levels are usually in the middle or lower part of the reference range in Exo SHyper, with a consequent increased T4/T3 ratio.[13–16] Therefore, endogenous and Exo SHyper (caused by Graves' disease or toxic nodular goiter) are not comparable biochemically due to differences in severity and in the pattern of circulating thyroid hormone levels.[69] This could suggest that a different mechanism of action may explain the adverse effects of endogenous and Exo SHyper on the CV system and bone structure. Some studies reported that high serum FT4 levels within the reference range might be associated with negative health outcomes in elderly patients in terms of AF and CV mortality.[70–73] Elderly subjects with serum FT4 in the highest quartile of their reference range can have an increased risk of AF and CV morbidity and mortality.[70–73] Moreover, lower TSH and higher FT4 within the reference range were associated with 22% to 25% increased risk of hip fractures in euthyroid postmenopausal women.[74] Prospective studies are needed to assess the role of increased T4/T3 ratio on the CV and bone risk in patients with DTC.

TREATMENT OF EXOGENOUS SUBCLINICAL HYPERTHYROIDISM

Large randomized controlled studies are required to prove causality in the cardiac and skeletal effects, and to assess the efficacy of TSH normalization on CV risk and fractures. No study has evaluated the effects of beta-blocking drugs on CV mortality, even though these drugs can improve CV parameters associated with increased morbidity in the general population. Treatment with alendronate could prevent trabecular bone loss in patients with thyroid cancer receiving thyroxine replacement.[75] However, the potential risk of AF should be considered and a risk-benefit assessment made.[76]

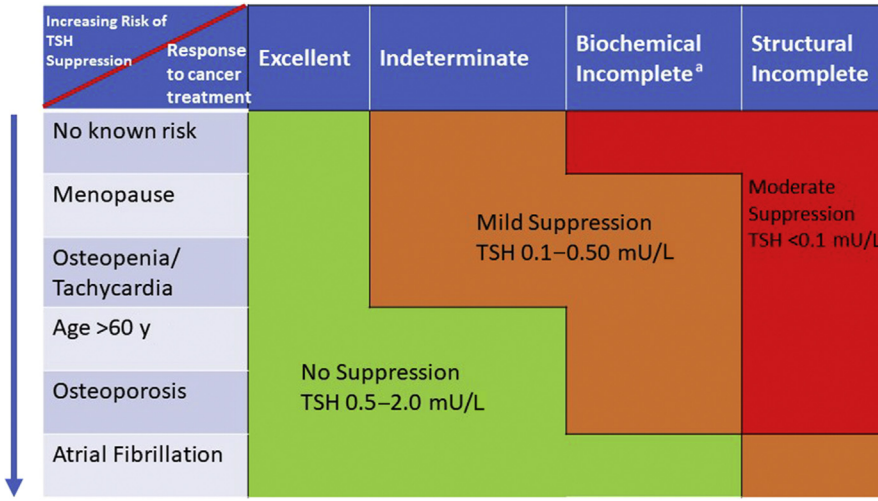

Fig. 1. 2015 ATA Thyroid Guidelines: long-term TSH suppression. [a] TSH target for patients with a biochemical incomplete response can be quite different based on original ATA risk, thyroglobulin (Tg) level, Tg trend over time, and risk of TSH suppression.

RECOMMENDATIONS FOR THYROID HORMONE THERAPY

Given the evidence that aggressive TSH suppression is of little to no benefit to almost all patients with thyroid cancer who are at low risk of recurrence and death, the ATA recommends a graded algorithm, considering that the potential benefits of such therapy must be balanced against CV and skeletal risks (**Fig. 1**).[17] Using the concept of ongoing risk stratification, the ATA recommends maintaining serum TSH levels between 0.5 and 2 mU/L in low-risk and intermediate-risk patients with an excellent response to treatment but using mild TSH suppression (TSH 0.1–0.5 mU/L) in high-risk patients who have had an excellent response (negative imaging and undetectable suppressed thyroglobulin). Mild TSH suppression is also recommended in patients with a biochemically incomplete response. More significant TSH suppression (ie, serum TSH <0.1 but not necessarily undetectable) is recommended in patients with residual structural disease or a biochemically incomplete response if they are young or at low risk of complications from Exo SHyper. Ongoing assessment of the patient's clinical disease status, as well as the temporal development of risk factors such as advanced age, postmenopausal state, and the development of osteoporosis and/or CVD are essential to prevent the treatment from becoming worse for the patient than the disease being treated.

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