Chapter 18
Risks of Thyroid Hormone Suppression for Differentiated Thyroid Cancer in the Elderly

Swaytha Yalamanchi and David Cooper

Case Presentation

A 91-year-old woman presents for management of papillary thyroid carcinoma (PTC). She underwent a total thyroidectomy 6 years previously. Pathology demonstrated a 1.3 cm focus of PTC with focal tall cell features and metastases in one of four central and two of five left lateral lymph nodes. She was treated with 75 mCi of I-131 and her posttreatment scan showed two foci of radiotracer localization in the thyroid bed and three foci in the anterior lower thorax. The patient underwent resection of a level VI lymph node 4 years later. Pathology showed a 1.5 cm lymph node replaced by PTC and extensive skeletal muscle involvement. Chest CT scan showed multiple pulmonary nodules suspicious for metastatic disease, none of which were iodine-avid on subsequent I-123 scan. The patient also has a history of osteoporosis with a femoral fragility fracture and is being treated with risedronate.

Recent biochemical assessment includes serum thyroid stimulating hormone (TSH) 0.68 mU/L (0.50–4.50), serum free T4 1.6 ng/dl (0.8–1.8), and serum basal thyroglobulin 120 ng/ml with negative serum thyroglobulin antibody titers.

Assessment and Literature Review

PTC is associated with low rates of mortality and recurrence, particularly in patients with low-risk disease. Fully suppressive thyroxine (T4) therapy (serum TSH <0.1 mU/L) does not have a role in the long-term management of low-risk PTC, though

S. Yalamanchi, MD • D. Cooper, MD (✉)
Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins Hospital, 1830 E. Monument St, Suite 333, Baltimore, MD 21287, USA
e-mail: dscooper@jhmi.edu

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may improve survival in patients with high-risk disease. Iatrogenic hyperthyroidism may negatively impact cardiovascular and bone health, particularly in the elderly. Individualized goals regarding T4 suppressive therapy are thus necessary.

Prevalence

The incidence of differentiated thyroid cancer (DTC), particularly low-risk PTC, has increased rapidly over the past 15 years [1]. Although there has been increased detection of incidental subclinical disease on imaging studies, rates of aggressive PTC (tall cell variant histology, tumors with extrathyroidal extension, and distant metastases) and thyroid cancer-specific mortality in the past 10–15 years have also increased [2].

Efficacy of Thyroid Hormone Suppression Therapy

DTC treatment has traditionally included total thyroidectomy, suppression of serum TSH to undetectable levels, and, in selected cases, radioiodine ablation (RAI). Older studies suggested that suppressed TSH levels, regardless of the stage, may be associated with decreased rates of disease progression and recurrence and increased rates of relapse-free survival [3, 4]. Multiple studies since that time, however, have shown that thyroid hormone suppression is beneficial in high-risk, but not low-risk, disease. A prospective study of the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) ($n=617$) found no effect of thyroid hormone suppression in stages I and II disease with minimal effects seen in stages III and IV after adjustment by multivariate analysis [5]. A subsequent study of 4,047 patients in the NTCTCSG demonstrated that T4 suppressive therapy did not modify outcomes in stage I disease. Improved overall survival was seen with moderate suppression in stage II disease and aggressive suppression in stage III and IV disease. T4 suppressive therapy was associated with improved disease-specific survival in high-risk patients, but had no effect on disease-free survival at any stage [6]. Hovens et al. confirmed these findings ($n=366$, mean follow-up = 8.85 years) and found that median serum TSH levels >2 mU/L in patients with T1-3, M0 tumors were associated with higher rates of thyroid cancer recurrence (HR 1.41; 95 % CI 1.03–1.95) and death (HR 2.03; 95 % CI 1.22–3.37) as compared to individuals with serum TSH <2 mU/L [7]. Most recently, in a non-inferiority randomized control trial of low-risk DTC patients ($n=433$, mean follow-up = 6.9 years), Sugitani et al. demonstrated that disease-free survival in euthyroid patients (mean serum TSH 3.2 mU/L) was similar to that of patients with suppressed serum TSH. Of note, the majority of patients in this cohort underwent central neck dissection and did not receive radioiodine, patterns of care that differ from that seen in North America and Europe [8].

Overall, patients with low-risk DTC have an excellent prognosis, and aggressive TSH suppression is unlikely to be beneficial. In contrast, current evidence suggests

that TSH suppression may lower recurrence rates and improve disease-specific survival in patients with more aggressive disease. The appropriate degree of TSH suppression by thyroid hormone suppression therapy remains unknown.

Recommendations for Serum TSH Suppression Goals

The 2015 ATA guidelines recommend initial serum TSH suppression goals for high- and intermediate-risk thyroid cancer patients of <0.1 mU/L and 0.1–0.5 mU/L, respectively. The recommended goal serum TSH for low-risk patients with detectable serum thyroglobulin regardless of remnant ablation status is at or slightly below the lower limit of normal (0.1–0.5 mU/L). Low-risk patients with undetectable serum thyroglobulin levels regardless of whether they have undergone remnant ablation may have serum TSH maintained at the lower end of the reference range (0.5–2 mU/L) [9].

Serum TSH goals at the time of initial assessment should be based on comorbidities (Table 18.1) [9]. TSH targets in the long-term follow-up of DTC depend on comorbidities, the risk of recurrence, and evidence of disease [9] (Table 18.1).

Adverse Effects Associated with Suppressive T4 Therapy in the Elderly

While T4 suppressive therapy may reduce recurrence and mortality rates in individuals with high-risk DTC, there are inherent risks associated with iatrogenic hyperthyroidism. Suppressive thyroxine therapy may negatively impact quality of life [10]. Iatrogenic hyperthyroidism also adversely affects cardiovascular and bone health, particularly in the elderly.

It is unclear if endogenous hyperthyroidism and exogenous hyperthyroidism cause similar adverse event profiles. Serum free T4 levels are high normal or elevated in both situations, but it is uncommon for serum T3 levels to be high

Table 18.1 Suggested long-term serum TSH targets in patients with DTC

Risk from T4 therapy	Response to therapy			
	Excellent (mU/L)	Indeterminate (mU/L)	Biochemically incomplete (mU/L)	Structurally incomplete (mU/L)
Minimal	0.5–2.0[a]	0.1–0.5	<0.1	<0.1
Moderate	0.5–2.0[a]	0.5–2.0[a]	0.1–0.5	<0.1
High	0.5–2.0[a]	0.5–2.0[a]	0.5–2.0[a]	0.1–0.5

Adapted from 2015 ATA guidelines [9]

[a]Serum TSH of 0.5 mU/L represents the lower limit of the reference range for specific TSH assays; this level may be 0.3–0.5 mU/L depending on the assay

normal or elevated in iatrogenic hyperthyroidism, as compared to endogenous hyperthyroidism. The difference in serum T4/T3 ratios in endogenous and exogenous hyperthyroidism may thus result in different end-organ effects [11].

Cardiovascular Disease

Dysrhythmias

Elderly individuals with iatrogenic hyperthyroidism are at increased risk of dysrhythmias and cardiovascular (CV) disease. The elderly also tend to be less symptomatic than their younger counterparts and thus warrant heightened clinical suspicion [12].

The prevalence of atrial fibrillation (AF) in DTC patients 60 years and older has been estimated to be as high as 17.5 %, with paroxysmal AF more common than persistent AF [13]. A Scottish observational study including 17,684 patients (females 85.9 % with mean age of 60.3 years; males with mean age of 61.8 years; median follow-up 4.5 years) on levothyroxine for at least 6 months demonstrated that individuals with exogenously suppressed serum TSH levels of <0.03 mU/L were at increased risk for CV disease (adjusted HR 1.37; 95 % CI 1.17–1.60) and dysrhythmias (adjusted HR 1.6; 95 % CI 1.10–2.33) after adjustment for age, sex, previous thyroid condition, socioeconomic status, and history of diabetes mellitus. The subset of patients with low but non-suppressed serum TSH levels ranging from 0.04 to 0.4 mU/L did not have an increased risk of cardiac events [14].

Cardiovascular Mortality

There has been conflicting data regarding whether exogenous hyperthyroidism results in increased cardiovascular mortality. Bauer et al. found no difference in mortality rates between women on long-term thyroxine therapy and nonusers (relative hazard 1.11, 95 % CI 0.98–1.24, $p \leq 0.09$), even when stratified by serum TSH (<0.5 mU/L vs. >5 mU/L). A prior history of hyperthyroidism, however, was associated with a small increase in all-cause and cardiovascular mortality [15]. In contrast, a population-based observational study (mean age 49 ± 14 years, median follow-up = 8.5 years) demonstrated an increase in CV mortality and all-cause mortality by 3.3- and 4.4-fold, respectively, in patients with DTC independent of age, sex, and CV risk factors. Each tenfold decrease in geometric mean serum TSH was associated with a 3.1-fold increase in CV mortality [16]. Yang et al. similarly observed that among thyroid cancer patients, cardiac disease and cerebrovascular disease were the most frequent causes of non-cancer mortality [17]. The mechanism for increased CV mortality is unclear, but is postulated to be related to an increased risk of AF, impaired diastolic function, and increased left ventricular mass, leading to increased risk of stroke, heart failure, and myocardial infarction, respectively [16].

Bone Health

Bone Mineral Density and Fracture Risk

Data regarding the effect of iatrogenic hyperthyroidism on BMD are conflicting, but largely suggestive of a decrease in BMD and increase in fracture risk in postmenopausal women. The majority of data have not shown compelling evidence of a significant change in bone health in premenopausal women or men treated with T4 suppressive therapy [18–20].

Bauer et al. prospectively followed 686 women at least 65 years of age with subclinical hyperthyroidism (both exogenous and endogenous) and demonstrated that women with a suppressed serum TSH level (≤0.1 mU/L) had a threefold increased risk of hip fracture (relative hazard, 3.6 [95 % CI, 1.0–12.9]) and a fourfold increased risk of vertebral fracture (odds ratio 4.5, 95 % CI 1.3–15.6) as compared to controls (serum TSH 0.5–5.5 mU/L) [21]. The Thyroid Epidemiology Audit and Research Study (TEARS) also demonstrated an increased risk of fractures in both individuals with suppressed serum TSH (<0.03 mU/L) (adjusted HR 2.02, 95 % CI 1.55–2.62) and elevated serum TSH (>4.0 mU/L) (adjusted HR 1.83, 95 % CI 1.41–2.37). Elevated serum TSH levels in the latter group were considered to be a marker for poor compliance with medical therapy. Similar to the pattern seen in cardiovascular events as previously described, individuals with low but non-suppressed serum TSH levels (0.04–0.4 mU/L) did not have an increased risk of fracture [14].

A meta-analysis including five population-based prospective studies demonstrated a nonsignificant increase in the risk of hip fractures (HR 1.38 [CI, 0.92–2.07]) and non-spine fractures when patients with endogenous and exogenous subclinical hyperthyroidism were pooled. The strength of the relationship between subclinical hyperthyroidism and fractures appeared stronger in the setting of a suppressed serum TSH (<0.1 mU/L), but only two studies provided such data [22]. These findings are in keeping with meta-analyses by Faber et al. and Uzzan et al. suggesting that T4 suppressive therapy results in bone loss at an annual rate of 1 % in postmenopausal women [23, 24]. Differences in studies may be partially explained by varying rates of thyroid hormone suppression and calcium intake in the studies [20].

Treatment

Calcium and bisphosphonates are useful in managing bone health in iatrogenic hyperthyroidism. Kung et al. demonstrated that calcium monotherapy (1000 mg/day) was effective in mitigating bone loss, while intranasal calcitonin offered little further benefit [25]. Panico et al. stratified 74 postmenopausal women with DTC and a history of low BMD (T score ≤ −2.5) into three groups based on the duration of T4 suppressive therapy of 3, 6, and 9 years, respectively. All individuals,

including controls, were treated with bisphosphonates, calcium, and vitamin D for 2 years, and all demonstrated an increase in lumbar spine BMD. Bisphosphonates were most effective in increasing BMD in the lumbar spine and femoral neck in postmenopausal women receiving T4 suppressive therapy in the short term [26].

Management of Patient

Our patient has recurrent stage IVc PTC with likely pulmonary metastases. Given her persistent high-risk disease, she qualifies for suppressive thyroxine therapy (serum TSH < 0.1 mU/L) by the ATA guidelines. However, the patient is postmenopausal with known osteoporosis. She also is elderly with increased risk of AF and may have underlying cardiac disease that could increase her risk of cardiovascular mortality. In weighing the benefits and risks of suppressive therapy, the patient's goal serum TSH is in the mildly suppressed range (0.1–0.50 mU/L). Given proximity to goal TSH in the low-normal range, the patient's dose of levothyroxine was not adjusted.

Clinical Pearls/Pitfalls

- T4 suppressive therapy does not improve survival in patients with low-risk DTC though it is likely to be beneficial in high-risk patients.
- Serum TSH targets in the long-term follow-up of individuals with DTC depends on the risk of recurrence, evidence of disease, and comorbidities.
- The elderly are at the high risk of developing complications from T4 suppressive therapy, particularly atrial fibrillation and osteoporosis.
- Calcium and bisphosphonates may be useful in mitigating the risk of bone loss in postmenopausal women on suppressive doses of T4.
- Risks of adverse cardiovascular and skeletal effects are minimized by targeting subnormal, rather than fully suppressed serum TSH levels (Table 18.1).

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