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REVIEW

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Thyroid hormone therapy in differentiated thyroid cancer

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Abstract

Surgery—with or without postoperative radioiodine—is the standard of care for most patients with differentiated thyroid carcinoma (DTC). Thyroid hormone replacement therapy is the mainstay of long-term medical management. Patients treated with total thyroidectomy and some who undergo lobectomy alone require thyroid hormone therapy to restore euthyroidism with normal serum thyroid-stimulating hormone (TSH) levels. Because TSH acts as a growth factor for thyroid follicular cells (including those that are neoplastic), it can potentially affect the onset and/or progression of follicular-cell derived thyroid cancer. For this reason, some patients are placed on thyroid hormone therapy at doses that suppress secretion of TSH (suppression therapy). This mini-review looks at the potential benefits and risks of this practice in patients diagnosed with DTC. Aggressive TSH-suppressive therapy is of little or no benefit to the vast majority of patients with DTC. Practice guidelines, therefore, recommend a graded algorithm in which the potential benefits of suppression are weighed against the associated cardiovascular and skeletal risks. Large randomized controlled studies are needed to confirm the presumed oncological benefits of TSH-suppression and its causal role in adverse cardiac, skeletal, and quality of life effects and to assess the efficacy of TSH normalization in reversing or reducing these effects.

Keywords Differentiated thyroid carcinoma · Thyroid-stimulating hormone · TSH suppressive therapy · TSH replacement therapy · Levothyroxine

Introduction

In the management of differentiated thyroid carcinoma (DTC), surgery—with or without postoperative radioiodine—is the standard of care in most patients [1]. For those treated with thyroidectomy and some who undergo lobectomy alone [2], thyroid hormone therapy, usually with levothyroxine, is necessary to restore euthyroidism and maintain normal serum levels of thyroid-stimulating hormone (TSH).

TSH suppression (resulting in serum levels below the lower limit of the reference range) was proposed as a therapeutic intervention in thyroid cancer on the assumption that subnormal serum levels of TSH would favor slower growth and spread of thyroid cancer cells. TSH is considered to be a growth factor for thyroid follicular cells, potentially affecting initiation or progression of follicular-cell derived thyroid cancer. Serum TSH also regulates thyrocyte differentiation by modulating the expression of genes with important effects on the transcription of the *sodium-iodide symporter* (*NIS*) gene, which becomes markedly downregulated after prolonged TSH suppression [3]. TSH stimulates iodine uptake by thyrocytes via NIS, the organification of iodide through the activity of thyroid peroxidase (TPO), the cleavage and release of thyroid hormone from thyroglobulin, and thyroid blood flow in general—in short, all the processes involved in upregulation of thyroid hormone production and secretion from follicular thyroid cells. TSH-mediated enhancement of thyrocyte differentiation also increases the uptake of therapeutically administered radioiodine and extends its half-life within these cells [4], thereby enhancing the anti-tumoral efficacy of this intervention. Radioiodine uptake is minimal when patients are on TSH-suppressive doses of levothyroxine. For this reason, levothyroxine must be withdrawn for several weeks before radioiodine therapy is administered; alternatively, recombinant human TSH (rhTSH) can be

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given to upregulate NIS expression and ensure high uptake of the radioisotope [5]. The use of rhTSH instead of levothyroxine withdrawal offers the advantage of improving patients' quality of life and reducing the risks of hypothyroidism morbidity [6]. More importantly, experimental data generated in vitro and in animal models have shown that thyroid-cell proliferation is TSH-dependent. Binding between circulating TSH and TSH receptors (TSHRs) expressed by thyrocytes leads to the activation of the growth-promoting cyclic-AMP cascade [7, 8]. TSHR expression is conserved by well-differentiated thyroid cancer cells [9–11], so it is reasonable to assume that, along with numerous oncogenes and proteins implicated in the development and progression of thyroid cancer, TSH can stimulate the growth of thyroid cancer [12]. This hypothesis is supported by several lines of evidence. Studies on autoimmune thyroid disease and thyroid cancer have revealed an increased incidence of thyroid cancer in patients with Graves' disease, individuals with TSHR-stimulating autoantibodies, and those with Hashimoto's thyroiditis and elevated TSH levels [7]. Furthermore, serum TSH concentrations seem to be an independent predictor of the development of DTC [13], and TSH levels of 2.26 mU/L or more are reportedly associated with a three-fold increase in the likelihood of thyroid nodule malignancy [14]. In addition to their association with thyroid malignancy in general, higher preoperative serum TSH levels have been linked to more aggressive histological variants of thyroid cancer and with advanced-stage tumors at diagnosis [12, 15]. As suggestive as they are, however, none of the data generated by these association studies can reliably confirm that TSH is causatively linked to thyroid cancer or that its suppression will improve patients' outcomes.

Clinical efficacy of TSH suppression

To clarify whether levothyroxine-mediated suppression of TSH secretion provides real advantages in terms of the clinical outcome of DTC treatment, Sugitani and Fujimoto conducted a randomized controlled trial involving 433 patients with papillary thyroid cancer (PTC) [16]. Participants were randomized to receive levothyroxine at doses that would keep serum TSH levels within the normal range or doses that would suppress levels to less than 0.01 μU/mL. Disease-free survival rates (documented by neck ultrasonography and computed tomography scans of the chest) in the two treatment arms were not significantly different.

Most authors consider TSH suppression appropriate for DTC patients with a high-risk of recurrence [17], because there is at least some evidence that it improves disease-specific survival in these cases. A classic study conducted in 1950–1990 demonstrated that levothyroxine suppression of TSH secretion was associated with reduced rates of tumor recurrence and cancer-related mortality [18]. This conclusion was reconfirmed by the results of a meta-analysis of ten studies conducted between 1934 and 2001, which showed that TSH suppression was indeed effective in decreasing thyroid cancer morbidity and mortality (relative risk 0.71 for the composite outcome of disease progression/recurrence and death) [19]. Importantly, however, some of the studies included in the meta-analysis were performed before sensitive assays of serum thyroglobulin levels and neck sonography were available, and without these tools, the accuracy of the initial risk-stratification and the chances of detecting the subclinical disease during follow-up were almost certainly reduced.

In two studies by the National Thyroid Cancer Treatment Cooperative Study Group, therapeutic suppression of TSH to maintain serum levels <0.1 mU/L, which causes a condition of exogenous subclinical hyperthyroidism, was of no value for patients at low-risk for recurrence but was of benefit in high-risk patients [17, 20]. The results of two more recent studies suggest that aggressive reduction of serum TSH levels may also confer survival benefits in patients with distant metastases [21, 22]. In a cohort of 71 Japanese patients with PTC distant metastases [22], TSH suppression therapy had no statistically significant effect on patient prognosis, although the cancer-specific survival (CSS) rate at 10 years was 15% higher in the TSH-suppressed patients. Similar conclusions emerged from a retrospective analysis of CSS in 157 German DTC patients with distant metastases [21]. Patients with suppressed TSH levels (median: ≤0.1 mU/L) had markedly better CSS than those with non-suppressed TSH (median survival: 15.8 vs. 7.1 years, $p < 0.001$), but no additional benefits were achieved with more substantial degrees of suppression (TSH ≤ 0.03 mU/L).

Klubo-Gwiezdzinska et al. recently analyzed data on 867 DTC patients with intermediate or high risks of recurrence who were treated and followed in tertiary referral centers or local clinics in the United States [23]. The study was not adequately powered to explore links between TSH suppression and overall survival. However, suppression therapy was not associated with any significant improvement in progression-free survival rates at 18 months, 3 years, or 5 years [23].

Evidence-based guidelines [5] recommend that serum TSH levels initially be kept below 0.1 mU/L in patients classified as high-risk after primary treatment (Table 1). Once the structural disease has been excluded, however, the levothyroxine dose can be adjusted to maintain TSH levels in the low-normal range (0.5–2 mU/L).

Evidence for the benefit of TSH-suppressive therapy in low- and intermediate-risk patients is more limited. The

Table 1 Current ATA-recommended targets for serum TSH levels during the initial follow-up of DTC

Patient groups	Target range for serum TSH	Evidence quality
High-risk	<0.1 mU/L	Moderate
Intermediate-risk	0.1–0.5 mU/L	Low
Low-risk, RAI remnant-ablated with undetectable Tg levels	0.5–2 mU/L	Low
Low-risk, RAI remnant-ablated with low Tg levels	0.1–0.5 mU/L	Low
Low-risk, no RAI remnant ablation	0.1–0.5 mU/L	Low
Lobectomy	0.5–2 mU/L	Low

ATA American Thyroid Association, *DTC* differentiated thyroid carcinoma, *Tg* thyroglobulin, *RAI* radioiodine

Table 2 Current ATA-recommended targets for serum TSH levels during long-term follow-up of DTC

Risk factors	Response to treatment			
	Excellent	Indeterminate	Biochemical incomplete[a]	Structural incomplete
None	No suppression (0.5–2 mU/L)	Mild suppression (0.1–0.5 mU/L)	Moderate-to-complete suppression (<0.1 mU/L)	Moderate-to-complete suppression (<0.1 mU/L)
Menopause			Mild suppression (0.1–0.5 mU/L)	
Tachycardia				
Osteopenia				
Age >60 years		No suppression (0.5–2 mU/L)		
Osteoporosis				
Atrial fibrillation			No suppression (0.5–2 mU/L)	Mild suppression (0.1–0.5 mU/L)

ATA American Thyroid Association, *DTC* differentiated thyroid carcinoma

[a]TSH targets for patients with biochemical incomplete responses vary widely depending on initial ATA risk class, serum Tg levels, Tg trend over time, and risk-factor profiles

2015 ATA guidelines [5] recommend a careful assessment of risks and benefits, based on the individual patient's response to treatment (excellent, indeterminate, biochemical incomplete, or structural incomplete response) and potential risk factors for adverse events during TSH suppression (Table 2). In patients with biochemical incomplete responses, adequate evidence is lacking for a strong position for or against suppression. The ATA recommendation is therefore based mainly on expert opinion, and rather than influencing disease outcomes, its aim is to facilitate the interpretation of temporal trends in serum thyroglobulin levels. Because thyroglobulin production is TSH-dependent, the thyroglobulin trend and doubling time is difficult to estimate in a setting characterized by fluctuating levels of TSH.

As for patients with excellent responses to the initial treatment, current thinking holds that levothyroxine therapy should be titrated to maintain normal-low TSH levels (0.5–2 μIU/mL) [24]. In this setting, suppression of TSH is not expected to provide any benefits at all, but it can cause several non-negligible side effects [25], including arrhythmias [26], osteoporosis [27], anxiety, and insomnia [26]

Specific situations

Before the first response-to-treatment assessment

The recommendations of the ATA summarized in Table 2 are, however, applicable only when the first post-treatment evaluation has been completed and the response to treatment has been defined—generally, that is, 6–18 months after primary treatment. Before this point, the target TSH ranges considered optimal vary according to the patient's risk of recurrence, and the recommendations contained in the different evidence-based guidelines are not always consistent. The 2014 British Thyroid Association guidelines recommend keeping serum TSH levels below 0.1 mU/L during this period, regardless of the risk of recurrence [28]. By contrast, the 2015 American Thyroid Association guidelines [5] recommend this level of TSH suppression only for high-risk patients (Table 1), while the range recommended for intermediate-risk patients is 0.1–0.5 mU/L.

The use of TSH suppression during the months between surgery and the initial post-operative disease assessment appears to have no significant effect on the rate of structural

disease detected 1 year or 3 years after the primary treatment, in low- and intermediate-risk patients [29]. In these categories of individuals, TSH suppression might be avoided before the first disease assessment, with an adjustment to the optimal TSH range only upon confirmation of disease status.

The lack of effect of TSH suppression on disease recurrence rates after initial therapy has also been documented in intermediate- and high-risk PTC patients whose stimulated serum Tg level prior to radioiodine remnant ablation was below 1 ng/mL [30]. During a median follow-up period of 5.8 years, structural recurrence was observed in only four patients of this type, and the rates were not significantly different between patients with different levels of serum TSH during the first post-treatment months.

After lobectomy

According to the ATA guidelines, thyroid lobectomy alone may be used for low-risk, intrathyroidal tumors up to 4 cm in size with no lesions in the contralateral lobe. The choice of this size threshold has been recently questioned by a European perspective on 2015 ATA guidelines recommendations. Furthermore, in countries with long-standing iodine deficiency, bilateral involvement of the gland is frequent: this may limit a conservative surgical approach [6]. The rate of hypothyroidism after lobectomy ranges from 23.6 to 47%, and up to 75% of lobectomized patients may need replacement therapy [6]. Patients with normal serum TSH levels after surgery may not require levothyroxine treatment at all, and there is no need for TSH suppression.

In 1528 low-risk patients treated with lobectomy alone, only 21 (1.4%) experienced recurrence during the 5.6 years of follow-up, and recurrence-free survival rates were unaffected by mean and dominant TSH values [31]. In a propensity score-matched cohort study of 446 patients, recurrence rates were similar in groups receiving TSH-suppressive and non-suppressive doses of levothyroxine, and no relation was found between serum TSH levels and disease-free survival [32].

Follicular and Hürthle-cell thyroid cancer

Follicular thyroid cancer, the second most common DTC histological type, formerly included the rare variant known as Hürthle-cell thyroid cancer, which is now classified by the WHO as a separate histological type. Follicular and Hürthle-cell thyroid cancers are each characterized by presentations and prognoses that distinguish them from other DTCs, and yet specific recommendations for their management are lacking in practice guidelines, largely because there is no evidence (and certainly no randomized trial data) to support such recommendations [33]. The gap also applies to issue of TSH-suppression in patients with these tumors. "Suppressive therapy" after initial treatment has been advocated on the basis of observational data [34–40], but no indications have been provided on the optimal degree of suppression.

Active surveillance

Guidelines for DTC management issued in 2015 by the American Thyroid Association/American Association of Clinical Endocrinologists proposed active surveillance as a viable option for papillary microcarcinomas of the thyroid (PMTC). This conclusion was based on data from pivotal trials conducted in Japan [41, 42] and is now supported by additional data from studies conducted in the United States [43]. The interest in the long-term management of patients during active surveillance is therefore increasing.

In a recent study of 127 PTMCs in 126 patients, the adjusted hazard ratio for tumor progression was significantly higher in the subgroup with the highest serum TSH levels (HR 3.55; 95% CI, 1.22–10.28) [44]. The cut-off point was suggested to be 2.50 mUI/mL [44]. An earlier study of the same type, however, had found no significant association between TSH levels and the progression of PMTC [45]. The conflicting findings on this issue might be related to differences between the studies' definitions of progression (based on changes maximum tumor diameter vs. changes in volume) or the TSH variability estimation.

Risks

The potential benefits of long-term TSH-suppression therapy have to be weighed against the known adverse effects of subclinical exogenous hyperthyroidism [8, 46]. If serum thyroid hormone levels are kept within the reference range but serum TSH levels are subnormal (≤0.4 mU/L), the patient may experience symptoms and signs of hyperthyroidism. The adverse effects of this condition can be significant [25] and their impact felt at various levels, including quality of life (psychological, social, and physical domains);[26] and the integrity of the cardiovascular and skeletal systems. (Details are provided in the sections that follow.)

Cardiovascular system

Several retrospective studies have found that long-term TSH-suppressive therapy increases heart rate and left ventricular mass, causes myocardial strain, impairs diastolic function, reduces arterial elasticity, and diminishes cardiac reserve and exercise capacity [47]. The increases observed in left ventricular mass were more closely related to the duration of TSH suppression than to the circulating thyroid

hormone levels achieved, suggesting that the cardiac remodeling was triggered mainly by the chronic hemodynamic overload and persistent hyperkinetic cardiovascular state caused by the mild excess of thyroid hormone. The most important adverse cardiovascular events observed in DTC patients with exogenous subclinical hyperthyroidism were atrial fibrillation and a prothrombotic state. The likelihood of adverse cardiovascular events related to TSH-suppression increases with age and leads to a higher risk of hospitalization for cardiovascular disease [8, 48]. A cohort study, including 3822 thyroid cancer survivors, diagnosed from 1997 to 2012 identified using the statewide Utah Population Database, reported that administration of TSH-suppressive therapy was associated with an increased cardiovascular disease risk, along with distant metastases at diagnosis and a higher Charlson comorbidity index [49]. On the whole, the studies conducted thus far to investigate the cardiovascular effects of long-term TSH-suppressive therapy point to advanced age, duration of TSH suppression, and associated morbidities as the most likely predictors of negative cardiovascular outcomes in patients with exogenous subclinical hyperthyroidism [8].

Bone

Thyroid hormone excess affects bone remodeling by shortening the remodeling cycle and accelerating bone turnover. Endogenous hyperthyroidism is associated with an increased risk of osteoporosis due to increased osteoclastic resorption and decreased bone formation, but the effect of therapeutic TSH-suppression on osteoporosis remains unclear [50]. In patients with DTC, TSH-suppression exerts more marked effects on bone mineral density in postmenopausal women than in men or premenopausal women [8, 51, 52]. The duration of TSH suppression and patient age are also important factors to consider. A 5-year or longer history of TSH-suppressive therapy is associated with bone loss and fracture risk, especially in men and women over 50 and postmenopausal women of any age [8]. The increased risk of fractures observed in patients on TSH suppressive therapy [53] might be due in part to the negative effects of the mild thyroid hormone excess typical of subclinical hyperthyroidism on muscle strength, body weight, and lean body mass deterioration, as well as to the possible cognitive decline in elderly patients, also potentially worsened by TSH suppression.

A meta-analysis of 11 cross-sectional studies (571 patients, 836 controls) revealed that TSH suppression therapy for DTC was associated with decreased bone mineral density at the levels of the hip (weighted mean difference [WMD] −0.023; 95% CI, −0.047 to 0.000; $P = 0.05$) and spine (WMD −0.041; 95% CI, −0.057 to −0.026; $P < 0.001$) but only in postmenopausal women [54]. A large study with long-term follow-up should be undertaken to gain further insight into this issue.

Quality of life

Health-related quality of life may be reduced in DTC patients receiving TSH-suppressive levothyroxine treatment [55]. Various general effects have been reported in patients with chronic thyrotoxicosis, including emotional changes (nervousness, anxiety), mood disorders (depression, sleep disturbance, lack of energy), and diverse alterations of cognitive function—all of which are likely to have a negative impact on the quality of life [46, 53]. TSH-suppressive therapy can diminish the quality of life as measured by psychological, social, and physical indices, particularly when the serum TSH drops below detectable levels [25].

Conclusions

Thyroid hormone treatment plays a central role in the postoperative management of DTC: thyroid hormone therapy is needed to restore euthyroidism and maintain normal serum TSH levels in all patients undergoing total thyroidectomy and roughly half of those treated with thyroid lobectomy. Despite our decades of experience in prescribing levothyroxine therapy, it is not easy to select or achieve an appropriate TSH target range for each single patient.

In athyreotic individuals, daily levothyroxine doses of 1.6–1.8 mg/kg are required to achieve a normal serum TSH level, while TSH-suppressive doses range from 2.0 to 2.2 mg/kg. In each patient, however, the chances of achieving target levels depend on multiple factors, including body mass index, concomitant medications, and drug bioavailability. In clinical practice, the initial levothyroxine dose required to achieve a mild TSH suppression is sometimes overestimated, and subsequent reductions are frequently needed [56]. The second key issue for clinicians is the selection of patients who require TSH-suppressive therapy. On the one hand, it is important to consider the risk of persistent or recurrent disease, evaluated according to American Thyroid Association (ATA) class of risk [5], the presence of distant metastases, and the response to the initial treatment; on the other hand, whether advanced age, risk factors, and underlying comorbidities contraindicate TSH suppression. The optimal TSH level for patients with well-differentiated thyroid carcinoma and an intermediate- or high-risk for recurrence (or structural evidence of persistent or recurrent disease) is one that maintains the beneficial effects on tumor recurrence without increasing the risk of adverse cardiovascular and skeletal events or diminishing

the quality of life. There is no evidence that suppression offers any benefits for low-risk patients or patients with no evidence of disease during clinical monitoring [27].

Either poor general health status or history of cardiac and bone disease can place patients at risk for TSH suppression therapy. Vulnerable subjects include the elderly, frequently affected by multiple comorbidities, and all those with chronically deteriorated health status. Risk factors for cardiac adverse events include a history of myocardial infarction, congestive heart failure, valvular heart disease, atrial fibrillation or ischemic stroke, age >65 years, hypertension, and diabetes. The risk of adverse skeletal events is increased in patients with a history of fracture, post-menopausal women not receiving hormone replacement therapy, and women with estrogen deficiency of any cause. It is also important to assess patients' smoking habits, weight loss, any complaints they may have regarding the axial skeleton, and signs and symptoms of parathyroid dysfunction [46].

Decisions on suppressive therapy can be especially difficult in elderly patients, who are generally highly vulnerable to the adverse effects of TSH suppression and more likely to present with advanced thyroid cancer [46].

Given the evidence that aggressive TSH-suppressive therapy is of little to no benefit to almost all patients with DTC, who are at low risk of recurrence and death, ATA recommends a graded algorithm in which the potential benefits of this therapy are carefully weighed against its cardiovascular and skeletal risks [5] (Table 2).

Large randomized controlled studies are needed to demonstrate that suppression does indeed have oncological benefits, that it plays a causal role in the adverse effects associated with it, and that these negative effects can be reversed or reduced by normalization of serum TSH levels. Further study is also needed to assess drug therapies capable of improving cardiovascular parameters, bone metabolism, and quality of life in patients with DTC who receive thyroxine replacement therapy.

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Compliance with ethical standards

Conflict of interest Author Cosimo Durante declares that he has received a speaker honorarium from Eisai Europe Limited. The remaining authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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