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*Title Page

Short Report

TSH suppression in the long-term follow-up of differentiated thyroid cancer

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Highlights

- The prognosis for differentiated thyroid cancer is generally favourable
- Long-term TSH suppression with thyroxine is indicated for intermediate and high risk disease only
- Degree of TSH suppression is first based on assessment of individual disease risk
- Following initial surgical treatment TSH suppression is guided by dynamic risk stratification
- Benefits of TSH suppression are balanced against cardiovascular and skeletal adverse effects

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TSH suppression in the long-term follow-up of differentiated thyroid cancer

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ABSTRACT

Differentiated thyroid cancer is the commonest form of thyroid cancer, and its prognosis is favourable in the majority of cases. Suppression of thyroid stimulating hormone (TSH) by supra-physiological thyroid hormone replacement has been the mainstay of long-term management for over 60 years. However, evidence for a beneficial outcome of TSH suppression is conflicting and intervention must be balanced against adverse effects, particularly affecting the cardiovascular system and skeleton. Here we discuss the role of TSH suppression in the long-term management of differentiated thyroid cancer in the context of risk-stratification for disease recurrence and the latest clinical guidelines.

KEY WORDS

Differentiated thyroid cancer

TSH suppression

Subclinical thyrotoxicosis

INTRODUCTION

Differentiated (or non-medullary) thyroid cancer (DTC) is the commonest form of thyroid cancer, consisting mainly of papillary thyroid carcinoma (PTC) and follicular thyroid cancer (FTC). Prognosis is generally favourable in DTC, with better outcomes for papillary than follicular-type thyroid cancers. Rates of disease recurrence are so low for low-risk tumours that it is recognised that the traditional treatment options of (i) thyroidectomy with or without lymph node clearance, (ii) adjuvant radio-iodine ablation and (iii) suppression of serum thyroid stimulating hormone (TSH) by levothyroxine treatment may not be necessary. While it is easy to rationalise the restriction of more radical neck surgery and radio-iodine remnant ablation (RRA) to cases that are demonstrably of higher risk, decisions regarding long-term TSH suppression are less well defined.

DISCUSSION

Evidence for TSH suppression

The goal of TSH suppression is to reduce endogenous stimulation of remnant DTC cells, given that TSH stimulates the number, size and activity of thyrocyte cells from which DTC arises [1]. After total thyroidectomy, TSH suppression is achieved by providing supra-physiological doses of levothyroxine replacement. The rationale for this approach arose from observations that the incidence of thyroid cancer correlates with the level of serum TSH in the normal population [2-5], and a prospective study showing that a lesser degree of TSH suppression is an independent predictor of disease progression in patients at high risk of tumour recurrence [6]. TSH suppression thus became standard practice based largely on the logical plausibility of its benefit, rather than demonstrable evidence of benefit. Objective conclusions have been hard to derive from various observational studies that lack blinding, randomisation, or adequate controls, although a meta-analysis demonstrated that patients with TSH suppression had a decreased risk of disease progression, recurrence and death (RR = 0.73;

CI = 0.60± 0.88; P < 0.05) [7]. Nevertheless, of the 28 studies identified between 1934-2001, only 10 could be included in this meta-analysis because of heterogeneity, variable design and other confounding factors.

Other studies have investigated the optimal degree of TSH suppression, and tried to identify which patients are most likely to benefit. In a multicentre cohort study of almost 3000 patients that compared TSH suppression to undetectable levels versus subnormal concentrations, a benefit in overall survival was only observed in patients with tumours at the highest-risk of disease recurrence [8] while no significant benefit was seen for disease-specific or disease-free survival. In the same study, patients with lowest risk DTC did not benefit from any degree of TSH suppression, a finding substantiated subsequently by other investigators [9].

Harms of TSH suppression

Consequences of supra-physiological levothyroxine replacement result from the long-term mild thyrotoxicosis induced by the intervention. Thyroid hormones have direct physiological actions on the skeleton and thyrotoxicosis is an established cause of osteoporosis [10]. Cohort studies have shown that, in postmenopausal women with DTC, the risk of osteoporotic fractures is higher in those with fully suppressed TSH [11, 12]. In a prospective observational study of women with DTC, TSH suppression caused a reduction in bone mineral density in women who were postmenopausal despite maintenance of normal free T3 levels [13, 14].

Thyroid hormones also have direct actions on the myocardium. Overall mortality and cardiovascular mortality is higher in patients with undetectable suppressed TSH due to levothyroxine treatment in long-term follow-up for DTC [15], or indeed from any other cause [16, 17]. TSH suppression is a state of iatrogenic subclinical thyrotoxicosis, and has been associated with increased resting heart rate [18], tachyarrhythmias [19], and predisposition towards a reduction in cardiac function [20]. Of most

concern, the incidence of atrial fibrillation (AF) is up to three times higher in elderly patients with suppressed TSH including those taking exogenous levothyroxine [21, 22].

There are few studies to guide the use of prophylactic cardio-protective or anti-osteoporosis medications to offset the detrimental effects of TSH suppression. While beta-blockers may rescue the cardiac dysfunction caused by TSH suppression [23], there have been no studies to show beneficial effects on cardiovascular mortality. Bisphosphonates are the mainstay of current osteoporosis treatment, but one study has shown their efficacy to be reduced in the presence of long-term TSH suppression [24]. Moreover, bisphosphonates have been shown in a large meta-analysis to confer a significantly increased risk of AF [25]. Given that AF is itself an adverse effect of TSH suppression, the theoretically compounded higher risk of AF would have to be balanced against any potential benefit for fracture reduction [26], and there is currently insufficient evidence to support a universal recommendation for the prophylactic use of bisphosphonates.

Risk stratification and individualised decision making

Given the need to balance the benefit of TSH suppression versus its adverse effects, the latest international guidelines for the management of DTC advise that the use and degree of TSH suppression should be based on a stratified assessment of individual disease risk [27, 28]. The 2014 British Thyroid Association (BTA) and 2015 American Thyroid Association (ATA) thyroid cancer guidelines suggest initial risk stratification according to the degree of local invasion of the tumour, presence of local and distant metastases, and aggressiveness of tumour histology (Table 1) [29, 30]. Subsequent dynamic risk stratification is recommended for patients who underwent complete tumour resection and RRA based on measurement of 'stimulated serum thyroglobulin' in addition to surveillance imaging at 9-12 months after thyroidectomy (Table 2). In this context, a single measurement of stimulated thyroglobulin provides a robust prediction of future risk of metastases

[31]. Thyroglobulin is secreted by normal thyroid tissue and DTC cells. When detected after thyroidectomy, it is suggestive of the presence of remnant thyroid cells or residual or recurrent cancer. Sensitivity of thyroglobulin measurement is enhanced in the presence of stimulation by raised TSH. The preferable alternative to achieving raised TSH by thyroid hormone withdrawal is to provide exogenous stimulation by recombinant human TSH, administered in 2 intramuscular injections 24 hours apart.

The BTA and ATA guidelines recommend that if the patient's risk is so low that RRA is not indicated, then TSH suppression is not required at all (Table 1). On the basis of expert opinion, it is recommended to maintain TSH in the low-normal range at less than 2.0 mU/L [32]. Patients with Encapsulated Follicular Variant of PTC, recently reclassified as a condition with low malignant potential due to the favourable outcomes with this histology, would automatically be categorised in this low risk group [33].

All other patients are initially assumed to be at higher risk and should have TSH suppression to less than 0.1 mU/L following total thyroidectomy and RRA. The need for long-term TSH suppression should then be decided based on the dynamic risk stratification following stimulated thyroglobulin measurement at 9-12 months (Table 2). Patients with a stimulated thyroglobulin of <0.1 µg/L and neck ultrasound that is negative for recurrence no longer require TSH suppression but should have the TSH concentration maintained at less than 2.0 mU/L [32]. Patients whose dynamic risk stratification indicates an incomplete response to initial treatment should continue to have their TSH concentration suppressed to below 0.1 mU/L indefinitely. Patients who fall into an intermediate category with suppressed thyroglobulin < 1 µg/l and stimulated thyroglobulin of ≥1 and <10 µg/L, or with nonspecific changes on imaging, should have TSH suppression to the intermediate level of suppression to between 0.1-0.5 mU/L for at least 5-10 years, at which point the requirement can be re-assessed. Monitoring of serial unstimulated thyroglobulin levels is a key component of regular follow-up of these patients.

With regard to historical patients who never received dynamic risk stratification, the BTA guidelines suggest they should be suppressed to below 0.1 mU/L for 5-10 years after which the need for continuing TSH suppression should be re-evaluated. In no instance is suppression of TSH to less than 0.1 mU/L recommended, given the increased risk of osteoporosis and cardiovascular harm and the doubtful benefit for DTC long-term outcomes and mortality [34]. Accordingly there are individual situations when the benefit:risk ratio of TSH suppression weighs against its use, for example in individuals who may suffer from heightened effects on the heart or skeleton, those who tolerate TSH suppression poorly, or when life-expectancy is reduced to such an extent that DTC risk-modification would provide little overall benefit [28].

CONCLUSIONS

It is unlikely that future randomised controlled trials will be performed on use of TSH suppression, given the ethical issues involved, and the high numbers needed to achieve sufficient power to detect the small differences in outcomes that would be achieved. Further clinical data is likely to continue to be observational in nature. A current challenge is to ensure widespread uptake of the current guideline recommendations to reduce the over-use of TSH-suppression, and to prevent the indiscriminate long-term use of overly stringent TSH-suppression, the harms of which outweigh the long-term risks from past treated DTC in many patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Table 1: Post-operative risk stratification

Low Risk	Intermediate Risk	High Risk
• No metastases • Complete surgical resection • No local invasion • Low-risk histology	• Microscopic invasion of tumour into soft tissue outside the thyroid • Cervical lymph node metastasis • High-risk histology (e.g. poorly differentiated elements) or angioinvasion	• Extra-thyroidal invasion • Incomplete surgical resection • Distant metastases

Table 2: Dynamic Risk Stratification: response to initial therapy of DTC

Excellent Response	Indeterminate Response	Poor Response
• Suppressed and stimulated Tg < 1 lg/l • Neck US (or other imaging) without evidence of disease	• Suppressed Tg < 1 lg/l and stimulated Tg ≥1 and <10 lg/l, **OR** • Neck US (or other imaging) with nonspecific changes or stable sub-centimetre lymph nodes	• Suppressed Tg≥1 lg/l or stimulated Tg ≥ 10 lg/l • Rising Tg values • Persistent or newly identified disease on cross-sectional or nuclear medicine imaging

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