# Thyroid-hormone therapy and thyroid cancer: a reassessment

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## SUMMARY

Experimental studies and clinical data have demonstrated that thyroid-cell proliferation is dependent on thyroid-stimulating hormone (TSH), thereby providing the rationale for TSH suppression as a treatment for differentiated thyroid cancer. Several reports have shown that hormone-suppressive treatment with the L-enantiomer of tetraiodothyronine (L-$T_4$) benefits high-risk thyroid cancer patients by decreasing progression and recurrence rates, and cancer-related mortality. Evidence suggests, however, that complex regulatory mechanisms (including both TSH-dependent and TSH-independent pathways) are involved in thyroid-cell regulation. Indeed, no significant improvement has been obtained by suppressing TSH in patients with low-risk thyroid cancer. Moreover, TSH suppression implies a state of subclinical thyrotoxicosis. In low-risk patients, the goal of L-$T_4$ treatment is therefore to obtain a TSH level in the normal range (0.5–2.5 mU/l). Only selected patients with high-risk papillary and follicular thyroid cancer require long-term TSH-suppressive doses of L-$T_4$. In these patients, careful monitoring is necessary to avoid undesirable effects on bone and heart.

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## INTRODUCTION

Secretion of thyroid-stimulating hormone (TSH) by the pituitary gland is stimulated by hypothalamic TSH-releasing hormone (TRH) and inhibited by high serum levels of two hormones produced by the thyroid: tri-iodothyronine ($T_3$) and tetraiodothyronine ($T_4$, or thyroxine), which contain three and four atoms of iodine, respectively. $T_4$ acts at hypothalamic and pituitary levels after enzymatic local conversion into $T_3$.[1,2] Both $T_3$ and $T_4$ have two ENANTIOMERS; the L-enantiomers (L-$T_3$ and L-$T_4$) are responsible for their biologic effects.

Although $T_4$ is the main hormone produced by the thyroid gland, $T_3$ is the active thyroid hormone in many organs. The most important pathway for $T_4$ metabolism is its mono-deiodination to active $T_3$. This reaction is catalyzed by type 1 and type 2 deiodinases. Type 1 deiodinase is highly expressed in human liver and kidney, and type 2 deiodinase is expressed in skeletal and cardiac muscles, the central nervous system and the pituitary gland (Figure 1).[1,2] Orally administered L-$T_4$ (levothyroxine) is efficiently converted to L-$T_3$, thereby reproducing the pathway of endogenous $T_4$ processing. Serum $T_3$ levels remain stable after L-$T_4$ administration, but vary widely after oral administration of L-$T_3$ (liothyronine);[3,4] this is why L-$T_4$ has been the drug of choice for long-term treatment of thyroid cancer patients. Moreover, the administration of L-$T_4$ is preferred because serum $T_4$ is more effective as a regulator of TSH secretion than serum $T_3$ is.

There is general agreement that all thyroid cancer patients should be treated with L-$T_4$ after total thyroidectomy.[5–7] This therapy has two objectives: hormone replacement (i.e. correction of surgically induced hypothyroidism) and hormone suppression (i.e. reduction of the serum level of TSH, which can stimulate the growth of persistent or recurrent neoplastic tissue). For years, life-long TSH suppression with exogenous L-$T_4$ therapy was recommended in all guidelines for the postoperative management of thyroid

cancers, but more recently this strategy has been challenged. The change came about consequent to a better understanding of the adverse effects of L-T$_4$ suppressive treatment and of the natural history of thyroid cancer, which raised the possibility of a reliable diagnosis of cure in low-risk patients. Here we review the basic principles of L-T$_4$ treatment for thyroid cancer and current indications for its use. Practical aspects such as dose calculation, adjustment for specific clinical situations, and side effects are discussed in the second part of the review.

## RATIONALE FOR TREATMENT OF THYROID CANCER PATIENTS USING L-TETRAIODOTHYRONINE
### Historical setting

The rationale for administering L-T$_4$ therapy to patients with papillary or follicular thyroid carcinomas is based on evidence collected in numerous studies. In 1937, Dunhill[8] reported the regression of papillary thyroid cancer in two patients treated with thyroid extracts. It was later demonstrated that hypothyroidism stimulates neoplastic thyroid-cell growth by increasing serum TSH levels.[9,10] Indeed, administration of L-T$_4$ (resulting in lower levels of TSH) had the beneficial effect of limiting tumor growth.[11] Evidence supporting L-T$_4$ treatment as an essential part of thyroid cancer management was provided by two retrospective investigations[12,13] and one prospective,[14] non-randomized study. In Mazzaferri and Jhiang's[12] retrospective analysis of 30 years of follow-up data, patients treated with L-T$_4$ had 25% fewer recurrences (30% versus 40%) and 50% fewer cancer-related deaths (6% versus 12%) than those who did not receive L-T$_4$ therapy and who had serum TSH levels within the hypothyroid range.[12] Pujol *et al.*[13] showed that thyroid-cancer patients with TSH levels that were consistently below 0.1 mU/l had an improved rate of relapse-free survival compared with those whose TSH levels were always above 1.0 mU/l, and this effect was independent of age, gender, histology, and tumor stage. Finally, Cooper *et al.*[14] showed that a lesser degree of TSH suppression was an independent predictor of progression in patients with high-risk (stage III or IV) papillary thyroid cancers, but not in those with low-risk tumors. When patients treated with radioiodine were included in the multivariate analysis, the influence of TSH suppression dropped to borderline significance because radioiodine destroyed persistent neoplastic disease.
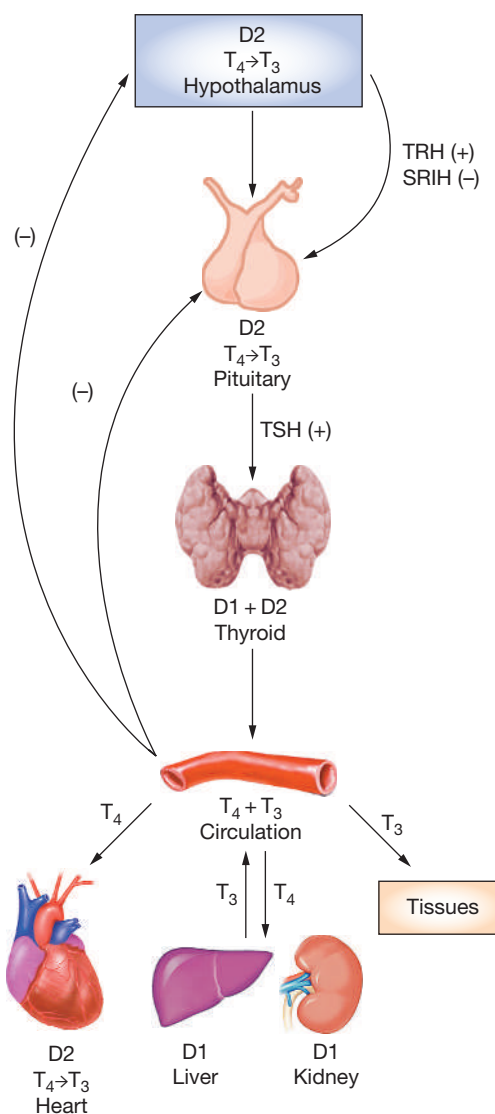
**Figure 1** Regulation of the pituitary–thyroid axis: the role of tri-iodothyronine and tetraiodothyronine in the feedback regulation of thyroid-stimulating hormone secretion. Secreted tetraiodothyronine must be converted to tri-iodothyronine to produce biologic effects. Type 1 deiodinase is produced in human liver, kidney and thyroid gland and these organs produce tri-iodothyronine in the serum. Type 2 deiodinase is widely distributed in cardiac and skeletal muscle, thyroid gland, the central nervous system and the pituitary gland.[1] The expression of type 2 deiodinase in the human heart suggests that cardiac tissue can respond to changes in serum tetraiodothyronine levels, as occurs in the pituitary gland. D1, type 1 deiodinase; D2, type 2 deiodinase; SRIH, somatotrophin (somatostatin)-release-inhibiting hormone; T$_3$, tri-iodothyronine; T$_4$, tetraiodothyronine; TRH, thyroid-stimulating hormone releasing hormone; TSH, thyroid-stimulating hormone.

## The effects of thyroid-stimulating hormone on thyroid growth

Experimental studies conducted *in vitro* and in animal models have elucidated the scientific basis for the above clinical observations. Thyroid-cell proliferation was shown to be TSH-dependent.[15] GOITROGENS, iodine deficiency, and partial thyroidectomy promote the development of thyroid cancers, but these tumors can be prevented by the oral administration of L-$T_4$ or by hypophysectomy, both of which reduce or suppress TSH secretion.[16]

Differentiated tissue in papillary and follicular thyroid cancers has functional TSH receptors (TSHRs),[17] and thyroid cancer cells in PRIMARY CULTURE respond to TSH stimulation by activating the cyclic-AMP cascade that promotes cell growth.[5,18,19] In contrast, expression of the TSHR (together with that of other thyroid-specific genes and proteins) is markedly decreased in poorly differentiated thyroid cancers.[20–22] Enhanced growth of well-differentiated thyroid cancer cells can thus be anticipated when TSH production is stimulated. This is consistent with the more extensive and aggressive disease observed in patients with Graves' disease, who have TSHR-stimulating immunoglobulins.[23,24]

Based on these findings, TSH-suppressive therapy with L-$T_4$ has become an integral part of the treatment of papillary and follicular thyroid carcinomas; however, these data provide no indication of the optimal degree of suppression.

## The effects of thyroid-stimulating hormone on thyroid-cell differentiation

Metastases from papillary or follicular thyroid cancers might retain several biologic functions fulfilled by normal thyrocytes, such as iodine uptake or the synthesis and secretion of thyroglobulin (a specific thyroid glycoprotein used for hormone synthesis), but they are rarely capable of synthesizing thyroid hormones.[21,22] The differentiation of neoplastic and normal thyroid cells (so that they take up iodine, and synthesize and secrete thyroglobulin), depends on TSH. Accordingly, no radioiodine uptake is seen when the patient is on L-$T_4$ therapy. Uptake by metastases occurs exclusively after TSH stimulation, and even then it is observed in only two out of three patients with metastatic disease. In patients with persistent or recurrent disease, serum thyroglobulin concentrations increase following TSH stimulation whereas significant decreases (sometimes to undetectable levels) are observed during L-$T_4$ therapy. This modulation is evident even when no radioiodine uptake is observed in the metastases. These observations confirm that TSH is capable of stimulating functional activity (and, consequently, growth) in most differentiated thyroid carcinomas and that functional receptors for TSH are also present in metastases from these tumors.[22]

## Features of thyroid cells that are independent of thyroid-stimulating hormone

Although TSH plays a major role in the regulation of thyroid-cell differentiation and proliferation, there is a body of evidence supporting the view that thyroid-cell regulation involves a complex network of mechanisms, including some that are TSH-independent. Neoplastic thyroid-cell growth can thus be affected by growth factors such as epidermal growth factor,[25] insulin-like growth factors,[26] basic fibroblast growth factor, platelet-derived growth factor, and transforming growth factor-α, and by activated oncogenes including *RET(PTC)*, *BRAF* and the *RAS family*.[27]

These biologic findings have been supported by clinical observations. One of the best models of 'autonomous' (i.e. TSH-independent) thyroid-cell growth is the functioning 'hot' thyroid nodule. These nodules are frequently the result of activating mutations of the genes encoding the TSHR[28] and the $G_s\alpha$ protein family, although these activations are rare in thyroid cancers.[29,30] Low-level TSH-independent secretion of $T_4$ has been demonstrated in normal thyroid glands,[31] which explains why higher doses of L-$T_4$ are required to reduce TSH levels in hypothyroid patients with thyroid cancer (when their thyroid glands have been totally ablated) than in those with benign disease, where at least some thyroid tissue remains functionally active.[32] A TSH-independent mitogenic cascade might remain active in neoplastic thyroid cells, and might be retained, therefore, even when serum TSH is maintained at low levels with L-$T_4$ treatment. This situation is most commonly observed in elderly patients with poorly differentiated thyroid carcinomas, which are probably characterized by an accumulation of genetic alterations.

## OPTIMAL SUPPRESSION OF THYROID-STIMULATING HORMONE

As mentioned above, increasing knowledge about the adverse effects of suppressive doses

of L-T$_4$ and about the natural history of thyroid cancer, which raised the possibility of a reliable diagnosis of cure in low-risk patients, caused some authors to challenge the universal use of suppressive therapy in thyroid cancer patients. In this context, two questions need to be addressed: what is the ideal serum level of TSH, and should the serum TSH be maintained at the same level in all thyroid cancer patients who receive L-T$_4$?

## What are optimal serum thyroid-stimulating hormone levels during thyroid cancer follow-up?

The concept of TSH-suppression therapy has changed over the years. From the initial empirical suggestion that all thyroid cancer patients should be placed on lifelong L-T$_4$ therapy with the highest tolerated dose, we now have reliable methods with which to assess the adequacy of suppressive doses of L-T$_4$.

In the 1970s, the optimal L-T$_4$ dose for TSH suppression was defined as the dose that abolished TSH release from the pituitary in response to TRH; however, TSH assays were not sufficiently sensitive to detect values in the lower end of the reference range . In the 1980s, assay sensitivity improved, and serum TSH levels as low as 0.1 mU/l could be detected. Nonresponse to TRH was thus found to correspond to a basal serum TSH level below 0.1 mU/l and, consequently, suppressive therapy was considered adequate only when the serum TSH level was below this detectable cut-off. Subsequent testing with ultrasensitive TSH assays, however, revealed that a high proportion of patients with levels in this range had subclinical thyrotoxicosis.

The goal of replacement therapy is to restore serum TSH to the reference range; however, the normal TSH range is a matter of controversy.[33–36] Overt thyrotoxicosis is reflected by a TSH level below 0.1 mU/l, with elevated levels of total and free (not bound to serum proteins) T$_3$ and T$_4$. Although it is difficult to define a TSH level that establishes the presence of subclinical thyrotoxicosis, current studies suggest that values below 0.5 mU/l might be associated with increased cardiovascular mortality in elderly patients;[37] in young and middle-aged patients the level of TSH suppression that eliminates the risk of subclinical thyrotoxicosis has yet to be defined. In studies conducted so far on the adverse effects of long-term L-T$_4$ therapy, no attempt has been made to correlate these effects with serum TSH values.[38]

Although the reduction in serum levels of thyroglobulin associated with low TSH levels provides indirect evidence of the efficacy of TSH suppression, increasing the degree of suppression to produce serum TSH levels below 0.5 mU/l does not result in further decreases in serum thyroglobulin levels. This supports the hypothesis that more aggressive TSH suppression might be of little benefit in terms of limiting tumor growth;[32,39] however, these studies were based on small numbers of patients and cannot exclude a benefit resulting from complete suppression in patients with persistent disease.

## Is suppressive L-tetraiodothyronine therapy always necessary?

As discussed above, several lines of evidence indicate that suppressive L-T$_4$ treatment decreases the risk of progression in patients with persistent disease, and reduces the rates of recurrence and cancer-related-mortality in high-risk cancer patients. In other subgroups of thyroid cancer patients, however, the use of L-T$_4$ therapy is not associated with any significant improvement in recurrence or survival rates.

A study designed to determine the effectiveness of radioiodine scanning in detecting recurrence of thyroid cancer after thyroid ablation and the withdrawal of L-T$_4$ after 12 months' therapy showed that the long-term risk of recurrence was less than 1% in low-risk patients with no evidence of persistent disease—that is, in patients who had undergone complete resection of all neoplastic tissues at initial surgery, had no uptake outside the thyroid bed (as shown on the postablation whole body scan), had no sonographic evidence of lymphadenopathy in the neck and had serum thyroglobulin levels that remained undetectable following TSH stimulation at the 6–12 months' follow-up appointment.[38] Furthermore, all recurrences were limited to the neck lymph nodes and could thus be cured.[40,41] These favorable results were obtained even though the majority of these patients presented with serum levels of TSH within the normal range.[40,41] Indeed, these favorable results can hardly be improved with long-term suppressive treatment.

Therefore, within the first year after initial treatment with L-T$_4$, it is possible to identify patients who show no evidence of disease and who have, consequently, no need for continued suppression of TSH secretion. In these patients, who represent over 80% of all thyroid cancer
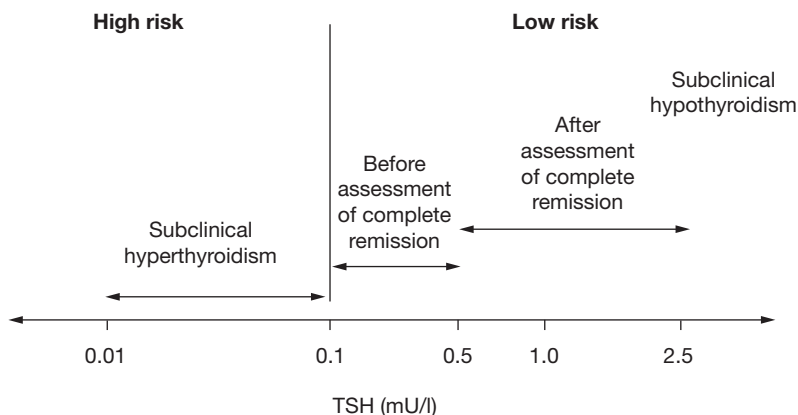
**Figure 2** Thyroid-stimulating hormone target level during treatment with L-tetraiodothyronine in high-risk and low-risk thyroid cancer patients. TSH, thyroid-stimulating hormone.

patients, the goal of L-$T_4$ treatment is to return TSH level to within the normal range (0.5–2.5 mU/l), and preferably at its lower end in young patients with a long life expectancy. Because the risk of persistent disease cannot be excluded, it seems safer to maintain serum TSH level below 0.5 mU/l, both from initial treatment until the 6–12 months' follow-up appointment when assessment of complete remission can be undertaken. By contrast, patients with persistent disease and those at high risk of recurrence require long-term TSH suppression, in particular when they are young and when they do not present with cardiovascular disease. In this group, the goal of L-$T_4$ treatment is to reduce the serum TSH level to below 0.1 mU/l and maintain free-$T_3$ level in the normal range (Figure 2).

### TREATMENT WITH L-TETRAIODOTHYRONINE
#### Pharmacology
Exogenous L-$T_4$ preparations should be close to 100% pure, with less than 3% variation in L-$T_4$ content, because bioavailability might vary between preparations. To ensure optimal dosing, each patient should always receive the same preparation.[42] L-$T_4$ has a blood half-life of 6–8 days, so a single daily dose is sufficient. Up to 80% of orally administered L-$T_4$ is absorbed by the gut, with considerable interindividual variability.[43] As food intake reduces L-$T_4$ absorption, patients should be instructed to take their medication on an empty stomach, preferably in the morning, at least 20 minutes before breakfast. Several substances—that is, cholestyramine, aluminum hydroxide, calcium carbonate, ferrous

sulfate, and sucralfate—are known to interfere with intestinal absorption of L-$T_4$.[44] Other substances can increase hepatic metabolism of L-$T_4$ (e.g. the anticonvulsant drugs carbazepine, phenytoin, and phenobarbital), whereas estrogens can increase thyroid hormone requirements (by increasing serum levels of $T_4$-binding globulin).[45] All these possibilities should be considered when a patient on a presumably suppressive dose of L-$T_4$ presents with an inappropriate serum TSH concentration. Chronic diseases such as regional enteritis, pancreatic disease, and cirrhosis can be associated with decreased L-$T_4$ absorption.[44] Spurious elevations in serum TSH can also result from interference in the assay system by heterophilic antibodies.[46]

In patients with thyroid cancer, some authors have advocated the use of replacement doses of L-$T_4$ together with tri-iodoacetic acid, a thyromimetic drug that was originally believed to act exclusively at the pituitary level, without eliciting biologic activity in other tissues, to obtain complete TSH suppression without overt or subclinical thyrotoxicosis. It is now clear that tri-iodoacetic acid does have effects on other tissues, and its use is no longer considered advisable.[47,48]

L-$T_3$ alone is not indicated for long-term treatment because of the widely varying serum levels that result from its administration. It is used only on a short-term basis preparatory to radioiodine administration.[49] It might also be given with L-$T_4$ for a few days, when the latter hormone is being resumed after a period of withdrawal, to restore euthyroidism more rapidly. The potential benefits of long-term therapy with both L-$T_3$ and L-$T_4$ have yet to be established. It has been suggested that, for patients who have undergone total thyroidectomy, combined therapy can alleviate the sense of diminished wellbeing reported by many patients during treatment with L-$T_4$ alone. The results of a prospective placebo-controlled double-blind clinical trial suggested that replacing part of the L-$T_4$ dose with L-$T_3$ improved quality of life,[50] but this effect was not confirmed in larger trials with different L-$T_4$/L-$T_3$ substitution regimens.[51–57]

#### Dose
The dose of L-$T_4$ should be carefully titrated to the individual needs of each patient. The dose required correlates roughly with body weight or (more accurately) with lean body mass. Athletes, in fact, require higher doses per kilogram of body weight than average, whereas lower doses

are necessary for obese patients.[58] The dose required to obtain low serum TSH levels after total thyroidectomy also decreases progressively with age (Table 1).[59] Further dose reductions might be needed for subjects with concurrent heart disease.[38]

The adequacy of L-$T_4$ therapy is verified by measuring serum TSH levels approximately 3 months after the start of therapy. If the dose is appropriate, serum TSH levels will be around 0.1 mU/l. To avoid the risk of iatrogenic thyrotoxicosis, it is important to verify that the serum free $T_3$ level is within the normal range, and that the serum free $T_4$ level is around the upper limit of the normal range.[6,7] Blood for measurement of free-$T_4$ levels should be drawn after an overnight fast and before patients take their daily dose of L-$T_4$. Free-$T_4$ levels are often as much as 25% higher when measured in specimens drawn within the first 3–4 h after the morning L-$T_4$ dose.

If TSH is not low enough, or in case of thyrotoxicosis, the daily dose of L-$T_4$ is increased or decreased by 25 µg/kg, respectively, and hormone levels are rechecked 3 months later. Fine-tuning might require smaller adjustments, and the parameter to be considered is the total weekly dose of L-$T_4$. Once the optimal dose has been defined, adjustments will be required only under particular circumstances (e.g. pregnancy, or significant weight gain or weight loss), and hormone levels can generally be rechecked once a year.

Thus L-$T_4$ treatment is initiated after ablation and is controlled 3 months later. A complete follow-up evaluation is carried out between 6 and 12 months after thyroid ablation. If it does not reveal any evidence of disease, TSH suppression is no longer necessary in low-risk patients, and the daily dose of L-$T_4$ should be reduced until the TSH level is in the normal range.

Dose adjustments are often required during pregnancy. In women receiving L-$T_4$ for replacement alone, the dose should be increased by 30% as soon as pregnancy is confirmed.[60] In women receiving suppressive doses, hormone levels should be checked every month during pregnancy, and the L-$T_4$ dose is increased if serum TSH level increases. When properly administered, L-$T_4$ treatment does not affect the outcome of pregnancy and, conversely, pregnancy has no effect on the outcome of thyroid cancer. The prepregnancy dose of L-$T_4$ should be resumed immediately after delivery.

**Table 1** The dose of L-tetraiodothyronine required to obtain low serum thyroid-stimulating hormone levels in athyreotic patients.

| Dose (µg/kg) | Age |
|---|---|
| 3–4 | Children |
| 2.5–2.2 | Adults |
| 1.4–1.2 | Older adults |

## Side effects of thyroid-stimulating hormone suppression

Concern has been expressed about the potentially detrimental effects of long-term suppressive L-$T_4$ therapy on target organs.[38] The theoretical argument underlying this concern is that, even if free $T_3$ and free $T_4$ are maintained in the normal range, a TSH level below the lower limit of the normal range during L-$T_4$ treatment implies a state of subclinical thyrotoxicosis.[61] The bones and heart are considered to be the organs at highest risk.[38]

An analysis of available data obtained from women with subnormal TSH levels induced by L-$T_4$ therapy revealed significant bone loss after menopause, but not before. There is no compelling evidence for a higher incidence of fractures among women with a history of suppressive thyroid hormone therapy.[38,62,63] In a prospective study with case-cohort sampling, an increased risk of fracture was reported in women over 65 years with low serum TSH levels,[63] but this study did not distinguish between overt and subclinical thyrotoxicosis. Furthermore, several studies have failed to demonstrate any decrease in bone mass in patients who received long-term L-$T_4$ treatment, and well-managed TSH-suppressive therapy does not contribute to osteopenia.[64] These data suggest that TSH-suppressive L-$T_4$ therapy does not have a strong effect on the skeleton, but it might contribute to spontaneous postmenopausal bone loss.[38] Prophylactic therapy should thus be considered when a postmenopausal patient must continue TSH suppression for cancer control.[38]

Even more controversial are the potentially adverse cardiac effects of long-term TSH suppression. Suppressive therapy with L-$T_4$ has been associated with increased 24 h mean heart rates, with increased numbers of premature atrial beats in younger and middle-aged patients[65] and with a higher incidence of atrial fibrillation in patients aged over 60 years.[66] Increased left-ventricular mass with a tendency

toward left-ventricular concentric remodeling has been reported in young and middle-aged patients with long-standing subclinical thyrotoxicosis. These changes are often accompanied by impaired diastolic function and sometimes by decreased exercise performance and reduced systolic performance during exertion.[67]

The prognostic implications of these cardiovascular observations have yet to be clarified.[38] Elderly patients with endogenous subclinical thyrotoxicosis have been reported to have increased rates of cardiovascular mortality associated with increases in the left-ventricular mass, heart rate, and frequency of atrial arrhythmias.[37,38] Therefore, in patients with known heart disease and in older patients, the daily L-T$_4$ dose should also be carefully monitored.[38] These subjects frequently complain of symptoms and signs of thyroid hormone excess (palpitations, heat intolerance, nervousness, and a feeling of reduced wellbeing) that impair their quality of life and their physical performance.[68] If long-term TSH suppression is necessary because of a high-risk cancer, a cardioselective β-blocking drug can be added to reduce the average heart rate and left-ventricular mass, and prevent supraventricular arrhythmias, thereby improving diastolic function, systolic performance during exercise, and quality of life.[68]

### Acute hypothyroidism following withdrawal of L-tetraiodothyronine

Symptomatic hypothyroidism will occur when L-T$_4$ is withdrawn 5 weeks prior to radioiodine scintigraphy or measurement of serum thyroglobulin levels or both. To minimize the duration and severity of symptoms, L-T$_3$ (which has a shorter half-life than L-T$_4$) can be given for the first 3 weeks of L-T$_4$ withdrawal. In this way, the interval of complete hormone withdrawal is reduced to the 2 weeks prior to testing. L-T$_4$ treatment is resumed immediately after the radioiodine treatment, and some physicians add T$_3$ for the first 3–5 days to accelerate the return to euthyroidism.

The withdrawal of thyroid hormone therapy can be risky in certain cases. The acute hypothyroidism caused by discontinuation of treatment might be associated with electrocardiogram abnormalities, reduced heart rate at rest and during exercise, increased systemic vascular resistance, reduced cardiac efficiency, and impaired left ventricular diastolic function and impaired systolic function during effort.[69,70]

These effects might cause a deterioration of cardiac function in patients who are elderly and have known cardiac disease (arterial hypertension, heart failure, coronary artery disease) or both. Moreover, the reduced renal clearance associated with acute hypothyroidism can lead to overdose of drugs commonly used for cardiovascular disease, such as digoxin and antiarrhythmic drugs. The ordeal of L-T$_4$ withdrawal can be avoided by using recombinant human TSH to stimulate radioiodine uptake and thyroglobulin production. Recombinant human TSH is clinically safe and devoid of cardiovascular effects, and it is an efficient alternative to L-T$_4$ withdrawal for diagnostic procedures in patients with thyroid cancer.[71]

### CONCLUSION

For the patient with thyroid cancer, L-T$_4$ treatment is a life-long prospect, and close monitoring is necessary to avoid adverse effects. For patients with papillary or follicular cancers, L-T$_4$-induced suppression of TSH secretion is necessary only when there is evidence of persistent or recurrent disease. In these cases, thyrotoxicosis must be avoided, and L-T$_4$ should be given at the lowest dose capable of producing target suppression levels. The vast majority of

### KEY POINTS

- Thyroid-cell proliferation is thyroid-stimulating hormone (TSH)-dependent, hence L-tetraiodothyronine (L-T$_4$)-induced TSH suppression should be included in the treatment strategies for differentiated thyroid carcinomas

- TSH suppression implies a state of subclinical thyrotoxicosis and becomes necessary only when there is evidence of persistent or recurrent disease; in low-risk patients, L-T$_4$ treatment serves to return TSH level to within the normal range

- To ensure optimal dosing, each patient must always receive the same preparation and the daily L-T$_4$ dose should be carefully tailored

- Adjustments of L-T$_4$ dosage will be required under particular circumstances, for example in pregnant women, patients with significant weight gain or weight loss, those with known heart disease and older patients

- If long-term TSH suppression is necessary because of a high-risk cancer, a cardioselective β-blocking drug can be added to reduce cardiovascular risk and to improve quality of life

patients (those who have no evidence of disease after thyroidectomy) should be placed on L-T$_4$ therapy with the aim of maintaining serum TSH levels in the normal range.

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