



Update on the treatment of hypothyroidism

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Purpose of review

Differentiated thyroid cancer is a malignancy that is rapidly increasing in frequency. As thyroidectomy plays a central role in the treatment of thyroid cancer, it is incumbent on physicians treating this patient group to be well versed in the intricacies of treating hypothyroidism.

Recent findings

Treatment of hypothyroidism may be refined by careful attention to dose selection, monitoring of therapy and achievement of thyrotropin goals that are specific to the individual patient's overall clinical situation. These goals are common not only to patients with a sole diagnosis of hypothyroidism, as discussed in the recent American Thyroid Association Guidelines, but also to patients with hypothyroidism in the setting of thyroid cancer. Several recent studies have illuminated our understanding of the benefits and risks of thyrotropin suppression therapy in patients with differentiated thyroid cancer. Multiple studies of combination therapy with levothyroxine and liothyronine for treating hypothyroidism have not led to a clear conclusion about its benefits over levothyroxine monotherapy. Animal studies have advanced our understanding of the altered serum and tissue milieu that characterizes levothyroxine monotherapy. Crossing the bridge from this translational research into clinical research using sustained release triiodothyronine preparations may ultimately enhance the health of our patients.

Summary

Continued refinement of our understanding of thyroid status and our ability to flawlessly implement thyroid hormone replacement is an active area of research.

Keywords

athyreotic, deiodinases, hypothyroidism, levothyroxine replacement therapy, sustained release triiodothyronine, thyroid cancer

INTRODUCTION

Patients with a thyroid malignancy most commonly have undergone a total thyroidectomy, and are hence athyreotic, and dependent on thyroid hormone replacement. American Thyroid Association guidelines for the treatment of hypothyroidism were published in December 2014. The literature review for these guidelines was completed in December 2013. Although these guidelines focus on hypothyroidism without an accompanying thyroid malignancy, many of the key points of these guidelines are pertinent to patients with thyroid cancer. The purpose of this review is to emphasize some of the key points from the hypothyroidism guidelines that are relevant to patients with thyroid cancer, and then discuss articles published since December 2013 that provide additional understanding or insight into these key points. Although many of the recent studies that are highlighted were conducted in individuals with autoimmune hypothyroidism, they have findings that are important for any individual taking thyroid hormone.

THE BASICS OF TREATING HYPOTHYROIDISM

The basics of treating hypothyroidism include selection of the levothyroxine (LT4) dose, selecting a patient-appropriate serum thyrotropin (TSH) goal and ensuring maintenance of that desired goal [1[¶]].

Selection of LT4 dose

Several approaches to estimating an appropriate LT4 dose have been used in athyreotic individuals [1[¶]]. These include weight-based or lean body mass-based formulae. Empiric dosing or formulae based on

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KEY POINTS

- Hypothyroidism is a lifelong condition in athyreotic patients, so optimization of therapy is critical.
- The complex interaction of factors such as patient age, sex and weight in determining levothyroxine dose requirement is being increasingly appreciated.
- New liquid levothyroxine preparations currently being studied may ease the burden for patients attempting to adhere to a levothyroxine regimen that maintains a steady serum TSH value.
- The benefits and risks of TSH suppression therapy should be carefully considered on an individual patient basis.
- There is hope, based on animal studies, that a sustained release triiodothyronine preparation may reverse the disappointing trend for combination studies to fail to show a clear improvement in patient outcomes.

anthropometric characteristics have also been utilized.

Weight and age

A weight-based LT4 dose in athyreotic patients is approximately 1.8 mcg/kg/day for achieving a normal serum TSH, but 2.1–2.7 mcg/kg/day for achieving a low or suppressed TSH [1[•]]. There seems to be a tendency for older studies to find that higher doses are required which could be accounted for by multiple factors including differences in LT4 formulations. A recent study found that dose requirements for maintaining a slightly subnormal serum TSH of 0.21 mIU/l were 1.95 mcg/kg/day and 1.77 mcg/kg/day in younger and older patients, respectively [2]. Empiric dosing based on ranges of weight, BMI and age have also been suggested, as well as formulae that include additional corrective factors combined with weight. A recent example of empiric dosing

based on a combination of age and BMI for athyreotic patients in whom a normal TSH is desired is shown in Table 1 [3[•],4]. A recent example of a formula to achieve a normal TSH in athyreotic individuals is $LT4 \text{ dose (mcg/kg/day)} = -0.018 \times BMI + 2.13$ [4]. The latter authors found that incorporation of BMI into their formula better predicted the dose in overweight and underweight individuals. Prior studies have shown conflicting results about whether deiodinase polymorphisms affect LT4 dose requirement [1[•]]. A recent study of LT4 doses required for TSH suppression in patients with differentiated thyroid cancer (DTC) showed minimal effect of one of two polymorphisms in the uridine 5'-diphospho-glucuronyl transferase system responsible for metabolizing T4, and no effect of deiodinase polymorphisms [5[•]]. In a regression model, the authors found that age, sex, body weight and TSH value accounted for 39% of the variation in LT4 dose, whereas the identified haplotype only accounted for 2% of the variation [5[•]].

Type of surgery

Although most patients with a cancer diagnosis undergo a total thyroidectomy, lobectomy is sometimes chosen for patients with low-risk papillary thyroid cancer. A recent study of patients undergoing lobectomy, 68% of whom were having surgery for a diagnosis of papillary thyroid, showed that a preoperative TSH of more than 2.5 and the presence of thyroid peroxidase antibodies predicted the need to initiate LT4 to keep the serum TSH below 4–7 mIU/l [6].

Thyrotropin goal

The specific serum TSH that is desired in a patient is determined based on the balance of benefits and risks [1[•]]. Some degree of TSH suppression is beneficial for patients with higher risk DTC, but this benefit must be balanced with the potential risks stemming from the individual patient's age and comorbidities.

Table 1. LT4 dosing in athyreotic individuals

Reference	Estimates of LT4 dose requirement			
[3 [•]]	Empiric dosing based on age and BMI ranges			
	LT4 dose (mcg/kg/day)	BMI ≤23	BMI 24–28	BMI >28
	Age ≤40 years	1.8	1.7	1.6
	Age 41–55 years	1.7	1.6	1.5
	Age >55 years	1.6	1.5	1.4
[4]	Formula-based dosing			
	LT4 (mcg/kg/day) = $-0.018 \times BMI + 2.13$			

Reproduced from [3[•]] with permission from the journal *Thyroid*.

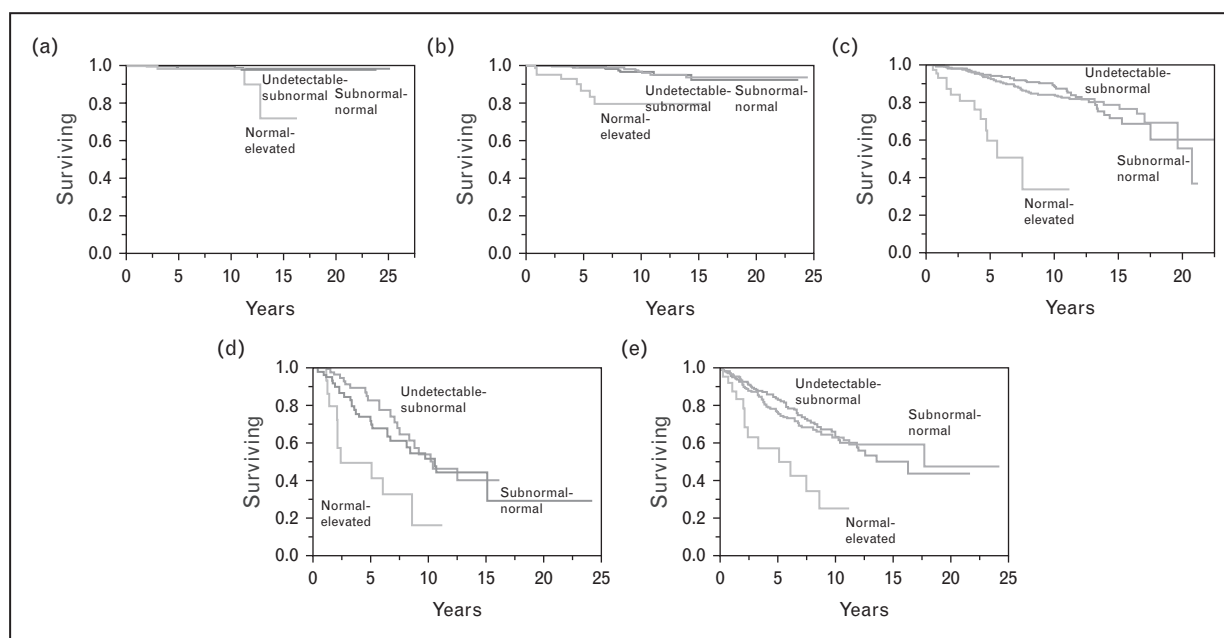


FIGURE 1. (a) Product-limit estimates of overall survival according to mean TSH category STAGE I patients ($P=0.002$). (b) Product-limit estimates of overall survival according to mean TSH category STAGE II patients ($P<0.0001$). (c) Product-limit estimates of overall survival according to mean TSH category STAGE III patients ($P<0.0001$). (d) Product-limit estimates of overall survival according to mean TSH category STAGE IV patients ($P=0.003$). (e) Product-limit estimates of overall survival according to mean TSH score category after diagnosis of distant metastases ($P=0.0003$). TSH, thyroid-stimulating hormone. Reproduced from [8**] with permission from *The Journal of Clinical Endocrinology and Metabolism*.

Age-appropriate thyrotropin goals

TSH reference intervals are affected by several factors including patient age. The upper limit of the reference interval increases with age [1[■]]. Based on this, it makes sense to modify the desired TSH goal for a patient with DTC depending on the patient's age, with a lesser degree of TSH suppression being the goal in an older patient. A recent study examining the effect of age, sex and circadian rhythms on TSH reference intervals showed that the 97.5% confidence interval for the upper limit of the reference interval increased from 6.45 to 7.55 mIU/l with age [7[■]]. In addition, the increased TSH values in older individuals were thought to occur because of a progressive increase in the nocturnal TSH surge [7[■]].

Disease or condition-appropriate thyrotropin goals

The main diseases or conditions to be considered when deciding what TSH value is appropriate for a particular patient are whether the patient has DTC or not, and then additionally whether the patient has coexistent conditions that could potentially be worsened by maintaining a low TSH, such as cardiac arrhythmias and osteoporosis. If the patient has DTC, lower TSH values have traditionally been maintained for intermediate-risk and high-risk patients.

A recent publication from the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) addressed the issue of what TSH values improve the outcomes for patients with various DTC risk categories. This prospective study showed that maintaining serum TSH values in the normal–subnormal range improved the overall survival of patients with stages I–IV disease (see Fig. 1a–d), increased the overall survival of patients with distant metastases (Fig. 1e) and also increased the disease-free survival of patients with stages I–III disease [8**]. Aggressive TSH suppression to achieve a subnormal-undetectable TSH was not necessary to achieve these benefits. The beneficial effect of modest TSH suppression on survival appeared to be maintained over 3 years of follow-up. In contrast with earlier reports from the NTCTCSG [9,10], aggressive TSH suppression may not be warranted, even in patients diagnosed with distant metastatic disease during follow-up. These latter patients had decreased survival if their TSH values were maintained in the normal-elevated range, compared with the survival of those with undetectable-subnormal and subnormal-normal TSH values [8**]. However, there was no additional benefit of undetectable-subnormal TSH values compared with subnormal-normal values.

Several recent studies have examined the risks of TSH suppression. A recent study of patients with

DTC with low-risk to intermediate-risk disease who were followed for 6 years found that those who were maintained with TSH values less than 0.4 mIU/l had similar recurrence rates but more osteoporosis than those with TSH values more than 0.4 mIU/l [11[■]]. Another recent study of elderly patients with DTC with 5 years of follow-up who were retrospectively divided into three groups of TSH values of less than 0.1, 0.1–0.3 or 0.3–0.5 mIU/l showed that recurrence rates were similar between the groups, but that complications increased in the groups with the lower TSH values. These complications included arrhythmias, osteoporosis and anxiety/insomnia [12]. Specifically examining bone health, a study in which the average TSH was 0.5 mIU/l in the 1-year period after thyroidectomy, initiation of LT4 was associated with decreased bone mineral density in both the hip and the spine [13]. However, this decline in bone density became insignificant after elapse of the initial 1-year postoperative period. This finding is in keeping with the study by Wang *et. al.* [11[■]], in which negative effects on bone health were no longer seen with maintenance of a median TSH of 1 mIU/l. In a cohort study of the Danish population, increased risk of hip fracture was seen during 7 years of follow-up after a TSH value of less than 0.3 mIU/l was documented, compared with those individuals who had a normal TSH value [14]. This study excluded patients taking LT4, but would be applicable to patients with DTC if endogenous and exogenous hyperthyroidism had similar effects on the skeleton.

In contrast to these former studies showing an adverse effect of TSH suppression, one recent study of TSH suppression showed that an average serum TSH of 0.17 mIU/l over a 5-year period was not associated with any cognitive impairment, as assessed using a battery of cognitive tests [15]. However, the comparison group was euthyroid individuals not requiring LT4, rather than individuals who were euthyroid while taking LT4.

Out-of-goal thyrotropin values

Iatrogenic thyroid disease occurs in a surprisingly high percentage of LT4-treated patients [1[■]]. In populations presumably being treated to achieve a normal TSH, approximately 20% of patients may be overtreated and another 20% undertreated, based on studies from 1993 to 2009 [16–19]. A recent study from 2014 shows that this trend continues: 5 years after LT4 initiation, 20% of patients had TSH values over 4 mIU/l and 10% had values less than 0.5 mIU/l [20]. Pregnancy is a time in which it is generally agreed that specific TSH goals should be maintained. Of concern, a study of pregnant women found that 63% of women had TSH values of more

than 2.5 mIU/l during the first trimester [21]. Not only is this above the recommended target, but also the study investigators found that these elevated TSH values were associated with an increased risk of miscarriage.

The percentage of patients with DTC that are maintained with TSH values in specific ranges according to the patient's disease stage is often not reported. In a cohort of 3238 patients with DTC [8[■]], in which staging was classified using the NTCTCSG system, 30% (427 of 1408) of patients with stage I disease had TSH values in the undetectable to subnormal range, whereas 10% (15 of 144) of patients with stage IV disease had TSH values in the normal to elevated range (see supplemental appendix 8 of cited article) [8[■]]. Moreover, in patients with distant metastases, 6% (28 of 452) of patients had normal to elevated TSH values (see supplemental appendix 9 of cited article) [8[■]]. This recent publication found that moderate TSH suppression was beneficial across stages I–IV and in patients with distant metastases (see Fig. 1a–e) [8[■]]. Thus, these data also suggest that LT4 therapy is often not optimized based on the patient's DTC risk category.

Maintenance of a specific thyrotropin goal

Once a specific TSH goal has been selected, there are several factors that can interfere with consistent maintenance of that particular target. These include altered absorption of LT4 caused by timing of LT4 ingestion, meals, beverages and medications, altered transport of LT4 associated with medications and altered metabolism of LT4 caused by medications [1[■]]. Most of these situations result in the need for an increased LT4 dose to counteract their impact. However, recently, some situations have been documented to either lower TSH or potentially reduce LT4 requirement.

Timing of LT4 administration

Several studies have examined the effect of the timing of LT4 on its absorption, as reflected in the resultant serum TSH [1[■]]. A recent review article [22] that compared the results of four studies which included bedtime dosing of LT4 in their study design [23–26] concluded that bedtime consumption of LT4 was a reasonable option for patients who not only wished to avoid taking their LT4 in close proximity to food, but also wanted a convenient regimen.

Decreased LT4 absorption, altered transport and increased metabolism

Two recent 'audits' have examined the medications associated with the development of an elevated TSH

and requirement for an increased dose of LT4. In one study, 21% of patients requiring an LT4 dose of greater than 225 mcg daily were found to also be taking medications commonly known to interfere with LT4 absorption or increase its metabolism, such as iron supplements, calcium supplements, anticonvulsants and proton pump inhibitors [27]. In patients thought to have medication-induced impaired LT4 absorption, altering the timing of their LT4 dose reduced their LT4 requirement by a mean of 31 mcg daily. In the second study, patients initiated on a medication that was potentially a culprit medication were monitored for changes in serum TSH values. The medications noted to be associated with a significant increase in serum TSH were iron, calcium, proton pump inhibitors and estrogen [28]. A group of interfering medications that is particularly pertinent for patients with DTC is tyrosine kinase inhibitors. Many of these agents are associated with an increased requirement for LT4 in athyreotic individuals (see Table 1 of cited article), possibly through several mechanisms including increased metabolism, possibly via induction of the type 3 deiodinase [29]. In a recent study of children and adolescents with medullary thyroid cancer who were taking LT4, TSH values rose from the normal range to values ranging from 12.5 to 137 mIU/l with initiation of vandetanib treatment [30].

New levothyroxine formulations

Several case reports and nonrandomized studies have suggested that liquid formulations of LT4 or formulations in which the LT4 is dissolved in glycerin and encased in a gelatin capsule may circumvent the impaired absorption of LT4 that may occur with tablet preparations. For patients receiving enteral feeding, liquid LT4 added directly to the feeding tube was associated with a similar serum TSH to that seen in another group of patients in whom the feeding was interrupted in order to administer crushed tablets [31]. The former procedure was found to be more convenient by providers. In another study of patients taking proton pump inhibitors, switching to an oral solution was associated with a decrease in serum TSH from a mean of 5.4 mIU/l to a mean of 1.7 mIU/l, suggesting better absorption of the liquid preparation in patients being treated with proton pump inhibitors [32]. A nonrandomized study of patients with gastritis who had a stable serum TSH while taking LT4 tablets and who were switched to a lower dose of LT4 gel capsules showed that two-thirds of patients had a similar TSH on the lower dose, again suggesting better absorption of the gel capsule

formulation [33]. Another nonrandomized study suggests that the serum TSH achieved by LT4 gel capsules is not affected by the timing with respect to breakfast [34]. If the findings of these studies are bolstered by randomized-controlled studies in the future, these LT4 formulations may prove to be very convenient for hypothyroid patients.

Medications associated with lowered thyrotropin values

At least three medications have been recently associated with lowered serum TSH values in patients taking LT4. These are statins, metformin and vitamin C. In an observational study, patients started on statins were noted to have a very small decrease in their TSH values from 1.62 to 1.45 mIU/l (*P* value 0.01) after beginning a statin [28]. A meta-analysis of four studies examining the effect of metformin on serum TSH found a small but statistically significant decline in TSH after metformin therapy was started [35]. Another study from 2014 also confirmed this TSH-lowering property of metformin [36]. However, a study of patients with DTC whose LT4 dose was lowered by 33% coincidentally with metformin or placebo initiation showed that both groups of patients experienced a similar increase in serum TSH from a subnormal value to 3.1 mIU/l [37], illustrating the very small, clinically insignificant, magnitude of the metformin effect. The mechanism of TSH-lowering effect of statins and metformin has not been fully elucidated, but seems unlikely to be because of enhanced absorption [28,36]. Vitamin C, on the other hand, may improve LT4 absorption in patients with gastritis [38]. In the latter study, patients with elevated TSH levels while taking LT4 had lowering of their TSH values from a median of 11.1 to a median of 4.2 mIU/l when they continued the same dose of LT4 with the addition of vitamin C solution [38].

FUTURE DIRECTIONS IN THE TREATMENT OF HYPOTHYROIDISM

One of the more complex issues to be considered when treating hypothyroidism is how to ensure that patients undergoing treatment are restored to optimal health [1]. Inherent in considering this issue are three related questions. The first question is whether quality of life is decreased in patients with hypothyroidism who are taking LT4 monotherapy, the second question is whether combination therapy with LT4 and liothyronine (LT3) is able to reverse the quality of life impairments and the third question is whether the inherent problem with LT4 monotherapy is the failure of deiodinases

to adequately compensate for the high T4/T3 ratio in athyreotic patients.

Quality of life

Several studies have shown decreased psychological well-being, more thyroid-related symptoms, more dissatisfaction, increased fatigue, more cognitive impairment and decreased well-being in patients being treated for hypothyroidism, compared with various control groups [1[¶]]. A recent review discussed the issue of fatigue in patients with DTC and concluded that most evidence was epidemiologic in nature, with diverse control populations, unclear relationship with biochemical indices and lack of randomized, controlled trials of treatment [39]. For a discussion of quality of life in patients with DTC also, see the review by Dr Sawka in this issue. A recent study has also shown that patients with hypothyroidism are at more risk of being diagnosed with a psychiatric disorder and being treated with antidepressive or antianxiety medications [40].

Combination therapy

The studies reported thus far have not clearly shown benefits of combination therapy on health-related quality of life, mood or neurocognitive functioning [1[¶]]. When combining the patients participating in cross-over studies, similar number of patients had preference for combination therapy ($n = 128$) as had no preference ($n = 101$). Combining the numbers from the parallel design studies, more patients had no preference ($n = 573$) than had a preference for combination therapy ($n = 130$) [1[¶]]. Although a meta-analysis did not find any association between positive outcomes with the use of combination therapy and the athyreotic state [41], there were relatively few athyreotic patients within the populations being studied. **Drawing conclusions from current studies is confounded by their heterogeneity. This heterogeneity involves study design, outcome measures, and results, and includes the use of different T3 doses and frequency of dosing.** When a clinical trial of a sustained release T3 preparation, given in a dose that is physiologic for humans, has been conducted, this will greatly advance the field. A metabolite of T3, T3 sulfate, has been shown to provide steady T3 levels for at least 48 h, but this property has only been demonstrated in profoundly hypothyroid patients undergoing a thyroid hormone withdrawal protocol for treatment of DTC [42].

The role of deiodinases in ensuring euthyroidism

A much-cited retrospective study raised the possibility that a positive response to use of combination

therapy may be associated with the presence of a type 2 deiodinase polymorphism [43]. **Although prospective clinical trials that examine the outcomes of combination therapy based on deiodinase polymorphism status or activity of deiodinases have not yet been published, several preclinical investigations have focused on the issue of deiodinase activity.** Mathematical modeling suggests decreased deiodinase activity, as well as decreased free T3/free T4 ratios, in LT4-treated patients, with decreases being more notable in athyreotic patients [44]. As a complement to prior animal studies by Escobar-Morreale *et al.* [45,46], a recent study conducted in rats suggested impairment of type 2 deiodinase activity in the whole body during LT4 monotherapy due to deiodinase inactivation, compared with maintenance of deiodinase activity in the hypothalamus. **The lesser degree of inactivation in the hypothalamus leads to efficient T3 production in the hypothalamus and normalization of TSH before T3 normalizes in the rest of the body.** Accompanying the inactivation of type 2 deiodinase in other tissues, lower serum T3 and higher T4/T3 ratios were seen in rats during monotherapy compared with combination therapy employing a subcutaneous slow release T3 pellet [47^{¶¶}].

CONCLUSION

Despite the advances made in the treatment of hypothyroidism, there are many knowledge gaps that must be surmounted in order to ensure that quality of life is optimized in all our patients with hypothyroidism. This is particularly necessary in patients who also have DTC, in whom quality of life may also be compromised because of knowledge of having a malignancy and the additional therapy, monitoring and expenses that this requires. LT4 monotherapy has been refined in many ways. We understand the factors affecting dose requirement, the means by which to maintain a therapeutic serum TSH and the importance of considering the desired TSH goal on an individual patient basis. We know that combination therapy with our current liothyronine preparations, when given as a once or twice daily dose, does not clearly improve patient outcomes. We eagerly await a sustained release liothyronine preparation that can be tested in athyreotic patients with the hope that the milieu of all tissues can be rendered euthyroid and that patient satisfaction with therapy and patient health outcomes can be concomitantly improved.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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