Managing symptoms in hypothyroid patients on adequate levothyroxine: a narrative review

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Short title (if needed): Managing symptomatic patients on optimised LT4
Abstract

The current standard of care for hypothyroidism is levothyroxine (LT4) monotherapy to reduce levels of thyrotropin (thyroid stimulating hormone, TSH) to within its reference range and amelioration of any symptoms. A substantial minority continue to report hypothyroid-like symptoms despite optimised TSH, however. These symptoms are not specific to thyroid dysfunction and are frequent among the euthyroid population, creating a therapeutic dilemma for the treating clinician as well as the patient. We present a concise, narrative review of the clinical research and evidence-based guidance on the management of this challenging population. The clinician may endeavour to ensure that the serum TSH is within the target range. However, the symptomatic patient may turn to alternative non-evidence-based therapies in the hope of obtaining relief. Accordingly, it is important for the clinician to check for conditions unrelated to the thyroid that could account for the ongoing symptoms such as other autoimmune conditions, anaemia or mental health disorders. Systematic and thorough investigation of the potential causes of persistent symptoms while receiving LT4 therapy will resolve the problem for most patients. There may be some patients that may benefit from additional treatment with liothyronine (LT3), although it is unclear as yet as to which patient group may benefit the most from combined LT4 + LT3 therapy. In the future, personalised treatment with LT4 + LT3 may be of benefit for some patients with persistent symptoms of hypothyroidism such as those with polymorphisms in the deiodinase enzyme 2 (DIO2). For now, this remains a subject for research.

Key words: levothyroxine; hypothyroidism; triiodothyronine
Introduction

Current management guidelines for the management of hypothyroidism focus on the administration of levothyroxine (LT4), with doses titrated to bring thyroid stimulating hormone (thyrotropin, TSH) within a locally-derived reference range of “normal” values [1-3]. Spontaneous hypothyroidism is a common condition, affecting approximately 1–2% of adults in iodine-replete areas of the world [4], although a much higher prevalence has been described in some countries, e.g. about 10% in a study conducted in eight large cities in India [5]. Many more people have subclinical hypothyroidism, with a prevalence estimated as 8% in women (10% in women aged >55 years) and 3% of men [4]. Current recommendations support the prescription of levothyroxine to some patients with subclinical hypothyroidism, particularly where TSH is >10 mU/L and FT4 is within the normal range [2], and the use of levothyroxine for the management of subclinical hypothyroidism appears to have increased [6,7].

Consequently, LT4 is given widely: this treatment is currently the most prescribed medication in the USA and the 3rd-most prescribed treatment in the UK (120 million prescriptions, and 19 million prescriptions each year, respectively) [8]. For most patients, administration of levothyroxine is sufficient to resolve symptoms of hypothyroidism and maintain quality of life [1-3]. However, a minority of people with hypothyroidism continue to report symptoms reminiscent of hypothyroidism, even following treatment with LT4 at doses sufficient to normalise TSH, with consequent impairment of their quality of life [9].

We present a narrative review that explores the extent and pathophysiologic nature of this problem. We also provide suggestions for managing this challenging population of patients.

Search methods

This is a narrative review. We searched the PubMed database for clinical trial data from inception to 30th March 2020 using the following search string:

((TSH OR thyrotropin) AND (hypothyroid OR hypothyroidism) AND symptoms) OR (Euthyroid [ti] AND symptoms [ti])

These searches provided a total of 7,868 hits. The searches were narrowed down using the PubMed filters of “Clinical trial”, “Randomised clinical trial”, “Practice guideline”, “Observational study”, and “Meta-analysis”. The titles and abstracts of the resulting 560 hits were examined manually to identify data of interest. Additional specific customised searches provided material on prevalence of hypothyroidism, etc. In addition, authors’ personal literature collections and references from articles identified in the search also provided source material.

We focussed on publications relating to current, guideline-driven care of hypothyroidism. Thus, the therapeutic use of combinations of LT4 with triiodothyronine (T3) is not addressed in detail, beyond a brief account of the current status of clinical trials in this area.
Persistent ill health on optimised levothyroxine therapy

Scale of the problem

A survey in the UK used questionnaires to measure psychological health and symptoms reminiscent of thyroid disorders in 597 LT4 recipients and 551 controls, from a population matched for age and gender, using the records of five primary care centres [10]. Psychological and, especially, thyroid-related wellbeing, were significantly poorer in LT4 users vs. controls. Wellbeing was impaired broadly similarly in LT4 recipients who did, or did not, have an adequately controlled TSH level. The differences between thyroid patients and controls persisted after multivariate adjustment for age, gender, concurrent medication use and comorbidities. Another study found a correlation between quality of life and levels of FT4 and TSH (but not FT3) in patients with TSH controlled to within the normal range [11]. These data suggest that persistence of symptoms, including those potentially related to thyroid dysfunction, may be a common problem. This situation has important implications for resource provision, as additional clinic visits to check and adjust LT4 doses were associated with increased direct and indirect costs to the healthcare system and to society [12].

Nonspecific nature of symptoms of hypothyroidism

Symptoms reminiscent of hypothyroidism tend to be nonspecific and difficult to distinguish from other conditions or general sub-optimal health (Table 1) [13-16]. There is some degree of association between elevation of TSH and the presence of hypothyroid-like symptoms, particularly when multiple symptoms were present or symptoms had appeared or intensified within the previous year, but many symptoms existed with equal frequency in hypothyroid and euthyroid subjects [17]. Also, people with overt or subclinical hypothyroidism in the Colorado Thyroid Disease Prevalence Study were more likely to have three or more of these symptoms than euthyroid subjects, and euthyroid subjects were more likely to be free of these symptoms [13]. However, the absolute difference in the prevalence of these symptoms between the two groups was small, and receiver operating characteristics analysis demonstrated sensitivity for detecting hypothyroidism of only 28% or less. A study from a population-based cohort in Denmark also found that symptoms reminiscent of hypothyroidism alone were a poor predictor of the presence of overt hypothyroidism [18]. Thus, being free of these symptoms does not reliably exclude the presence of hypothyroidism. Equally, the presence of symptoms that could potentially be attributable to hypothyroidism doesn’t consistently predict hypothyroidism either. Thyroid dysfunction may promote psychological disturbances, as described above [19].

Possible explanations for continuing symptoms despite ‘adequate’ biochemical euthyroid status

The normal thyroid gland produces both T4 and T3, yet LT4 monotherapy has been the mainstay of replacement since the 1970s due to ease of administration, good absorption via
the gut and its long half-life, thus allowing for once daily dosing with very stable serum profile [1-3]. In addition, T4 can be converted to T3 by the various tissues depending on local requirement consequently alleviating the need to add LT3 [20]. Furthermore, the majority of circulating T3 comes from peripheral conversion of T4 to T3 and not secretion from the thyroid gland, suggesting only a small role for secreted T3 in maintaining thyroid hormone homeostasis [21]. It is also clear that circulating T3 levels may be low in hypothyroid patients treated with LT4 monotherapy [22-25]. Experimental evidence suggests that LT4 monotherapy in hypothyroid rats fails to normalise T3 levels in all tissues [26].

Three types of deiodinases regulate the conversion of T4 to T3, and the inactivation of both hormones [27]. The expression of these enzymes varies between individuals, and between different cells in the body, and it has been suggested that such variations “fine tune” the actions of thyroid hormones in different physiological systems [28]. For example, it has been suggested that individuals with polymorphism in the deiodinase 2 gene (Thr92Ala) may have subtle changes in deiodinase activity leading to clinically important differences in tissue thyroid hormone bioavailability [29]. In addition, LT4 monotherapy reduces the expression of the type 2 deiodinase primarily responsible for converting T4 to T3 [30], which may in principle exacerbate the relative T3 deficiency in patients with hypothyroidism receiving LT4 therapy. Thus, it is argued that LT4 therapy may not be sufficient on its own to return hypothyroid tissues to normal thyroid hormone state although serum TSH levels may be within the euthyroid range.

A cross-sectional study identified 9,981 people with TSH within the normal range in the US national Health and Examination Survey (NHANES) [23]. Analysis of individuals stratified by those receiving LT4 versus non-users of LT4 showed that serum TSH levels were similar in both groups (2.13 and 2.15 mIU/L, respectively). However, LT4 recipients, compared with the euthyroid controls, had significantly lower total, LDL- and HDL-cholesterol, higher body mass index, higher total and free T4, lower total and free T3. Furthermore, the LT4-treated hypothyroid patients had higher body mass index and more use of cardiovascular medications compared with euthyroid controls despite normal TSH levels. These data suggest the presence of measureable biochemical differences between populations with and without hypothyroidism, even when TSH is controlled adequately according to guidelines.

Accordingly, considerable research interest has focussed on administration of combinations of T4 and T3 to a patient with symptoms of hypothyroidism that are apparently refractory to LT4 [31]. An initial double blind, randomised trial in patients with hypothyroidism demonstrated improvements in mood and neuropsychological function in patients for whom T3 was given in place of a proportion of their LT4 dose [32]. Further evidence from randomised or observational studies has supported the possibility of significant differences in quality of life (QoL) scores or psychological scores in favour of the combination vs. LT4 monotherapy [33,34], but a benefit for the combination for improved quality of life or other outcomes is not supported by systematic reviews or meta-analyses conducted as recently as 2018 [35-39]. Importantly, about half of patients enrolled in double-blind trials preferred the
combination to LT4 monotherapy, however [40]. Data on the safety of treatment with regimens including T3 are lacking [39], although long-term observational data from one LT4 + LT3-treated cohort did not raise safety concerns [41]. Nevertheless, care must be taken to avoid overtreatment in this setting, especially as the serum half-lives of LT4 (days) and T3 (hours) do not match well, and balancing the dosages of LT4 and T3 is challenging [39]. Current guidelines [42] and expert opinion [39] support the conduct of a carefully monitored trial of LT4 + LT3 replacement, by a physician experienced in the management of thyroid disorders, for a patient with hypothyroid-like symptoms despite optimised LT4 monotherapy, with dosages optimised according to the TSH level. However, the therapeutic administration of T3 remains a topic for research [3,42]. Physicians should be aware that LT3-LT4 combination therapy is promoted increasingly in the media, and patients may initiate or titrate therapy without involving their healthcare team [43].

Whether the overall results of these trials concealed subgroups that may have been more responsive to LT3 + LT4 combination therapy is unknown. In addition, trials may not have focussed on patients populations with persistent symptoms of hypothyroidism despite optimised TSH. A further possible explanation for this discrepancy in results may be the presence of the polymorphism of the gene encoding DIO2, described above [44]. Carriers of this polymorphism have been shown to demonstrate a relative state of hypothyroidism within the brain [45], and have tended in some studies to respond more favourably in terms of improved QoL to T4 plus T3 combinations, compared with treatment with T4 alone [46,47]. Other studies have not demonstrated a significant influence of variation in the gene for this enzyme on T4 requirement in hypothyroid patients [48], or on patient-reported outcomes on (or preference for) treatment with LT4 + T3 combination therapy [49]. Further research will be needed to confirm whether genetic variations in deiodinases, and indeed in other sites of cellular access or action of thyroid hormones (such as membrane transporters, nuclear receptors and other sites) may facilitate individualised treatment of hypothyroid patients in the future [44,50-52].

**Managing patients with persistent symptoms despite optimised levothyroxine therapy**

Symptoms associated with hypothyroidism are often non-specific in nature, and common within the euthyroid population, as described above, and a systematic and careful approach is needed to evaluate any association between the patient’s symptoms and thyroid status [52]. Box1 and Figure 1 summarise a pragmatic approach to managing these patients, with individual steps described in more detail below.

**Initial examination**

Initially, it is important to conduct a thorough examination to exclude causes of these symptoms that are not related to thyroid dysfunction, such as conditions producing chronic fatigue. Physicians need to be alert to the possibility that the “hypothyroid-like” symptoms are not, in fact, related to underlying thyroid dysfunction. Most individuals diagnosed with
hypothyroidism have an autoimmune aetiology underlying the condition, and the presence of one autoimmune disorder suggests an increased risk of a range of other conditions associated with reduced quality of life [53-55]. For example, an observational study from the UK found a prevalence of rheumatoid arthritis of 4.2% among patients with Hashimoto’s thyroiditis [53] (cf. <1% in the general population [56]). The relative risks of other autoimmune conditions (pernicious anaemia, systemic lupus erythematosus, Addison’s disease, celiac disease, and vitiligo) were increased by more than ten-fold in people with vs. without Hashimoto’s thyroiditis [53]. Patients with hypothyroidism and new or persistent symptoms may therefore be screened for other comorbid autoimmune conditions.

**Is TSH adequately controlled?**

As many as one-third of patients with hypothyroidism may have an elevated TSH level, consistent with sub-optimal replacement of LT4 therapy [57]. Possible causes of this finding include under dosing with LT4, patient non-concordance, aberrant assay results, and malabsorption of LT4: these are described briefly below. Correcting the level of TSH to within its reference range may be sufficient for most patients [1-3,58-60].

Variations of TSH levels within the euthyroid range have been reported to correlate with increased risk of a first adverse cardiovascular event [61], and with menopausal symptoms [62] or decreased bone mineral density/increased fracture risk [63] in perimenopausal or menopausal women. An increased risk of adverse cardiovascular outcomes and fractures has been observed in patients already receiving LT4 therapy who have TSH levels higher than the usual reference range of 0.4–4.0 mIU/L [64]. These studies suggest that minor variations on TSH could have important, long-term functional consequences. However, there is no evidence that varying the dose of LT4 treatment to alter TSH levels within the reference range is of benefit in the day-to-day management of people with hypothyroidism. Data from a case control study suggested that LT4 therapy was effective in improving symptoms associated with hypothyroidism, but this was mainly associated with correcting aberrant TSH levels [65]. Elsewhere, LT4-treated hypothyroid patients with TSH within the normal range were randomised to higher, unchanged or lower LT4 doses for 6 months (serum TSH at study end ranged from 1.5–9.5 mIU/L) [66]. Altering the LT4 dose was not associated with significant changes in questionnaire scores for mood, cognition or quality of life. A meta-analysis of 21 randomised trials did not support improvement in quality of life or thyroid-related symptoms associated with treatment of subclinical hypothyroidism with LT4 vs. placebo or no treatment [67]. Finally, aiming for TSH levels in the lower half of the reference range (<2 mIU/L) did not improve symptoms or measures of wellbeing or quality of life compared with less intensive management of TSH in a randomised trial [68]. This trial mitigates away from a policy of controlling TSH to within the lower half of the normal reference range, although further research will be needed to identify if there are specific subgroups of patients who could potentially benefit from such an approach.

In addition to the above, increased TSH secretion may occur in obese patients or in the elderly (where age-specific reference ranges are not used). Increased TSH secretion may also occur when the patient ingests certain therapies (e.g. lithium, amiodarone), foodstuffs (e.g.}
dietary soya) or toxins (e.g. endocrine disruptors) concomitantly with LT4 [69-71]. Dietary soya, as well as calcium, iron or iodide supplements may reduce the absorption of LT4 into the circulation [69-71]. The presence of rhesus factor (estimated prevalence ≤0.24% of the general population), macro-TSH (estimated prevalence 0.6–1.6%) and autoantibodies to thyroid hormones (estimated prevalence 1.8%) may interfere directly with a TSH test, providing aberrant results [72]. As many as 6% of patients may have heterophilic antibodies in their circulation [72], especially human anti-mouse antibody: these antibodies can recognise the animal-derived antibodies used in some immunoassays for TSH, leading to a falsely elevated TSH result [73,74]. Interference with a TSH test is a relatively uncommon reason for a mismatch between the measured TSH level and continuance of hypothyroid-like symptoms, but should be considered where other potential causes have been excluded.

Is the patient taking levothyroxine as directed?

Non-concordance to LT4 treatment is common and may increase over time [75]. A database study from the USA showed that about two-fifths of patients were non-adherent to LT4 at 6 months, and about half of patients were non-adherent at 12 months [75]. About one-third of patients were non-adherent to LT4 therapy in a survey in Turkey [76]. In addition, the likelihood of sub-optimal adherence to LT4 appears to vary according to the preparation prescribed [75,77]. Sub-optimal adherence to LT4 therapy has important negative consequences for long-term outcomes: better adherence to LT4 therapy has been associated with reduced need for healthcare resources and enhanced long-term health trajectory in a large database analysis [78]. A TSH test conducted after a period of supervised administration of LT4 can help to identify patients whose chronically elevated TSH is due to missed doses of LT4 [79].

Is there altered absorption or metabolism of LT4?

LT4 is absorbed via the intestine, and intestinal disorders may influence the absorption of LT4 and thus the dosage required to control the TSH level [80]. For example, one study showed that people with ulcerative colitis and hypothyroidism required doses of LT4 that were 26% higher compared with those without ulcerative colitis [81]. As with sub-optimal adherence described above, long-term elevation of TSH due to malabsorption of LT4 has adverse clinical consequences [82]. A switch to a different formulation of LT4 may help to resolve issues related to LT4 malabsorption [83], and a questionnaire-based tool is available to support the best choice of formulation [84]. Alternatively, the use of a LT4 absorption test may help to differentiate cases of true malabsorption from patients with poor adherence to therapy [85]. Liver cirrhosis also increases the dose requirement for LT4 [86,87]. Numerous medications alter the metabolism or excretion of thyroid hormones, and can influence circulating levels [88].

Is the patient using LT4 correctly?

Patients may need to be reminded to take their LT4 precisely as directed. The absorption of LT4 is also reduced by concomitant food intake, resulting in higher and more variable TSH
levels, compared with administration in the fasting state [89]. Dosing recommendations vary to some extent between regions. Levothyroxine should be taken “at least half an hour before breakfast” (some levothyroxine products in Europe) [90] or “preferably one-half to one-hour before breakfast” (USA) [91]. Patients need to understand precisely how to take their LT4.

The European labels for LT4 products note that the absorption of LT4 is influenced by a range of treatments, including antacids, proton pump inhibitors, calcium salts, cimetidine, oral iron, and cholesterol absorbing resins (colestipol and cholestyramine), with a recommendation that the dosing of LT4 and these agents should be separated by at least 4 hours [90]. LT4 also has pharmacodynamic interactions with a number of other treatments that can increase or decrease their effects [92].

It is worth checking that the patient’s LT4 tablets correspond to those prescribed, as dispensing errors are not unknown. In addition, check with the patient how they store their LT4 tablets (labelling typically recommends storing them away from light in their original packaging, and below a given temperature). Finally, if a patient is dissatisfied with their LT4 monotherapy, it is important to take some time to try to understand the nature and causes of their symptoms. A patient with distressing symptoms that they attribute to hypothyroidism (whether or not causally attributable to thyroid dysfunction) may turn for support to providers of “complementary/alternative medicine”, whose advice and products may be inappropriate, ineffective, or harmful [93]. Taking a holistic view and trying to ensure that the patient feels well will help to maintain trust and cooperation between the physician and patient, which will promote better concordance with treatment.

**Discussion and conclusions**

We have set out to provide a focussed and pragmatic review for the practising physician faced with a patient with symptoms reminiscent of hypothyroidism despite optimisation of LT4 according to current guidelines. Although this is not a formal systematic review, which is a limitation of our article, we used a priori criteria to guide our search strategy, which is a strength. The status of T3-LT4 combination therapy is perhaps the largest source of uncertainty in this area, with an apparent mismatch between persistent (especially observational) reports of psychological benefit and the largely neutral results of randomised trials and meta-analyses (reviewed above). We have not explored this subject in depth, in contrast with earlier reviews, which have described this area in more detail [31,39,42], as current guidelines advise clearly against this approach (if a trial period of treatment with a combination of T3 with LT4 is conducted for an individual patient, it is important to monitor carefully for signs of iatrogenic thyrotoxicosis [42]).

A substantial minority of patients with hypothyroidism continue to experience symptoms reminiscent of this condition, despite the application of levothyroxine therapy. It is important to exclude the presence of other conditions that may give rise to these symptoms. Chronically elevated TSH may be caused by under dosing of LT4, poor adherence to therapy, taking the treatment with food or drugs that interact with LT4, or intestinal malabsorption of
LT4. Careful and systematic evaluation of the cause of the raised TSH level will then facilitate the achievement of an optimal LT4 regimen.

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Figure legend

Figure 1. Overview of management of patients with hypothyroidism who continue to report symptoms of that condition despite receiving levothyroxine therapy.
Table 1. Typical symptoms of hypothyroidism.

| Examples of medical conditions or treatments that produce symptoms resembling hypothyroidism | Typical symptoms resembling those of hypothyroidism |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------|
| ● Chronic fatigue                                                                            | ● Constipation                                   |
| ● GI diseases that affect LT4 absorption                                                    | ● Feeling too cold                               |
| ● Addison’s disease                                                                          | ● Puffy eyes                                     |
| ● Anaemia                                                                                    | ● Slow thinking                                  |
| ● Stress                                                                                    | ● Hoarse/deep voice                              |
| ● Changes in weight                                                                          | ● Tired/lethargic                                |
| ● Pregnancy                                                                                 | ● Muscle cramps                                  |
| ● Medications that interfere with LT4 absorptiona                                            | ● Weight gain                                    |
| ● Carpal tunnel syndrome                                                                     | ● Depression                                     |
|                                                                                             | ● Dry or scaly skin                              |
|                                                                                             | ● Muscle weakness                                |
|                                                                                             | ● Loss of libido                                 |
|                                                                                             | ● Poor memory                                    |

aSee text. Compiled from refs 13–16. GI: gastrointestinal; LT4: levothyroxine.
Table 2. Pragmatic approach to managing a patient with continued symptoms of hypothyroidism despite apparently adequate levothyroxine therapy.

**Take a thorough medical history**

- Careful initial examination to identify potential other causes for hypothyroid-like symptoms

**Check the diagnosis of hypothyroidism and lab results**

- Ensure TSH is well controlled first
- Check for patient factors and concomitant drug treatments that might have interfered with the TSH assay

**Check for sub-optimal compliance**

- Is the patient taking all required doses?

**Check for factors that could alter the metabolism of thyroid hormones**

- Potential for malabsorption of LT4
- Some treatments affect thyroid hormone metabolism

**Check how the patient uses LT4**

- Does the patient take LT4 in the fasting state at the start of the day, as per label?
- Does the patient adjust the timing of other therapies that could interfere with LT4 absorption?
- Is the patient storing their LT4 correctly?
- Does the patient have the correct LT4 tablets, as per prescription?

See text for references
Figure 1. Overview of management of patients with hypothyroidism who continue to report symptoms of that condition despite receiving levothyroxine therapy.

179x174mm (600 x 600 DPI)