Chapter 8

Current and Future Prospects for the Role of Triiodothyronine in the Management of Hypothyroidism

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The thyroid gland secretes two principal thyroid hormones: thyroxine (T4) and triiodothyronine (T3). T4 is a prohormone that must be activated to T3 outside of the thyroid gland by specific iodothyronine deiodinases. Thyroid hormone replacement therapy with levothyroxine (LT4) for patients with hypothyroidism does not adequately restore circulating levels of T3 in all patients and could explain why some patients remain symptomatic despite normalisation of thyroid-stimulating hormone. In addition, genetic polymorphisms in the deiodinases or other components of thyroid homeostasis could exacerbate this situation. Given that T3 is the biologically active thyroid hormone, a consensus is building that restoring optimal T3 homeostasis is central to the management of hypothyroidism. Two meta-analyses of 18 randomised controlled trials (RCTs) that evaluated patient-reported outcomes (PROs) in patients receiving liothyronine (LT3) + LT4 versus LT4 alone did not identify differences

between both therapies, but did find a strong preference for LT4 + LT3 versus LT4 alone. However, these trials did not focus on patients exhibiting residual symptoms. One recent secondary analysis of an RCT found that patients with residual symptoms benefit the most from combination therapy with LT4 + LT3. Thus, new RCTs focussed on patients more likely to benefit from LT3, and using PROs and preferences should adequately address the hypothesis that adding LT3 to LT4 can resolve symptoms and improve quality of life in some people with hypothyroidism.

Introduction

Thyroxine (T4) and triiodothyronine (T3) are the two main hormones secreted by the thyroid gland, capable of triggering biological effects in almost every system within the body. The guideline-driven management of hypothyroidism is focussed strongly on the therapeutic use of levothyroxine (LT4) monotherapy, titrated to a dose that brings the level of thyrotropin (thyroid-stimulating hormone [TSH]) to within a pre-specified "normal" reference range. Nonetheless, a minority of LT4-treated patients continue to report residual symptoms reminiscent of hypothyroidism, despite being in a state of biochemical euthyroidism according to their TSH levels. There has been considerable clinical interest over the years in the potential of combination treatment with liothyronine (LT3) alongside LT4. To date, this approach has not gained traction in clinical guidelines, although there has been consistent support for a therapeutic trial of additional LT3 administration for some of these patients. This chapter reviews the current evidence base and future prospects for adding LT3 to LT4 therapy in patients with hypothyroidism.

The pathophysiological basis for combination treatment with LT4 + LT3

The deiodinases and thyroid hormone action

The rate of T4 secretion from the human thyroid gland outstrips that of T3 by a variable amount, from about 14:1 to 8:1, depending on the TSH levels. Nevertheless, T3 is the biologically active hormone: deiodinases inside and outside the thyroid parenchyma convert T4 to T3 (mainly the deiodinase 2 [DIO2] isoform, with some contribution from the DIO1 isoform), which reaches the circulation and acts systemically. In addition, T3 generated via DIO2 acts locally to influence the transcription of a wide range of genes (Table 1).[1–3] The deiodinases also mediate the conversion of T4 and T3 to inactive metabolites (DIO3 isoform), such as reverse T3 and 3,3'-diiodothyronine (T2), respectively. In practice, numerous metabolites of thyroid hormones have been found in the circulation, but their physiological role, if any, remains to be established.[4–7] DIO2 is also closely involved in the feedback mechanisms in the hypothalamus and pituitary gland, by which a relatively small change in the circulating T4 level causes a much larger change in TSH secretion.[8] This is illustrated through the observation that DIO2 inhibition by treatment with amiodarone increases TSH secretion.[9]

Pathophysiological consequences of polymorphisms in deiodinase genes

Polymorphisms or mutations in the genes encoding the deiodinases may affect the activity of these enzymes. For example, the *DIO2* Thr92Ala polymorphism was associated with a significantly lower T3 level in post-thyroidectomy patients receiving thyroid hormone replacement therapy with LT4.[10] The reduced T3 level was apparently due to a reduction in the stability of the DIO2 protein, which in turn caused a lower rate of conversion of T4 to T3.[11] This polymorphism has also been associated with hypothyroidism localised to the brain.[11] Other cross-sectional data demonstrated a significant effect of a *DIO1* polymorphism (rs2235544) on the LT4 dosage required to control hypothyroidism in a

Table 1 Overview of the metabolism of thyroxine by peripheral deiodinases.

	Deiodinase D1	Deiodinase D2	Deiodinase D3
Mainly expressed in	Liver, kidney, thyroid	Brain, pituitary, skeletal muscle, heart	Widely expressed
Principal reaction	T4 → T3	T4 → T3	T4 → rT3
Other important reactions	T4 → rT3 T3 or rT3 → T2	rT3 → T2	T3 → T2
Summary of physiological importance	• Important source of plasma T3 • Recovery of iodine from inactive thyroid hormone metabolites	• Regulation of local cellular T3 levels • Maintaining pituitary/hypothalamic feedback for thyroid hormone production	• Regulation of local cellular D3 levels, independent of local T3 or T4 levels • Degradation of thyroid hormones

rT3: reverse triiodothyronine; T2: 3,3′-diiodothyronine; T3: triiodothyronine; T4: thyroxine.

cohort of 76 patients.[12] A recent study in 200 LT4-treated women with primary hypothyroidism measured levels of thyroid hormones according to the presence of a single nucleotide polymorphism (SNP) in the *DIO3* gene.[13] There were significant differences in the serum levels of T2, T3 and T4 among three groups of women who had wild-type *DIO3*, or who were homozygous or heterozygous for the SNP. On the other hand, a cross-sectional study from the UK Biobank failed to find a significant association between any of three *DIO2* polymorphisms and a range of outcomes related to psychological well-being, cognitive function and cardiovascular risk. Polymorphisms of thyroid deiodinases have also been associated with an increased risk of other diseases, such as early-onset obesity, several cancer types, neurodegenerative diseases, bone diseases, hypertension and schizophrenia, among others.[10,14–18] The importance of polymorphisms of other proteins involved in thyroid homeostasis, such as thyroid hormone receptors and transfer proteins, remains an active area of research.[19]

It is possible that a given circulating level of T4, e.g. during treatment for hypothyroidism with exogenous LT4, may drive sufficient production of T3 in one organ system, but not in another.[20] For example, a state of local T3 deficiency in the heart (perhaps driven by up-regulation of DIO3,[21] which degrades T3 to T2 [Table 1]) has been implicated as a possible driver of adverse clinical outcomes in patients with heart failure.[22] Low T3 is commonly observed among populations with heart failure,[23,24] and intervening to improve T3 homeostasis has been suggested as a therapeutic approach to the management of heart failure with preserved ejection fraction.[25] Isolated low T3 ("euthyroid sick syndrome") is a risk factor for increased mortality in patients with various cardiac conditions.[26–28] Overall, it is clear that polymorphisms in deiodinases may underlie an inability of LT4 treatment to achieve a euthyroid state in peripheral tissues in some hypothyroid patients.[198]

The inability of LT4 to normalise T3 production in all patients with hypothyroidism

Several studies have reported that a low level of free T3 (fT3) persists in some patients who receive thyroid hormone substitution with LT4 that is sufficient to bring TSH and free T4 (fT4) to within their reference ranges.[29–33] For example, the recent Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) showed that LT4 treatment for hypothyroidism normalised serum TSH levels and increased average fT4 levels, as expected, but the mean fT3 level was reduced by 7%, with 15.6% of patients reporting at least one fT3 test result below its reference range during the average follow-up of 8 years.[31] An observational study in 9,850 LT4-managed adults with hypothyroidism found a non-linear relationship between levels of fT3 and fT4 such that there was little change in fT3 at higher levels of fT4.[34] Thus, increasing the LT4 dose was effective in reducing TSH and increasing fT4, but had little effect on fT3 beyond a certain level.[34] A meta-analysis comparing well-controlled patients with hypothyroidism (according to the TSH level) with a euthyroid control group showed that modest but statistically significant elevations of total cholesterol (mean difference +9.6 mg/dL [0.25 mmol/L]) and LDL-cholesterol (+3.3 mg/dL [0.09 mmol/L]) persisted in the hypothyroid group.[35]

The problem of persistent symptoms in some patients with hypothyroidism

The observation that TSH-guided thyroid hormone replacement for patients with hypothyroidism may not always establish effective euthyroidism (i.e. normalised levels of TSH, fT4 and fT3, see above) has refocused interest on the minority of patients who continue to experience hypothyroidism symptoms, e.g. impaired quality of life, even after the restoration of TSH to within its reference range.[36–40] Observational data suggest that people with hypothyroidism report a lower quality of life than their euthyroid peers, even if their TSH is well-controlled, and after adjustment for age, gender, comorbidities and associated medication use.[41] Elsewhere, quality-of-life scores provided by patients with well-controlled hypothyroidism were shown to correlate with levels of TSH

and fT4 within the normal range, but not with levels of fT3.[42] Finally, an RCT showed that additional LT4 administration did not improve psychological well-being or cognitive function in patients with symptoms reminiscent of hypothyroidism but a TSH level within the reference range.[43]

It should be noted that symptoms of hypothyroidism are non-specific and may arise from multiple comorbidities or their treatments, and exhaustive work-up is needed before these symptoms can be confidently associated with residual hypothyroidism.[35,36,38] Hypothyroid-like symptoms such as fatigue may arise from deficiencies of vitamins and minerals (especially B_{12}, folate and iron), menopause, coeliac disease and overweight/obesity with obstructive sleep apnoea.[38] Nevertheless, it is rational to hypothesize that correction of fT3 in addition to TSH and fT4 could be an effective strategy to improve the quality of life of patients with hypothyroidism who do not respond fully to LT4 monotherapy. The evidence base for intervention with LT3 in this population is summarised in the following section.

Clinical evaluations of LT4 and LT3 in combination

Randomised trials and meta-analyses

Table 2 summarises the main findings of numerous randomised trials that have evaluated combinations of LT4 + LT3 in comparison with LT4 alone in patients with hypothyroidism.[44–66] Several features of these trials are immediately striking: most were published more than 15 years ago, most are small and employed a relatively short treatment duration and – especially – most reported no differences in outcome between LT4 + LT3 treatment versus LT4 alone. A 2006 meta-analysis, after most of these trials had been published, found no overall differences between combination therapy versus LT4 monotherapy for bodily pain, depression, anxiety, fatigue, quality of life, body weight, any lipid parameter or adverse events.[67] Further meta-analyses published as recently as 2021 demonstrated no differences between LT3 + LT4 versus LT4 alone on symptoms, fatigue, quality of life, mood or cognition, which was unsurprising, given the number of neutral trials published at least 20 years ago.[68–71]

Table 2 Summary of randomised controlled trials that compared monotherapy with levothyroxine (LT4) with combinations of LT4 and liothyronine (LT3) in adult patients with hypothyroidism.

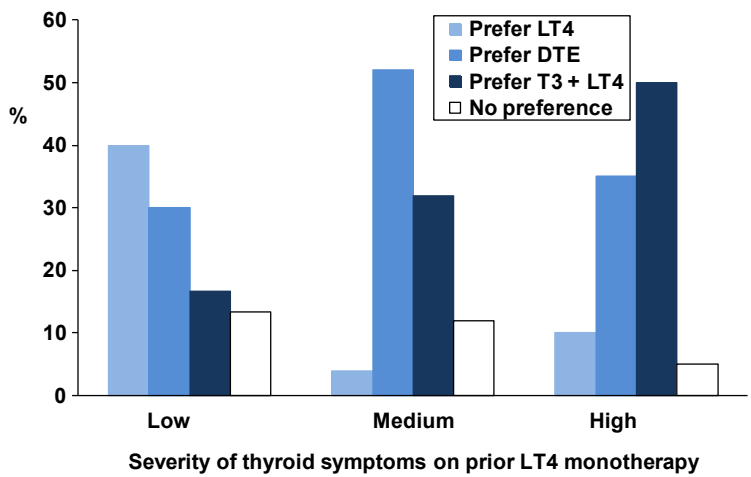
Ref	Year published	Duration (w)	N	Summary of main results
[44]	1970	8	99	18% preferred the combination vs. 33% for LT4; combination therapy was associated with troublesome side effects.
[66]	1999	5	33	Benefit for combination on 6/17 tests for cognitive function or mood and in 10/15 VAS assessments of mood and physical status; no changes in blood pressure or lipids.
[45]	2000	5	26	"Clear" improvement in cognition and mood on the combination.
[46]	2002	5	13	Trend to decreased symptoms and improved mood scores on the combination; no effect on cognition.
[58]	2003	10	110	No clear difference between LT4 and LT4 + LT3 for cognitive function, QoL, thyroid symptoms or subjective treatment satisfaction.
[59]	2003	16	46	No significant between-group differences for weight, lipids, QoL scores or neuropsychological tests.
[60]	2003	15	40	No significant between-group improvement in self-rated mood and well-being scores (Symptom Checklist-90, Comprehensive Epidemiological Screen for Depression, Multiple Outcome Study).
[47]	2004	12	23	No benefit of combination for mood and cognition scores.
[48]	2004	16	40	No additional effect of the combination on mood or well-being scores in patients with depressive symptoms on stable LT4.
[49]	2005	52	697	Transient improvement in QoL questionnaire scores at 3 months for the combination, but no sustained effect on these or on symptoms at 12 months.
[61]	2005	15	141	41.3% (10:1) and 52.2% (5:1) preferred the combination vs. LT4 alone (29.2%; p=0.024); this was the primary outcome. No difference for QoL questionnaires or neurocognitive tests.
[50]	2005	24	58	LT4 was associated with "unphysiologically" high fT4 and low fT3; LT3 supplementation had little effect on fT3.
[51]	2005	15	28	No benefit for the combination on most QoL or psychometric tests; 18 preferred the combination vs. 2 for LT4 alone.
[62]	2005	6	27	No between-group difference for fatigue, depression, working memory.

Ref	Year published	Duration (w)	N	Summary of main results
[52]	2009	16	71	Small reduction in anxiety/insomnia for the combination, but no between-group difference for other psychosocial scores, weight, heart rate, blood pressure and lipids.
[63]	2009	12	59	Benefit for combination on 7/11 scores for QoL or depression; 49% preferred the combination and 15% preferred monotherapy (p=0.002).
[53]	2010	24	36	No between-group difference for symptoms or bone function markers; some improvement in lipids on the combination.
[64]	2016	8	32	No effect of the combination on lipids, body weight or QoL; the combination increased mean heart rate but not blood pressure.
[54]	2017	12	45	60% of patients with biochemical euthyroidism on LT4 preferred LT4 + LT3; this increased to 100% for patients with polymorphisms in *DIO2* (Thr92Ala) and MC10 (rs17606253).
[65]	2021	22	72	No between-group difference for neurocognitive, QoL, psychosocial scores or patient preferences; however, patients with the most severe symptoms had improved questionnaire scores and expressed strong preference for the combination.
[55]	2022	12	59	Improvement for the combination in 12/13 domains of the ThyPRO thyroid-specific QoL instrument questionnaire (physical, mental and social domains) in patients with symptoms despite optimised LT4.
[56]	2023	52	38	Significant improvement in diastolic function with the combination group that correlated with improvement in fT3.
[57]	2024	24	141	No difference in QoL or preference for combination therapy vs. LT4 alone.

Duration refers to randomised treatment duration in weeks. Studies in patients with central hypothyroidism and of desiccated thyroid extract are not included here.
Abbreviations: DIO2: deiodinase 2; fT3: free triiodothyronine; fT4: free thyroxine; LT3: liothyronine; LT4: levothyroxine; N: number randomised; QoL: quality of life; VAS: visual analogue scale.

Nevertheless, a 2022 meta-analysis showed that patients expressed a significant preference for LT4 + LT3 combination therapy versus LT4 alone (risk ratio 2.47; 95% confidence interval [CI] 1.31 to 4.67).[68] In one of the studies summarised in Table 2, the use of inclusion criteria requiring patients to have LT4-resistant symptoms of hypothyroidism led to the demonstration of a benefit for the combination in 12/13 domains of a thyroid-specific quality-of-life questionnaire (ThyPRO).[65] Another study asked patients to rank three study treatments in order of preference; numerically more patients allotted rank 1 (best) to LT4 + LT3 (32%) or desiccated thyroid extract (45%; this preparation also contains T4 and T3), compared with LT4 (23%), although there were no significant differences within this dataset.[64] However, when the population was stratified for the severity of residual symptoms on their prior LT4 monotherapy, those with the most severe symptoms expressed a clear and significant preference for the LT3-containing regimens (Figure 1). The highest versus lowest severity of symptoms at baseline was also associated with significant benefits for LT3 + LT4 versus LT4 monotherapy relating to scores derived from the Thyroid Symptom Questionnaire-36,

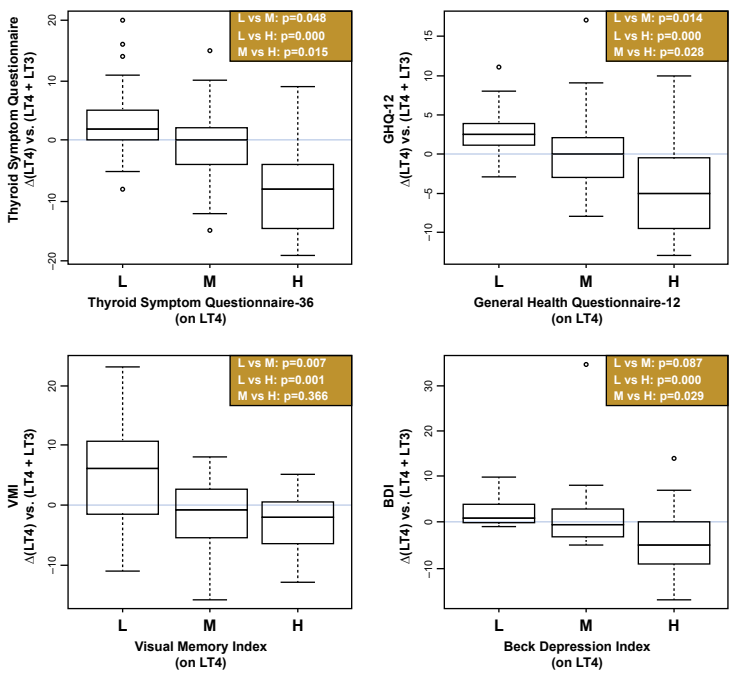
Figure 1 Patient preferences for levothyroxine (LT4), desiccated thyroid extract (DTE) or liothyronine (LT3) + LT4, according to the severity of hypothyroid symptoms during prior LT4-based monotherapy from a randomised trial in patients with hypothyroidism.



Drawn from data presented in ref 64.

the General Health Questionnaire, the Beck Depression Inventory and the Visual Memory Index (Figure 2). Finally, a study published in 2016 in 45 patients with overt hypothyroidism rendered biochemically euthyroid by LT4 monotherapy compared the effects of LT3 and placebo as add-on treatment, with patient preference as the main study outcome.[64] The impact of polymorphisms of *DIO2* (Thr92Ala) and the thyroid hormone transport protein MC10 (rs 17606253) on patient preference was evaluated. The proportions of patients preferring the combination (60% overall) were 42% for those with neither polymorphism, 63% for those with one polymorphism and 100% for those with both polymorphisms.

Figure 2 Thyroid symptoms and patient-reported outcomes according to the severity of hypothyroid symptoms during prior LT4-based monotherapy from a randomised trial in patients with hypothyroidism.



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"L", "M" and "H" refer to low, medium and high severity of hypothyroid symptoms on prior LT4 monotherapy.

Limitations of the current evidence base

An expert review from 2009 posed the question in its title, "*Do we need still more trials on T4 and T3 combination therapy in hypothyroidism?*".[72] The author's answer was "Yes – but not more of the same", acknowledging the multiple limitations inherent in the available clinical evidence base, especially:

- The short pharmacokinetic half-life of LT3 (hours), compared with the long half-life of LT4 (days), effectively precluded the establishment of a stable euthyroid-like physiological balance of T3 and T4. Wide variations in peak-to-trough levels of fT3 occur with the use of immediate-release LT3 preparations.[73] Extended-release formulations of LT3 are in clinical development, which may facilitate the establishment of biochemical euthyroidism based on fT3 levels, as well as fT4 and TSH.[74–76] Importantly, serum levels of fT3 have been shown to reflect tissue levels of fT3 sufficiently accurately that serum fT3 is suitable as a biomarker for systemic T3 status, which will aid the conduct and interpretation of future clinical trials in this area.[77]
- Trial participants were relatively unselected populations with hypothyroidism, mostly with no attempt to recruit patients likely to benefit from LT4 + LT3 combinations, such as those with documented polymorphisms of key proteins that might predispose to low T3 levels, and/or those with symptoms of hypothyroidism that were resistant to prior TSH-directed LT4 monotherapy.

A recent review of the literature echoed these concerns and concluded that clinical comparisons of LT4 with LT4 + LT3 in hypothyroidism were usually underpowered and failed to recruit sufficient patients with residual symptoms of hypothyroidism on prior LT4 monotherapy.[38] These authors also concluded that more recent studies that did recruit populations of patients with residual hypothyroid symptoms on LT4 reported benefits relating to reduced symptoms and/or improved quality of life for patients receiving the LT4 + LT3 combination rather than LT4 monotherapy, as described above.[38]

A computer modelling approach set out to define the conditions for successful intervention with LT4 and LT3.[78] The authors concluded that

the amount of residual thyroid function in each individual was key to optimising thyroid homeostasis with this combination and made recommendations on starting doses of LT4/LT3 for residual thyroid function of <10% (100 μg/10–12.5 μg), 10–20% (100 μg/7.5–10 μg) and >20% (87.5 μg/7.5 μg). Residual thyroid function appears to be another parameter that may be a source of variability in the therapeutic response to LT3-containing interventions in the management of hypothyroidism that needs to be controlled more carefully in clinical trials.

Current guidelines

Unsurprisingly, major guidelines have not provided strong support for the use of LT3 in the management of hypothyroidism, given the neutral results of the older clinical studies summarised above. Nevertheless, the European Thyroid Association (ETA) provided good evidence for the combination approach in a guideline published in 2012.[72] According to the ETA, additional LT3 may be given "*solely as an experimental treatment modality*" with specialist physician supervision for patients with hypothyroid symptoms despite good adherence to optimised LT4 therapy, with the treatment withdrawn after 3 months if there is no benefit. LT3 should be given twice daily at an LT3:LT4 ratio between 13:1 and 20:1. Pregnant women and patients with cardiac arrhythmias should not receive LT3. The stated goal of treatment is to improve or optimise levels of TSH, fT3, fT4 and the fT4:fT3 ratio, measured in a morning blood sample before taking any thyroid hormone tablets. A 2015 position statement from the British Thyroid Association supported this approach.[79]

The American Thyroid Association (ATA) 2014 guideline for the management of hypothyroidism provides a weak (due to lack of evidence) recommendation to avoid the routine use of LT3 + LT4.[80] There is also no recommendation on the suitability of add-on LT3 for patients with residual hypothyroid symptoms despite optimised LT4, and no support for the use of thyroid extracts, which contain T4 and T3. The ATA updated its guidance on the therapeutic use of LT3, with a consensus statement published in 2021.[81] The ATA recognised that LT4 monotherapy produces a lower fT3:fT4 ratio than is seen in euthyroid individuals, and that this can be corrected with LT4 + LT3 combination therapy (to some extent, at

least, with available immediate-release LT3 preparations). Importantly, the consensus recognises that generic quality-of-life instruments are likely to miss some classic hypothyroid-related symptoms, such as tiredness and emotional instability, and that thyroid-specific instruments should be used in future.

Where next?

The report from the ATA, described above, recognised that patients most likely to benefit from LT4 + LT3 combination therapy "*may not yet have been included in trials in sufficient numbers to provide adequate power for detecting a response*", particularly those dissatisfied with, or with residual symptoms on, LT4 monotherapy.[80] Accordingly, the hypothesis that adding LT3 to LT4 may improve the management of some people with hypothyroidism has not been adequately tested so far, and new and more appropriately designed trials are needed. Box 1 summarises the results of a formal consensus procedure undertaken by the ATA to provide guidance on the conduct of new clinical trials in this area that will avoid the design pitfalls described above.[80] The statement addresses the need for: recruitment of patients with residual symptoms on LT4 alone; robust, randomised trial designs; validated, thyroid-specific patient-reported outcomes as primary outcomes; and sustained-release LT3 preparations; and the potential for impact of polymorphisms in deiodinases and thyroid receptors on outcomes from thyroid hormone replacement, among other recommendations. A 2023 UK expert consensus provided similar recommendations, focussing on patients with the loss-of-function *DIO2* Thr92Ala polymorphism as a population likely to have a high symptom burden and a strong biological rationale for intervention with LT3 in addition to LT4.[76]

The results of trials designed to address these issues will finally answer the outstanding questions relating to the efficacy of additional LT3 for patients who are uncontrolled or unwell on LT4 monotherapy. A double-blind RCT in the Netherlands (T3-4-Hypo) is currently comparing LT4 + LT3 and LT4 monotherapy in adults with autoimmune hypothyroidism, ≥3 months of TSH within reference on LT4 ≥1.2 μg/kg and tiredness unexplained by other conditions.[82] Treatment is for 1 year, and the study is powered to detect treatment effects on the ThyPRO

Box 1 Abbreviated overview of key outcomes from a consensus process on the design of new trials evaluating LT4 + LT3 in the management of hypothyroidism conducted by the American Thyroid Association.

Level of consensus: **90–100%;** **70–90%;** **50–70%**

- Need for **double-blind, randomised, placebo-controlled, parallel-group** trials **of ≥1 year**
- Consider powering trials to **study effects of polymorphisms** in deiodinases and TH receptors
- Consider measuring **canonical and non-canonical TH pathways** (e.g. TG levels, cardiac function)
- **Include patients with comorbidities** so that results can be generalised to the wider population
- **Standardise interactions of patients with physicians** as this influences treatment satisfaction
- **Slow-release LT3 is needed** for future trials (for now, give immediate-release LT3 twice daily)
- Trials should use **validated thyroid-specific PROs** at baseline and be powered to detect changes (especially ThyPRO-39) as primary outcomes with patient preference as a secondary outcome
- **ThyPRO-39 or the tiredness scale of 85-item ThyPRO** can be used to measure fatigue
- **Body weight and lipids should be key metabolic outcomes** (REE is a secondary measure)
- Include **HR for cardiac efficacy**, **fluid cognition testing (NIH Toolbox) for cognition** outcomes (ideally these can measure changes in "brain fog") and **bone biomarkers for musculoskeletal outcomes** (DXA scan if the trial is >12 months' duration
- **Measure thyrotoxicosis, hypothyroid and general AE**
- **ECG monitoring at baseline** and 3-monthly intervals
- **Measure trough fT4 and total T3 and peak T3** in a nested PK study in combination trials
- **Specifically recruit patients with LT4-resistant symptoms** for trials (eligible patients should be on at least 1.2 µg/kg/day of LT4)
- Consider a **qualitative study to explain patient preferences for TH**
- Future trials should **aim at achieving a physiological fT3/fT4 ratio**
- **Consider a 2x2 factorial design** with TH and lifestyle intervention arms
- Consider including **an arm evaluating DTE**
- **Recruit patients with low T3 on LT4** and stratify results based on changes in T3 on LT4 + LT3
- **Pilot studies could explore additional outcomes of interest** within a larger trial

Consensus statements have been abbreviated and similar statements have been merged for conciseness. Colour coding for level of consensus and use of bold text is arbitrary to aid visual interpretation and applied by the author of this chapter. Statements with consensus <50% were omitted. Abbreviations – AE: adverse event(s); DTE: desiccated thyroid extract; DXA: dual-absorption X-ray absorptiometry scan; ECG: electrocardiogram; fT3: free triiodothyronine; fT4: free thyroxine; HR: heart rate; LT4: levothyroxine; NIH: National Institutes of Health; PROs: patient-reported outcomes; REE: resting energy expenditure; T3: triiodothyronine/liothyronine; TG: triglyceride(s); TH: thyroid hormone(s). Compiled from information presented in ref 80.

tiredness scale (the main study outcome), as well as the impact of the *DIO2* Thr92Ala polymorphisms and the polymorphism of the MC10 thyroid hormone transporter. Accordingly, this study incorporates the key design requirements for new trials proposed by international experts in thyroid research, as described above.

Safety of LT4 + LT3 combination therapy

Establishing the safety of a medication is paramount, especially for a lifelong condition that is prevalent in a relatively young population, some of whom will be exposed to the treatment for decades. The safety of therapy with LT4 or the LT4 + LT3 combination depends on avoiding under- or over-treatment with thyroid hormones, as per the usual management of hypothyroidism (Chapter 7 of this book summarises the clinical consequences of under- or over-treatment). Meta-analytic evidence shows that the incidence of adverse events is similar for populations receiving LT3 + LT4 and LT4 monotherapy, including for thyroid extracts.[69,83] A recent meta-analysis has revealed that treatment with LT3 is safe for patients undergoing cardiac surgery, although more data on this population are needed.[84,85]

Conclusions

T3 is the active thyroid hormone, and a consensus is building that establishing optimal homeostasis of this hormone is central to the optimal management of hypothyroidism.[86,87] The use of LT3 + LT4 in the treatment of hypothyroidism is as safe and effective as LT4 alone, as verified in a series of RCTs. However, most of these trials did not recruit the patients most likely to benefit from LT3 treatment and did not employ appropriate thyroid-specific instruments to measure effects on symptoms and quality of life. There is evidence from more recent, well-designed studies that patients with residual symptoms of hypothyroidism on optimised LT4 monotherapy express a strong preference for the LT4 + LT3

combination versus LT4 alone. A new series of clinical trials, designed using the lessons learned over the past two decades, will adequately address the hypothesis that adding LT3 to LT4 can improve symptoms and quality of life in some people with hypothyroidism.

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