

REVIEW ARTICLE

Advances in the Treatment of Hypothyroidism

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ABSTRACT

Hypothyroidism is a prevalent endocrine disorder managed primarily with levothyroxine (LT4) monotherapy. While this treatment effectively restores serum thyroid hormone levels in most patients, approximately 10–20% continue to experience persistent symptoms, such as cognitive dysfunction, fatigue, and metabolic abnormalities, despite normalized TSH levels. This review explores recent advances in hypothyroidism management, including combination therapy with LT4 and liothyronine (LT3), development of slow-release T3 formulations, and personalized treatment approaches based on genetic polymorphisms such as DIO2 Thr92Ala. Additionally, novel strategies including thyroid organoid transplantation, tissue-specific T3 delivery systems, and thyromimetic agents targeting THR β in hepatic tissue are discussed. These innovations aim to improve therapeutic efficacy, address residual symptoms, and advance individualized care in hypothyroidism. The article highlights both the scientific rationale and the clinical evidence behind these emerging therapies, signaling a paradigm shift from hormone normalization toward restoring thyroid hormone action at the tissue level.

KEYWORDS

• Hypothyroidism • Levothyroxine (LT4) • Liothyronine (LT3) • Combination therapy • Thyroid hormone replacement • T3 deficiency • DIO2 polymorphism • Slow-release T3 • Thyroid organoids • THR β agonists • Tissue-specific thyroid therapy • Desiccated thyroid extract • Personalized medicine

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INTRODUCTION

Hypothyroidism results from inadequate thyroid hormone (TH) secretion, due to genetic defects, thyroidectomy, radioactive ablation, autoimmune destruction, or accelerated TH clearance.^{1,2} Reduced TH levels impair TH signaling and gene expression, causing clinical symptoms that affect mood, cognition, and metabolism; if untreated, the condition can be life-threatening. Standard treatment aims to normalize TH levels and tissue-specific gene expression.³ Therapies have evolved from thyroid transplants and animal thyroid extracts to desiccated thyroid extracts (DTE) and eventually to synthetic levothyroxine (LT4) and liothyronine (LT3).⁴ Prior to the 1960s, dosing focused on symptom relief. The development of the TSH assay enabled more precise, lower-dose LT4 therapy.⁴ While DTE was effective, variability in potency and pharmacological inconsistencies limited its use. The discovery that T4 is converted to active T3 outside the thyroid and that LT4 monotherapy sustains plasma T3 led to its adoption as the standard therapy.⁴ LT4 is generally safe, effective, and easy to administer, enabling broad use by non-specialists.⁴ However, some patients experience persistent cognitive issues, weight management challenges,^{5–8} and elevated cholesterol despite statin use.^{9–11} Resistance to switching from DTE and reports favoring combination LT4+LT3 therapy emerged, supported by early clinical findings from the 1960s.^{12–14} Although RCTs in the 1980s–1990s confirmed both treatments were effective and safe, LT4 remained the standard. Recent meta-analyses show some patient preference for combination therapy,^{15,16} and ongoing residual symptoms plus new scientific insights in the 2010s have renewed interest in LT3 inclusion.

REVIEW

The first key finding was that maintaining normal plasma T3 is the main goal of the HPT axis.¹⁷ Genetically modified mice lacking deiodinases thus unable to convert T4 to T3—still maintained normal serum T3 by increasing thyroidal T3 output, despite elevated T4 and TSH levels. This was first observed in 2007¹⁸ and later confirmed.¹⁹ A similar pattern appears in mild to moderate iodine deficiency: low T4, elevated TSH, but normal T3.²⁰

The second discovery revealed that hypothyroid patients on LT4 with normalized TSH may still have a relative or absolute T3 deficiency. First reported in 1974²¹ and later confirmed in large studies,²² this has been overlooked by guidelines.²³ Some studies found no T3 difference between LT4-treated and control groups,²⁴ likely due to assay limitations and small effect size (~15% T3 reduction). Mechanistically, T4 normalizes TSH via pituitary feedback, but doesn't fully restore T3 in peripheral tissues, partly due to T4-induced D2 inactivation.^{25,26}

The third finding involves the DIO2 Thr92Ala polymorphism. Patients with this variant had better outcomes with LT4+LT3 than with LT4 alone,²⁷ correlating with ~40% reduced D2 activity.^{28,29} Mouse models confirmed reduced brain T3 signaling and responsiveness to combination therapy. While not all studies replicated this,³⁰ larger recent ones support its role in reduced LT4 efficacy, indicating that genetics and comorbidities may contribute to persistent symptoms.³¹

Today, leading professional societies the American, British, and European Thyroid Associations and the Society for Endocrinology acknowledge that LT4 therapy alone leaves 10–20% of patients with residual hypothyroid symptoms.^{32,33} They also agree that T3 levels may remain suboptimal in some patients despite normalized TSH and free T4 levels. These important considerations have not been emphasized enough in clinical practice.

In the absence of definitive clinical trial data for these patients, guidelines recommend confirming the diagnosis and ruling out comorbidities that could mimic hypothyroid symptoms.^{34,35} If persistent symptoms remain unexplained, a trial of LT4+LT3 therapy is advised.³² Consequently, the number of patients receiving combination therapy in the United States has doubled over the past decade. Today, approximately 1.4 million people use desiccated thyroid extract (DTE), and 400,000 use synthetic LT4+LT3 combinations.³⁶

This article reviews the latest research on hypothyroidism treatment. A literature search was conducted in PubMed and Google Scholar using the keywords “liothyronine,” “desiccated thyroid extract,” “thyroid organoids,” and “slow-release T3,” covering the period from January 2020 to February 2024. Older literature (1850–1980) from major endocrinology texts

was also reviewed. Readers seeking more comprehensive insights are referred to other recent reviews.^{37–41}

THERAPY WITH LT4

For over five decades, LT4 has been the standard of care for hypothyroidism.³⁹ Although regulatory bodies such as the FDA did not require randomized controlled trials (RCTs) for its full approval, substantial evidence confirms that LT4 restores clinical and biochemical euthyroidism in most patients. Accordingly, LT4 should continue to be regarded as the first-line treatment.³

However, LT4 is not universally effective at restoring true clinical euthyroidism. Despite achieving normal TSH levels, some patients continue to experience symptoms.³² Given the high prevalence of hypothyroidism, even a small proportion of treatment-resistant cases affects a large number of individuals. For these patients, alternative or adjunctive treatment strategies are needed and discussed in this review.

THERAPY WITH LT4+LT3

The ideal candidate for combination therapy is a patient who has been treated with LT4, maintains normal serum TSH levels, but continues to experience residual symptoms of hypothyroidism.³² Detailed inclusion and exclusion criteria, as well as practical strategies for initiating combination therapy, have been discussed elsewhere.³⁴

The core principle in transitioning from LT4 monotherapy to LT4+LT3 therapy involves reducing the LT4 dose and introducing an appropriate dose of LT3. Various T4:T3 ratios have been explored, and dosing formulas have been developed to guide initial therapy.^{35,42} A reasonable starting point is a dose ratio approximating the physiological secretion by the human thyroid, typically ranging from 13:1 to 20:1. For example, if a patient is stable on 100 µg of LT4 daily, the corresponding LT3 dose would be calculated as $100/20 = 5$ µg. This LT3 dose should be split into two daily doses one in the morning and the second approximately 8 hours later, or 1–2 hours before dinner. The new LT4 dose would be adjusted using the equation: $100 - (5 \times 3) = 85$ µg, which is commonly rounded to 88 µg. Thus, the revised regimen would be LT4 88 µg daily plus LT3 2.5

µg twice daily.

In clinical practice, such formulas serve as an initial guide but are typically followed by minor dose adjustments based on clinical response and biochemical markers (e.g., serum TSH and T3), which should be maintained within the normal range.

Effectiveness

Both synthetic LT4+LT3 and desiccated thyroid extract (DTE) normalize serum free T4 and T3 levels, correcting the imbalance often seen with LT4 monotherapy, which raises T4 but leaves T3 low. Hormone doses can be adjusted to achieve this without suppressing TSH.^{43–47} However, whether this improves residual symptoms remains debated.

Over 50 years of RCTs show both LT4 and LT4+LT3 effectively relieve overt symptoms and normalize TSH, though this nuance is often overlooked in practice. A meta-analysis of 18 RCTs found no significant differences in clinical outcomes, quality of life, psychological distress, or fatigue, but did note a statistically significant patient preference for combination therapy.^{15,16} A key limitation is the underrepresentation of symptomatic LT4-treated patients.³² A crossover RCT involving 75 such patients found no overall difference among LT4, LT4+LT3, and DTE, but subgroup analysis showed that those with high symptom burden improved with combination therapy or DTE.⁴³ An open-label study also supported combination therapy in this population.⁴⁹

Pharmacokinetics and Safety of T3 Therapy

Synthetic T3, whether alone or in DTE, is rapidly absorbed and peaks 2–3 hours post-ingestion, with a half-life of 12–24 hours, leading to rapid serum decline.⁴⁸ Dose-dependent T3 fluctuations remain within the normal range.⁵⁰ Despite concerns about long-term safety, no evidence links LT3-containing therapy with adverse cardiovascular or skeletal outcomes when TSH is normal. A meta-analysis of 18 RCTs reported similar adverse event rates between LT4 and LT4+LT3 groups.¹⁶

Long-term safety data from a Scottish cohort (1997–2014) found no increased risk of mortality, cardiovascular disease, atrial fibrillation, or fractures among LT3 users (n=400) versus 34,000 LT4 monotherapy users.⁵¹ Similar results were seen in Sweden (52), though a Korean study suggested higher

heart failure and stroke risk, but lacked key dosing and TSH data.⁵³ Other RCTs also found no significant differences in adverse events among LT4, LT4+LT3, and DTE groups.^{43–46}

However, current T3 formulations cause sharp serum fluctuations, prompting the ATA to call for improved slow-release options. Matrix-based tablets using excipients like methylcellulose modestly delayed absorption (~5 h Tmax) and reduced peak T3 (~9%) but failed to sustain levels.^{54–56} Commercial “slow-release” LT3 lacks clinical validation.

Novel T3 prodrugs offer promise. T3-sulfate (T3-S), once thought unabsorbable, is now known to be reactivated in the liver and gut, leading to prolonged T3 effects in rats and humans, with plateaus lasting up to 48 hours.^{57–61} Combining T3-S with LT4 maintained stable T3 and a physiological T4:T3 ratio without adverse effects.⁶²

Poly-zinc-LT3, a mucoadhesive zinc-T3 complex, releases T3 gradually via hydrolysis. In animals, it delayed and blunted T3 peaks (~30% lower Cmax, ~6h delayed Tmax) and showed extended action.⁶³ A first-in-human trial confirmed its slower, sustained release compared to LT3.⁶⁴

Regenerative Approaches

Early hypothyroidism treatments involved thyroid transplantation heterologous and autologous which showed temporary benefit due to high thyroid hormone (TH) content but lacked lasting efficacy.⁴ Advances in organoid culture now enable in vitro growth of functional thyroid tissue, paralleling progress in liver, pancreas, and skin regeneration. Using mouse embryonic stem cells (ESCs), researchers induced lung and thyroid progenitors by modulating pathways like TGF- β , BMP, and FGF.⁶⁶ Overexpression of NKX2.1 and PAX8 led to differentiation into follicular cells expressing TSH receptor, sodium/iodide symporter, and thyroglobulin.⁶⁷ These cells self-organized into 3D follicles and secreted T4 post-transplantation in hypothyroid mice, lowering TSH. Mature thyroid follicular organoids from mouse ESCs restored hormone levels and rescued hypothyroid mice.⁶⁸ Human ESC-derived thyroid organoids transplanted into athyreotic mice similarly restored TH levels,⁶⁹ confirming therapeutic potential.

Another strategy uses immunoprotective

encapsulation: porcine thyroid cells encapsulated in alginate-poly-L-ornithine-alginate microcapsules exchanged TH and TSH while blocking immune responses.⁷⁰ Stimulated cells formed 3D follicles and released TH, supporting xenotransplantation without immunosuppression. This may extend to human thyroid organoids, though long-term viability remains a challenge, as seen in islet transplantation, due to persistent proinflammatory cytokines.^{71,72} Addressing this is vital for future regenerative therapies.

Tissue-Specific Restoration of T3 Signaling

While hypothyroidism is systemic, TH action can be tissue-specific. A high-fat diet reduces transcriptional regulators critical for T3 signaling in the liver.^{73–75} Liver biopsies from obese individuals show downregulation of T3-responsive genes,⁷⁴ a clinically relevant finding given TH's key role in hepatic metabolism, including autophagy, β -oxidation, and mitochondrial function.⁷⁶

Impaired hepatic TH signaling may drive NAFLD pathogenesis through lipid buildup and fibrosis. Supporting this, low-dose LT4 lowers intrahepatic lipids in type 2 diabetes and metabolic fatty liver disease,⁷⁷ while TH resistance worsens liver lipid profiles.⁷⁸

The liver predominantly expresses THR β , prompting development of thyromimetics synthetic T3 analogs targeting THR β to restore hepatic signaling with minimal systemic effects.⁷⁹ VK2809 and resmetirom (MGL-3196) have shown promise: VK2809 enhances autophagy and lipid oxidation in mice,⁸⁰ and resmetirom reduces liver fat in humans over 12–36 weeks, offering potential for NAFLD/NASH treatment.⁸¹

Another strategy, ligand-directed delivery, uses a glucagon-T3 hybrid to target T3 to the liver via glucagon receptors.⁸² In obese mice, this conjugate improved hyperlipidemia, steatohepatitis, atherosclerosis, glucose intolerance, and obesity, suggesting dual-hormone conjugates could enable organ-specific T3 effects.

OTHER EMERGING TRENDS INCLUDE

Personalized (Precision) Medicine

Genetic testing (e.g., DIO2 polymorphisms) may help identify patients who respond better to combination therapy.

Pharmacogenomics is being explored to tailor treatment based on individual variations in deiodinase activity, receptor sensitivity, and hormone transport.

Novel Drug Delivery Systems

Slow-release LT3 (e.g., sustained-release liothyronine) is under development to improve tolerability and mimic natural diurnal rhythm.

T3 prodrugs and nanoparticle formulations aim to enhance bioavailability and tissue targeting.

Alternative and Adjunctive Therapies

Nutritional optimization (e.g., adequate iodine, selenium, iron, and vitamin D) is recognized as critical for thyroid function.

Emerging interest in gut microbiome's role in thyroid hormone metabolism and absorption.

DISCUSSION

This comprehensive review examines evolving therapeutic strategies for hypothyroidism, particularly addressing the limitations of standard levothyroxine (LT4) monotherapy, which fails to fully restore triiodothyronine (T3) levels in 10–20% of patients despite normalized TSH. Key scientific discoveries underpinning this shift include:

Homeostatic T3 regulation by the HPT axis, independent of T4/TSH.

Persistent T3 deficiency in many LT4-treated patients.

DIO2 Thr92Ala polymorphism, which impairs T4-to-T3 conversion and is associated with better outcomes from combination therapy (LT4+LT3).

The document reviews combination therapy approaches using synthetic LT4+LT3 or desiccated thyroid extract (DTE), highlighting patient preference and comparable safety profiles. It also explores the pharmacokinetics and safety of these therapies, noting no major adverse cardiovascular or skeletal effects when TSH remains within range.

Significant focus is placed on the development of slow-release T3 formulations, such as:

T3-sulfate (T3-S): reactivated slowly by liver enzymes and gut microbiota.

Poly-zinc-LT3: a novel prodrug offering more stable T3 serum levels.

The review further discusses regenerative therapies, such as:

Stem cell-derived thyroid organoids capable of hormone production.

Microencapsulation technologies that allow immune-isolated hormone delivery.

Finally, tissue-specific T3 restoration strategies are covered, especially in the liver using THR β -selective thyromimetics (e.g., VK2809, resmetirom) and glucagon-T3 conjugates that target metabolic diseases like NAFLD.

The treatment landscape for hypothyroidism is evolving, driven by new insights into thyroid hormone physiology and the clinical limitations of levothyroxine (LT4) monotherapy. While LT4 remains the cornerstone of therapy, emerging evidence suggests that it may not fully restore triiodothyronine (T3) levels or thyroid hormone action in a subset of patients. This discrepancy is increasingly acknowledged in updated clinical guidelines, reflecting a shift toward a more nuanced and individualized approach to treatment.

Three key discoveries have contributed to this paradigm shift. First, studies in genetically modified mice and humans indicate that serum T3 homeostasis is tightly regulated by the hypothalamus-pituitary-thyroid (HPT) axis, sometimes at the expense of elevated TSH and T4 levels. Second, clinical and biochemical findings demonstrate that many LT4-treated patients exhibit relative or absolute T3 deficiency, despite having normal serum TSH. This is particularly relevant for patients with polymorphisms such as DIO2 Thr92Ala, which impairs local T4-to-T3 conversion and may explain persistent symptoms in certain individuals. These insights challenge the traditional reliance on TSH as the sole biomarker for therapeutic adequacy.

In response, combination therapy using LT4 and liothyronine (LT3) has gained renewed interest. Although randomized controlled trials (RCTs) comparing LT4+LT3 to LT4 alone generally show equivalent biochemical outcomes and symptom resolution, patient preference consistently favors combination therapy. Importantly, these trials may be underpowered to detect differences in symptomatic subpopulations. Stratified analyses suggest that patients with persistent symptoms on LT4 derive the greatest benefit

from combination regimens, including desiccated thyroid extract (DTE), which naturally contains T3.

Safety concerns surrounding T3 therapy especially rapid fluctuations in serum T3 have prompted efforts to develop slow-release T3 formulations. Novel approaches such as T3-sulfate and poly-zinc-LT3 demonstrate promising pharmacokinetics, offering more stable serum T3 levels and potentially improved clinical outcomes without increasing cardiovascular or skeletal risks. These innovations represent critical steps toward safer, more physiological T3 replacement.

Beyond hormone replacement, regenerative and tissue-targeted therapies signal the next frontier in hypothyroidism management. Thyroid organoids derived from stem cells have demonstrated the ability to restore hormone production in animal models, providing a proof-of-concept for future cell-based therapies. Concurrently, liver-specific thyromimetics (e.g., VK2809, resmetirom) and hormone conjugates (e.g., glucagon-T3 hybrids) are being developed to selectively restore T3 signaling in metabolically relevant tissues while minimizing systemic side effects. These tissue-targeted strategies are particularly relevant in comorbid conditions such as nonalcoholic fatty liver disease (NAFLD), where impaired T3 signaling contributes to disease pathology.

CONCLUSION

LT4 treatment for patients with hypothyroidism does not fully restore normal thyroid hormone (TH) homeostasis. While this is not a problem for most patients, about 10–20% do not fully benefit from LT4 treatment and may show improvement with a combination of LT4 and LT3. LT3 is commercially available as a sodium salt, allowing for rapid duodenal absorption. More than 20 prospective randomized controlled trials (RCTs) comparing LT4+LT3 with LT4 alone have demonstrated that the combination is both safe and effective. Its safety has also been confirmed in retrospective, population-level analyses.

In response to professional guidelines, pharmaceutical companies are actively developing slow-release formulations of LT3 and exploring new strategies to enhance

T3 signaling in a tissue-specific manner. Additionally, thyroid organoids capable of restoring TH levels in thyroidectomized mice and suitable for transplantation have been developed.

While these emerging approaches and technologies are both exciting and promising, it is important to remember that rapidly absorbed LT3 is already commercially available and, as supported by current clinical guidelines, can be used safely to improve the lives of millions of hypothyroid patients who continue to experience symptoms despite LT4 therapy.

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