Review Article

Role of triiodothyronine in hypothyroidism: Consensus statement from the Indian Thyroid Society

ABSTRACT

Hypothyroidism is a chronic endocrine disorder resulting from the deficiency of thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Globally, its prevalence is gradually increasing, affecting up to 5% of the general population, with an additional 5% estimated to remain undiagnosed. In India, the prevalence of hypothyroidism is more than twice that reported in Western countries. A large cross-sectional Indian study reported an overall prevalence of 10.95%, with 8.02% of patients having subclinical hypothyroidism. The clinical manifestations are diverse and often nonspecific, including fatigue, weight gain, depression, poor concentration, and menstrual irregularities. If untreated, hypothyroidism can lead to cardiovascular disease and increased mortality. Levothyroxine (LT4) monotherapy remains the cornerstone of treatment, aimed at restoring euthyroidism and alleviating symptoms. However, nearly one-third of patients continue to experience residual symptoms despite achieving biochemical targets, raising interest in combination therapy with LT4 and liothyronine (LT3). In addition, LT3 plays a role in specific clinical contexts such as preparation for radioactive iodine ablation in thyroid cancer and management of myxedema coma. This consensus aims to update recommendations for the optimal management of patients with hypothyroidism who experience suboptimal outcomes with LT4 monotherapy and may benefit from LT3 therapy. The document, developed by experts from the Indian Thyroid Society through extensive review and deliberation, provides practical, evidence-based guidance to help clinicians achieve improved therapeutic outcomes and enhanced quality of life for their patients.

Keywords: Hypothyroidism, Indian Thyroid Society, triiodothyronine

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INTRODUCTION

Hypothyroidism is a chronic condition associated with the deficiency of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]).[1] Globally, the prevalence of hypothyroidism is increasing gradually.[2] Up to 5% of the general population is affected by hypothyroidism, with an additional estimated 5% remaining undiagnosed.[1] The

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prevalence of hypothyroidism in India is over twice as high as in Western countries.[3] The data from a cross-sectional study conducted in India revealed that the overall prevalence of hypothyroidism was 10.95% with 8.02% of patients diagnosed with subclinical hypothyroidism.[4]

The symptoms of hypothyroidism are generally nonspecific and diverse. They include mild-to-moderate weight gain, fatigue, poor concentration, depression, and menstrual irregularities. If left untreated, hypothyroidism can lead to serious consequences such as cardiovascular disease and increased mortality.[1]

The goal of treatment is to relieve symptoms and normalize thyroid hormone levels, with levothyroxine (LT4) being the primary medication used to manage hypothyroidism.[1,5] Despite appropriate diagnosis and treatment, nearly one-third of patients with hypothyroidism continue to experience symptoms reminiscent of hypothyroidism, impairing their quality of life. Therefore, optimizing LT4 therapy and identifying those who may benefit from a combination of LT4 and liothyronine (LT3) therapy is crucial.[1] In addition to the growing interest in using combination therapy with LT4/LT3 for hypothyroid patients, LT3 is also employed in the preparation of postoperative thyroid cancer patients before radioactive iodine ablation (RAI).[5]

Objective

The aim of this consensus is to update recommendations for the appropriate management of a subset of hypothyroid individuals who experience suboptimal outcomes on LT4 monotherapy and may benefit from liothyronine (LT3) therapy. The use in special situations like myxedema coma is also discussed.

METHODS

The sections and recommendations addressed in the consensus were formulated based on insights from previous trials and guidelines. This document provides much-required insights and useful, practical, and accurate guidance that aids a practicing clinician. The draft was prepared meticulously by the members of the Indian Thyroid Society with a series of reviews and modifications.

A well-defined grading system [Table 1] for the critical appraisal of evidence and grading strength of recommendations was followed.

Table 1: Level of evidence and grading strength of recommendations

	Description
Level of evidence	
Level A	Data derived from multiple randomized trials or meta-analyses or evidence-based clinical practice guidelines
Level B	Data derived from a single randomized trials or large nonrandomized trial
Level C	The consensus of opinion of experts or small studies, retrospective studies or registries, or narrative/ literature reviews
Level D	Data derived from clinical experience
Class of recommendations	
Class I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful, or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established, and recommendations may be considered
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful, or effective, and in some cases may cause harm. Not recommended

CLINICAL QUESTION: WHAT IS THE ROLE OF LT3 IN THE MANAGEMENT OF HYPOTHYROIDISM IN THE BELOW-MENTIONED CLINICAL SCENARIOS?

Refractory hypothyroidism

Primary hypothyroidism is considered treatment refractory when residual symptoms of hypothyroidism or biochemical signs of hypothyroidism (level of thyroid-stimulating hormone [TSH] above the target range, usually 5.5 mIU/L) persist despite increasing dosages of LT4 >1.9 µg/kg/day.[6,7] Approximately 15%–20% of patients taking L-T4 experience refractory hypothyroidism.[8,9]

In such a situation, increasing the thyroxine dose further may not always resolve the issue. In addition, supratherapeutic doses can lead to cardiovascular and other side effects. If unexpectedly high doses of thyroxine are required, then the first step in the evaluation is to check the compliance of the patient. If the patient adheres to the prescribed treatment, a levothyroxine absorption test to differentiate between true malabsorption and pseudo-malabsorption can be included here. However, the dilemma remains as to whether adding T3 would help in cases of true malabsorption. Other potential causes of refractory hypothyroidism, such as switching to a generic levothyroxine with different bioavailability, drugs that treat gastrointestinal conditions/dietary considerations, pregnancy, concomitant

Table 2: Recommendations for the use of T3

Guidelines	Recommendation/consensus statement
2023 Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for Endocrinology consensus statement[14]	For patients with confirmed overt hypothyroidism and experiencing ongoing symptoms despite sufficient LT4 treatment, and where other potential comorbidities have been ruled out, a trial of combined LT3 and LT4 therapy might be considered
2014 Guidelines for the Treatment of Hypothyroidism Prepared by the American Thyroid Association[15]	There is currently insufficient evidence to support the routine use of a trial of a combination of LT4 and LT3 therapy
2013 Clinical practice guidelines for the management of hypothyroidism: Thyroid consensus – Brazil[16]	If symptoms of hypothyroidism continue despite proper treatment, it is important to rule out other potential comorbidities. Increasing the LT4 dosage or using a combination therapy with triiodothyronine is not advised
2012 ETA Guidelines: The Use of LT4/LT3 in the Treatment of Hypothyroidism[11]	The LT4/LT3 combination therapy should be regarded as an experimental treatment option

LT4: Levothyroxine, ETA: European Thyroid Association, LT3: Liothyronine, T3: Triiodothyronine

gastrointestinal diseases, and changes in body weight/body mass, should be investigated.[10]

Poor conversion of T4 to T3 is one of the causes of refractory hypothyroidism. It has been suggested that a genetic variation in deiodinase D2 may help to explain why some patients who do not achieve control of their hypothyroidism with LT4 therapy respond better to the LT4/LT3 combination therapy.[6,10] This alteration was observed in 16% of the "poor converters."[10,11]

In 2012, *European Thyroid Association* (ETA) released a guideline on the use of LT4/LT3 in the treatment of hypothyroidism, which revealed the data on the preference of patients for either T4 monotherapy versus LT4/LT3 combination therapy in a randomized control, crossover, or parallel study designs. The results indicated that 27% of participants preferred LT4 monotherapy, 25% had no preference, and 48% favored the LT4/LT3 combination therapy. Patient preference for combination therapy was linked to improvements in quality of life, cognition, mood, and symptoms.[11]

A systematic review and meta-analysis of seven blinded randomized controlled trials involving 348 individuals with hypothyroidism showed that approximately half of the participants reported preferring combination L-T3 and L-T4 therapy compared to L-T4 alone.[12] Another systematic review and meta-analysis found no significant advantage in improving psychological health with T4 + T3 combination therapy compared to T4 monotherapy.[13]

Table 3: Side effects associated in both the groups[31]

Side effects	THW (%)	rhTSH (%)	*P*
Leukopenia	28	30	0.61
Thrombocytopenia	0	10	0.37
Xerostomia	12	0	0.20
Restrictive pulmonary disease	2	0	0.73

rhTSH: Recombinant human thyrotropin, THW: Thyroid hormone withdrawal

The recommendation by ETA 2012 states that LT4/LT3 combination therapy might be considered as an experimental approach in compliant LT4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously been given support to deal with the chronic nature of their disease and associated autoimmune diseases have been ruled out. It also provides guidance on long-term therapy by adding that a period of 3 months for the trial seems reasonable in view of the finding that any improvement upon LT4/LT3 combination treatment initiation in the randomized clinical trials was observed in this time frame. If LT4/LT3 combination therapy is effective and well-tolerated, it may be continued beyond the trial period.[11]

Various guidelines have also reached a consensus on the use of LT3 therapy in refractory hypothyroidism [Table 2].

Consensus statement

There is a limited evidence from randomized controlled trials and long-term studies demonstrating that the combination therapy is superior to LT4 alone, however majority of the patients have preferred the LT4/LT3 combination therapy. Hence, a trial of combined LT3 and LT4 therapy may be considered in patients on long-term levothyroxine therapy with ongoing symptoms and where other comorbidities have been ruled out. (A/IIb)

Preoperative management of hypothyroidism

Patients with hypothyroidism may occasionally need surgery.[17] Low levels of serum thyroid may affect clinical outcomes in the perioperative period.[18] However, limited data is available on the use of oral T3 in this context. For patients with severe hypothyroidism requiring urgent or emergency surgery, perioperative treatment with oral T4 and T3, alone or in myxedema coma, the combination with glucocorticoids is generally administered. Elective surgeries should be postponed until these patients achieve euthyroid status, which typically requires six weeks to two months of oral thyroxine therapy.[17]

In a case-based study conducted in India, 12 patients with hypothyroidism and severe neurological symptoms who were planned for semiurgent neurosurgical procedures within a week of presentation were administered 100 µg T4 orally daily. Moreover, the patients were managed perioperatively by

administering oral T3 in addition to oral T4. Oral T3 was given at a dosage of 20 μg, three times daily, for 5 days before the surgery and continued at the same dosage for 3 days following the surgery. After administering the medication, the authors did not observe any perioperative complications related to low thyroid hormone levels. In addition, all patients remained hemodynamically stable during the perioperative period, and the authors did not observe any adverse effects of cardiovascular stimulation or angina. The study demonstrated that patients with hypothyroidism can be considered for semiurgent surgeries with adequate perioperative oral T3 supplementation along with oral T4 without any perioperative complications.[17]

A Class I Level D recommendation by a 2007 guideline for perioperative evaluation revealed that:[19]

- Elective surgery should only take place when the thyroid function of the patient is normal
- The half-lives of T4 and T3 are 7 days and 1.5 days, respectively. Therefore, a patient on T4 can skip their dose on the day of elective surgery, while a patient on T3 should take their medication as scheduled
- For patients with severe hypothyroidism or myxedema coma undergoing urgent surgeries.
    - Administer 40 μg of IV T3 or 10–25 μg of oral T3 at 8 h intervals before surgery
    - For maintenance, administer oral LT3 at a dose of 10–20 μg every 24 h.

Palace conducted research on perioperative management of thyroid dysfunction in 2017, which concluded with the following recommendation:[20]

- Nonemergent surgery should be postponed until the hypothyroidism has been treated
- For patients suspected of having myxedema coma who need urgent surgery, it is crucial to quickly normalize thyroid hormone levels by concurrently administering LT3 and IV LT4 (loading dose of 200–500 μg followed by 50–100 μg IV daily).

A 2022 literature review conducted by Manzullo and Ross and Malhotra and Bhadada revealed that IV LT3 should be administered concurrently with LT4 therapy at a dose of 5–20 μg. Subsequently, LT3 at a dose of 2.5–10 μg should be given every 8 h, adjusted according to the patient's age and any existing cardiac risk factors.[21,22]

Consensus statement

No data is available regarding the optimal dose of T4 and T3 to be used in this situation in the perioperative period in people who require emergency surgery with suboptimally controlled hypothyroid status. If initiating thyroid replacement therapy for the first time, It may be prudent to initiate thyroid hormone therapy with low doses of T3 (5-10 mcg every 8 hours IV or PO). (C/IIb)

It is suggested to start combination therapy in an L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight (L-T4 once daily, and the daily L-T3 dose in two doses)[11]

Myxedema coma

Myxedema coma is a life-threatening condition caused by prolonged hypothyroidism, where the body's ability to maintain homeostasis is severely impaired. Despite early diagnosis and treatment of myxedema coma, the mortality rate varies significantly, ranging from as high as 60% to as low as 20%–25% even when advanced intensive care is available.[23] The underlying cause of myxedema coma is the reduction of intracellular T3 secondary to hypothyroidism, leading to hypothermia and decreased cardiac function.[24] Therefore, timely diagnosis and treatment are crucial for managing myxedema coma effectively.[25] The management of myxedema coma requires a multidisciplinary treatment plan, including respiratory support, circulatory stabilization, adrenocortical hormone therapy, and thyroid hormone replacement. Of these treatments, thyroid hormone replacement therapy with LT4 is particularly crucial.[26] Administering LT4 alone resulted in a steady and smooth, although slower, onset of action with a low risk of adverse effects. In contrast, LT3 had a quicker onset, reaching peak levels within 2–4 h after administration. Its 10–20-fold higher affinity for the nuclear receptor compared to T4 may be crucial for enhancing survival rates.[25,26]

A retrospective observational study was conducted among patients diagnosed with myxedema coma. The research focused on the mortality rate among patients receiving the LT4/LT3 combination ($n = 120$) vs. LT4 alone ($n = 11$). The maximal per-day dosage of LT4 was categorized into <100, 100–199, and ≥ 200 μg, and the maximal per-day dosage of LT3 was categorized into <20, 20–49, and ≥ 50 μg. The results from the research revealed that patients treated with a combination therapy experienced lower mortality rates compared to those on LT4 alone; however, this difference was statistically insignificant (18.2% vs. 30.0%, $P = 0.66$). The results from the research could not provide recommendations regarding the dosage and use of LT4 alone or both LT4 and LT3 for managing myxedema coma due to the small sample size and unknown severity of the myxedema coma.[27]

In a case series of data from 8 patients, Yamamoto *et al*., treated the first 3 myxedema coma patients with high-dose IV LT3 and the other 5 patients with a smaller amount of either LT3 or LT4 (LT4 ≥ 500 μg/d or LT3 ≥ 75 μg/day). The results revealed that two of three patients treated with high-dose LT3 died, whereas the other five who were treated with smaller doses of LT3 or LT4 survived. The authors concluded that high doses of LT3 (≥75 μg/day) were associated with fatal outcomes.[28]

In a case study, an 84-year-old Japanese man diagnosed with myxedema coma was promptly administered intensive supportive care and a combined treatment of 200 μg LT4 and 50 μg LT3 for the first 5 days of hospitalization. This was then switched to LT4 monotherapy at a daily dose of 150 μg. The treatment approach successfully normalized thyroid hormone levels within a few days without leading to any cardiovascular disease. The case highlighted the effectiveness of combining LT4/LT3 in treating myxedema coma.[25]

In another case study, a patient experienced presyncope alongside generalized fatigue, reduced appetite, lack of interest in usual activities, and slowed speech and movement. A comprehensive examination identified pituitary dysfunction, leading to the diagnosis of myxedema coma and adrenal crisis. The patient was treated with a regimen of 300 μg IV LT4 and 5 μg IV LT3 every 8 h, resulting in complete symptom resolution. There were no observed endocrinological complications, and then the patient was advised to continue with oral-only LT4. This combined treatment approach effectively managed the myxedema coma.[29]

Guidelines for the treatment of hypothyroidism, prepared by the American Thyroid Association Task Force on thyroid hormone replacement, revealed a weak recommendation with low-quality evidence that oral LT3 may be administered in addition to LT4. High doses should be avoided due to the link between elevated serum T3 levels during treatment and increased mortality. In patrients with myxedema coma the treatment should include a loading dose of 5–20 μg LT3, followed by a maintenance dose of 2.5–10 μg every 8 h. A low dosing range can be chosen for patients who are elderly, as well as those with a history of coronary artery disease or arrhythmias. Therapy should be maintained until the patient shows signs of recovery or demonstrates improvement in clinical parameters.[15] In another 2013 clinical practice guidelines for the management of myxedema coma , it was suggested to add 10–20 μg bolus of T3 to the T4 therapy followed by 10 μg of T3 every 4–6 hourly.[16]

Consensus statement

LT3 to be administered at a loading dose of 5–20 μg, followed by a maintenance dose of 2.5–10 μg every 8 hours, until the patient shows signs of recovery.

Administration of LT3 in addition to LT4 therapy in patients diagnosed with myxedema coma resulted in normalization of thyroid hormone levels and resolution of symptoms, leading to successful management of the disease. (D/IIa)

Administration of LT3 therapy in patients diagnosed with myxedema coma was associated with lower mortality rates. However, a dose of >75 μg/day may be associated with fatal outcomes. (D/IIa)

LT3 in thyroid hormone withdrawal as preparation for radioactive iodine ablation

RAI is administered following a total thyroidectomy to eliminate any normal thyroid remnant and microscopic residual disease.[30] The administration of RAI required TSH stimulation, which could be accomplished through one of two methods: (i) withdrawing LT4 and LT3 to induce endogenous TSH elevation (thyroid hormone withdrawal [THW]) or (ii) using recombinant human TSH (rhTSH) for exogenous stimulation.[31] However, the effectiveness is unclear.

A retrospective study compared the effectiveness and side effects of THW versus rhTSH preparation for RAI therapy in metastatic differentiated thyroid carcinoma (DTC). The study included 56 patients with RAI-avid distant metastases of DTC. These patients were treated with either rhTSH (n = 15) or THW (n = 41) and were monitored for a period ranging from 72 months. In the THW group, LT4 was discontinued approximately 6 weeks before treatment. After total thyroidectomy, patients in this group were given LT3 for 4 weeks and then withdrawn from it 2 weeks before RAI therapy. The results of the research revealed that complete response, stable disease, progressive disease, and progression-free survival were similar between the two groups. The comparison of recombinant human thyrotropin with thyroid hormone withdrawal for radioactive iodine ablation shows no significant difference in treatment outcomes. The complete response rates were similar (hazard ratio 0.97, confidence interval 0.08–11.42, p = 0.982). There was a non-significant trend toward more stable disease with recombinant human thyrotropin (hazard ratio 3.22, confidence interval 0.79–13.18, p = 0.104). The risk of progressive disease appeared lower (hazard ratio 0.26, confidence interval 0.52–1.26, p = 0.094), and progression-free survival showed a possible benefit (hazard ratio 0.41, confidence interval 0.14–1.23, p = 0.112), but none of these findings reached statistical significance.. Moreover, the rate of side effects

(leukopenia, thrombocytopenia, xerostomia, and restrictive pulmonary disease) after RAI was also similar between the two groups [Table 3]. In patients with metastatic DTC, those who were pretreated with THW achieved similar benefits from RAI therapy as those who were pretreated with rhTSH.[31]

A similar result was obtained from another meta-analysis of randomized controlled trials, where six trials with a total of 1660 patients were included in a study to evaluate the effectiveness of THW versus rhTSH prior RAI in thyroid cancer. The standard protocol for THW includes stopping LT4 therapy and switching to LT3 therapy for 2–4 weeks, followed by withdrawal of LT3 for 2 weeks, or discontinuing LT4 therapy for 2–3 weeks without using LT3. Ablation success was defined as a thyroglobulin (Tg) cutoff of 1 ng/mL (risk ratio [RR], 0.99; 95% confidence interval, 0.96–1.03) or a Tg cutoff of 1 ng/mL plus imaging modality (RR 0.97; 0.90–1.05). The results of the research revealed that there were no significant differences when ablation success was defined as a Tg cutoff of 2 ng/mL (RR 1.03; 0.95–1.11) or a Tg cutoff of 2 ng/mL plus imaging modality (RR 1.02; 0.95–1.09).[32]

Various guidelines throw light on LT4 withdrawal and the use of LT3 as a part of a patient preparative method for RAI [Table 4].

Consensus statement

The standard protocol for THW includes stopping LT4 therapy and switching to LT3 therapy for 2-4 weeks followed by withdrawal of LT3 for 2 weeks. (A/I)

T3 medication should be withdrawn at least 10 days before initiating RAI. (A/I)

CLINICAL QUESTION: WHICH SUBSET OF HYPOTHYROID PATIENTS WOULD POTENTIALLY BENEFIT FROM LT3 THERAPY?

While T4 remains the preferred therapy for individuals with hypothyroidism, experts have also provided practical insights on the effective use of T3 in managing the condition. Patients who might benefit from LT3 therapy include those who report low satisfaction with LT4 treatment and continue to experience persistent symptoms, such as fatigue, despite having an optimized LT4 dosage. In addition, LT3 can be administered to patients experiencing severe or symptomatic hypothyroidism requiring rapid symptom relief. This group may also include individuals awaiting preanesthetic clearance for surgery and those experiencing thyroid distress. Another set of individuals who may benefit from LT3 therapy are those with central or secondary hypothyroidism resulting from pituitary disease. The potential indicators for LT3 therapy are mentioned in Figure 1.[2]

CLINICAL QUESTION: WHAT IS THE APPROPRIATE DOSE OF LT3 WHEN ADMINISTERED WITH LT4?

LT3 is prescribed as part of a combination therapy with LT4 for thyroid replacement. It can be used for both initiating treatment and for intensifying the therapy. LT3 can be administered at the same time as LT4, which is generally taken once daily before

Table 4: Timelines for T3 therapy withdrawal before radio iodine ablation or scan

Guidelines	Recommendation/consensus statement
2023 Patient preparation and radiation protection guidance for adult patients undergoing radioiodine treatment for thyroid cancer in the UK[33]	The traditional approach is withdrawal of thyroid hormone replacement (LT4 for 3–4 weeks or LT3 for 2 weeks) combined with restricting iodine intake for up to 3 weeks prior to treatment
2023 EANM guideline on radioiodine therapy of benign thyroid disease[34]	Withdraw T3 medication 10–14 days before initiating RAI
2022 ETA Consensus Statement: What are the indications for postsurgical radioiodine therapy in differentiated thyroid cancer?[35]	For thyroid hormone withdrawal, one approach was switching from LT4 to LT3 for 2–3 weeks, followed by discontinuing LT3 for 2 weeks
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer[36]	The experts strongly recommended to withdraw thyroid hormone 2–3 weeks before RAI. LT3 may be substituted for LT4 in the initial weeks if LT4 is withdrawn for 4 or more weeks. In such cases, LT3 should be withdrawn for at least 2 weeks. It is recommended to measure serum TSH before radioisotope administration to evaluate the degree of TSH elevation
2015 The American Cancer Society[37]	To maximize the effectiveness of RAI therapy, the society advises patients to stop taking their thyroid hormone medication for several weeks before the treatment
2009 American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer[38]	In patients undergoing RAI, endogenous TSH elevation can be achieved by switching to LT3 for 2–4 weeks, followed by withdrawal of LT3 for 2 weeks

EANM: European Association of Nuclear Medicine, RAI: Radioactive iodine ablation, ETA: European Thyroid Association, TSH: Thyroid-stimulating hormone, LT3: Liothyronine, LT4: Levothyroxine, T3: Triiodothyronine

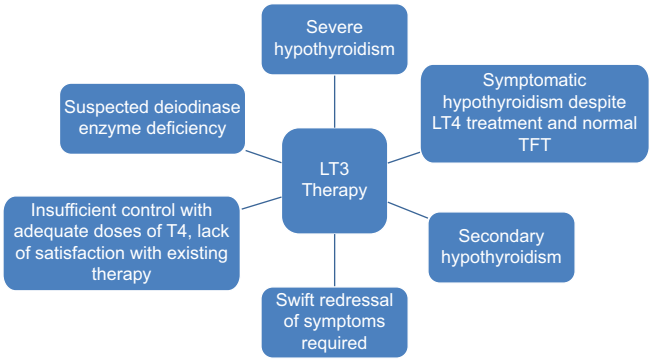

Figure 1: Potential indicators for LT3 therapy[2]

breakfast. When prescribing this combination, the appropriate T4:T3 ratio must be determined. In addition, when introducing T3 into an existing T4 regimen, deciding whether to maintain or reduce the current T4 dosage is important.[2]

The LT3/LT4 combination is used to initiate treatment in patients with severe symptoms or those seeking rapid relief from the disease. More commonly, T3 is introduced for substitution (interchange) or intensification purposes. Substitution is required for patients who have reached biochemical euthyroidism but still display clinical signs of the disease.

Intensification is recommended for individuals who still exhibit biochemical hypothyroidism (high TSH with or without low T3) despite receiving a sufficient dose of T4 (1.5–2 μg/kg/day) over an adequate duration (6–12 weeks). Because of its shorter half-life, LT3 might need to be administered twice daily for some individuals. Dosage titration can be performed every 6–12 weeks, depending on the reason for initiating LT3 therapy.[2]

A randomized placebo-controlled trial was conducted by Brigante *et al*. (2024) on levothyroxine and liothyronine combination therapy in 160 patients with hypothyroidism after thyroidectomy. Medications were adjusted to keep the T4/T3 ratio between 13:1 and 20:1, and TSH was measured at all time points. This study showed no significant difference between those treated with LT4 alone or LT4+LT3 regarding peripheral tissue markers of thyroid function, quality of life, and BMI. The FT3/FT4 ratio persisted in the low range in the LT4+placebo group at the end of treatment, while the ratio increased to the normal range in the LT4+LT3 group.[39]

Various guidelines have recommended the dose of LT3; however, there is no established consensus on the optimal T4 to T3 ratio [Table 5].

Table 5: Dosage recommendation of T3 therapy

Guideline	Recommendation/consensus statement
Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for endocrinology consensus statement 2023[14]	LT3 is available as licensed 5, and 20 μg preparations The experts agreed that due to the short half-life of LT3, splitting the doses across 24 h would be beneficial for many people To initiate combination treatment, the panel recommended substituting LT3 at approximately 1/17th of the current LT4 dose, and reducing the LT3 dose by three times the LT4 dose E.g. If the baseline LT4 dose is 100 μg, the LT3 dose is calculated to be approximately 1/17th of the current LT4 dose which is ~5 μg. The revised LT4 dose would therefore be ~ 85 μg (reduced by 3 times the LT3 dose
Evidence-based use of LT4/LT3 combinations in treating hypothyroidism: A 2021 Consensus Document[40]	The panel recommended that the pharmacological equivalence of LT3 to LT4 is approximately a 1:3
2015 American Thyroid Association Guideline on Treatment of Hospitalized Patients with Hypothyroidism and Use of Thyroid Hormone Analogs[15]	In the management of myxedema coma, in addition to LT4 therapy, LT3 therapy can be initiated at a dose of 5–20 μg, followed by a maintenance dose of 2.5–10 μg every 8 h Lower doses of LT3 should be administered to patients who are smaller in stature, older, or have a history of coronary disease or arrhythmia
2012 ETA guidelines: The use of LT4/LT3 in the treatment of hypothyroidism[11]	The panel agreed on Initiating the LT4/LT3 combination treatment with a dose ratio of 13:1 to 20:1 by weight Dividing the daily LT3 dose into two doses if possible, with one taken before breakfast and the larger dose before bedtime Using separate LT4 and LT3 tablets for combination therapy as the currently available preparations contain an LT4/LT3 dose ratio lower than 13:1

LT3: Liothyronine, LT4: Levothyroxine, ETA: European Thyroid Association

Consensus statement

L-T4 + L-T3 combination treatment should be started in a L-T4/L-T3 dose ratio between 13: 1 and 20: 1 by weight, LT3 can be administered at the same time as LT4, either as once daily or in divided doses. (B/IIa)

CLINICAL QUESTION: DOES LT3 THERAPY REQUIRE ROUTINE MONITORING?

The necessity of continuing LT3 intake should be reassessed if a finite endpoint such as euthyroidism (to facilitate elective surgery) is achieved. The same evaluation should be made if symptoms persist or surrogate laboratory results remain abnormal. In these situations, a thorough clinical evaluation should be conducted to identify the underlying cause of the concern for refractory hypothyroidism. Individuals who respond well to LT3 therapy may continue their treatment indefinitely, provided they are monitored with the same pharmacological and clinical vigilance as those undergoing T4 management.[2]

A 17-year population-based observational study was conducted to evaluate the adverse outcomes for patients on long-term LT3 therapy (n = 400) compared to patients on LT4 therapy (n = 33955). The results of the study revealed that patients on LT4 alone had a higher median TSH level (2.08 vs. 1.07 mU/L; $P < 0.001$). The long-term treatment with LT3 was not associated with any additional risk of atrial fibrillation, cardiovascular disease, or fractures. There was an increase in antipsychotic use with T3 in this study. Hence, monitoring the response to the treatment is important.[41]

Various guidelines have released the consensus statements for monitoring LT3 therapy in patients with hypothyroidism [Table 6].

Consensus statement

Routine monitoring of LT3 therapy is necessary with thyroid function tests including serum TSH, free T4, free T3, and the free T4/free T3 ratio. (C/IIa)

CLINICAL QUESTION: WHAT ARE THE CONTRAINDICATIONS ASSOCIATED WITH LT3 THERAPY?

A recent literature review elucidated that LT3 should not be used by women who are planning to conceive, those who are pregnant, or those who are breastfeeding. It is also advisable to avoid LT3 in patients with unstable heart disease or severe osteoporosis. Prescribers should be aware of the potential for LT3 misuse as a weight-loss drug.[2] Various guidelines have delineated the contraindications associated with LT3 therapy [Table 7].

Consensus statement

LT3 therapy is contraindicated in patients:

Pregnant or planning pregnancy (C/I)

Patients with cardiac arrhythmias (C/I)

Executive summary of the consensus statements

- There is limited evidence from randomized controlled trials and long-term studies demonstrating that the combination therapy is superior to LT4 alone; however, the majority of the patients have preferred the LT4/LT3 combination therapy. Hence, a trial of combined LT3 and LT4 therapy may be considered in patients on long-term levothyroxine therapy with ongoing symptoms and where other comorbidities have been ruled out (A/IIb)
- No data is available regarding the optimal dose of LT4 and LT3 to be used in this situation in the perioperative period in People who require emergency surgery with suboptimally controlled hypothyroid status. If initiating thyroid replacement therapy for the first time, it may be prudent to initiate thyroid hormone therapy with low doses of LT3 (5–10 μg every 8 h IV or PO). It is suggested to start combination therapy in an L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight (L-T4 once daily, and the daily L-T3 dose in two doses)
- Administration of LT3 in addition to LT4 therapy in patients diagnosed with myxedema coma resulted in normalization of thyroid hormone levels and resolution of symptoms, leading to successful management of the disease (D/IIa)

Administration of LT3 therapy in patients diagnosed with myxedema coma was associated with lower mortality rates. LT3 to be administered at an oral loading dose of 5–20 μg, followed by a maintenance dose of 2.5–10 μg every 8 h, until the patient shows signs of recovery. However, a dose of >75 μg/day may be associated with fatal outcomes (D/IIa)

- The standard protocol for THW includes stopping LT4 therapy and switching to LT3 therapy for 2–4 weeks, followed by withdrawal of LT3 for 2 weeks (A/I)
- LT3 medication should be withdrawn at least 10 days before RAI (A/I)
- L-T4 + L-T3 combination treatment should be started in a L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight, LT3 can be administered at the same time as LT4, either

Table 6: Monitoring and titration of T3 therapy

Guidelines	Recommendation/consensus statement
Evidence-Based Use of LT4/LT3 Combinations in Treating Hypothyroidism: A 2021 Consensus Document[40]	Administering LT3 once daily as part of an LT4/LT3 combination therapy results in increase of serum T3 level by up to 40% above baseline levels, thus requiring adequate monitoring The panel agreed that monitoring serum T3 levels and free T3/free T4 ratios with conventional LT3 preparations is challenging due to 24-h fluctuations. Consequently, interpreting TSH levels in patients on conventional LT3 preparations can also be difficult
2012 ETA guidelines: The use of LT4/LT3 in the treatment of hypothyroidism[11]	The panel advised that LT4/LT3 combination therapy should be monitored with thyroid function tests on blood samples taken before the morning dose, with the aim to achieve normal levels of serum TSH, free T4, free T3, and the free T4/free T3 ratio If adjustments to the LT4/LT3 combination therapy are needed to normalize serum TSH, free T4, free T3, and the free T4/free T3 ratio, it is recommended to alter the dose of only one component, preferably LT3

LT3: Liothyronine, LT4: Levothyroxine, ETA: European Thyroid Association, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine

Table 7: Contraindication for the use of T3

Guidelines	Recommendation/consensus statement
2023 Joint British Thyroid Association/Society for endocrinology consensus statement on the use of liothyronine (T3) in hypothyroidism[12]	The panel advised that LT3 should only be used as monotherapy in cases of confirmed allergy or intolerance to LT4 or its excipients The experts unanimously recommended that LT3 should not be used in pregnancy
2012 Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association[42]	The experts opined that thyroid hormones should not be used to address symptoms indicative of hypothyroidism in the absence of biochemical confirmation of the diagnosis to treat obesity in euthyroid patients in pregnant women or those planning pregnancy
2012 ETA Guidelines on the use of LT4/LT3 in the treatment of hypothyroidism[11]	Combination therapy of LT3 and LT4 is not recommended for pregnant women or patients with cardiac arrhythmias

LT3: Liothyronine, ETA: European Thyroid Association, LT4: Levothyroxine, T4: Thyroxine, T3: Triiodothyronine

as once daily or in divided doses. (B/IIa)

- Routine monitoring of LT3 therapy is necessary with thyroid function tests, including serum TSH, free T4/total T4, free T3/Total T4, and the free T4/free T3 ratio (C/IIa)
- LT3 therapy is
  Absolute contraindications in patients:
  - Pregnant or planning pregnancy (C/I)
  - Patients with cardiac arrhythmias (C/I).

Relative contraindications:

- Congestive cardiac failure/acute myocardial ischemia
- Severe osteoporosis
- Elderly population.

Author contribution

All authors contributed to data collection, article correction, and review. The first draft of the manuscript was prepared by Dr. Shashank R. Joshi, Dr. Krishna Seshadri, and Dr. Pramila Kalra. Manuscript editing and preparation of the final draft were carried out by all authors. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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