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Supplementing liothyronine to levothyroxine therapy for management of hypothyroidism: Current clinical practice and beyond

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Abstract

Hypothyroidism, the most prevalent endocrine disorder, is typically diagnosed by elevated serum thyrotropin (TSH) and low thyroxine (T₄) levels. However, even when TSH levels normalize with standard levothyroxine (LT₄) therapy, some patients continue to suffer from persistent symptoms. This review addresses the challenges in diagnosing and treating hypothyroidism, with a focus on the enduring symptoms encountered despite standard treatment. It also delves into the potential benefits of combining LT₄ therapy with LT₃ liothyronine (LT₃). The non-specific nature of hypothyroid symptoms makes accurate diagnosis a challenge. A subset of patients comprising 5% to 15% of hypothyroid patients have poor quality of life due to residual symptoms of hypothyroidism. Such patients complain of symptoms including brain fog, depression and inability to lose weight despite normalization of TSH by levothyroxine therapy. This review emphasizes the potential advantages of adding LT₃ to LT₄ therapy, particularly for subgroups of patients experiencing ongoing symptoms despite normal TSH levels. Furthermore it highlights the need for accurate diagnosis and personalized treatment, as well as the potential of combining therapies to alleviate symptoms for certain patients.

Keywords: Hypothyroidism, thyroid disease-related symptoms, levothyroxine, liothyronine, patient-reported outcomes, thyroid-stimulating hormone

Introduction

In India, hypothyroidism, is the most common thyroid disorder, observed in one in ten adults. The prevalence of hypothyroidism in India is 11% [6]. There is geographic variation as seen in coastal Indian cities, such as Mumbai, Goa, and Chennai, compared with cities located further inland such as, Delhi, Bangalore, Ahmedabad, and Hyderabad, which have a higher prevalence (11.7% vs 9.5%) [6].

Hypothyroidism is a frequently encountered condition in primary care, typically diagnosed via an elevation in serum thyrotropin (TSH) levels exceeding 4.5 mIU/mL [1]. Hypothyroidism occurs due to primary disease of the thyroid or secondary to hypothalamic-pituitary disease [2]. Primary hypothyroidism is the most common endocrine disorder throughout the world and accounts for more than 99% of all cases of hypothyroidism [3].

The grade of clinical features and complications related to hypothyroidism depend upon the progression and duration of untreated thyroid failure. Overt hypothyroidism is identified by an elevated TSH level accompanied by a serum total thyroxine (T₄) or free T₄ level below the population reference range [4]. Subclinical hypothyroidism, or mild thyroid failure, is characterized by a sustained elevation in TSH (>4.5 mIU/L) for 12 weeks or more, while total T₄ and free T₄ values consistently fall within the population reference range [4]. Subclinical hypothyroidism may convert to overt hypothyroidism in 2%-5% of patients annually [5, 7].

A subset of hypothyroid patients, comprising 5%-15% of patients who continue to present with residual symptoms of hypothyroidism with normal levels of TSH, despite adequate levothyroxine therapy, constitute a clinical challenge requiring special consideration. Such patients complain of poor quality of life due to symptoms suggesting thyroid insufficiency including brain fog, lethargy, depression, inability to lose weight and constipation. Recent studies have indicated a role for supplementing levothyroxine with liothyronine in such patients to address the residual symptoms of hypothyroidism.

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Research indicates a role of compromised activity of deiodinase enzymes in peripheral tissues in such patients who may not respond to adequate LT4 therapy. In such cases, LT4 therapy succeeds in normalizing TSH levels but may not adequately replenish tissue stores of T3, leading to hypothyroid symptoms.

Causes of Ill-health of Hypothyroid Patients [17]

Hypothyroidism has two primary categories: primary and secondary (central). Primary hypothyroidism occurs when the thyroid gland itself cannot produce sufficient thyroid hormone, often due to iodine deficiency in some regions. In contrast, secondary hypothyroidism is linked to issues with the pituitary gland or hypothalamus, while the thyroid gland remains normal.

The leading cause of primary hypothyroidism in iodine replete populations is autoimmune thyroid disease. Autoimmune thyroid disease, particularly Hashimoto thyroiditis, is the most common cause of hypothyroidism. Local factors like iodine fortification can influence the etiology.

Other common causes of hypothyroidism include

1. **Medications:** Several drugs, such as amiodarone, thalidomide, and others, can lead to hypothyroidism
2. **Thyroid treatments:** Procedures like radioactive iodine therapy and thyroid surgery can disrupt thyroid function.
3. **Radiation therapy:** Treatment to the head or neck area can also cause hypothyroidism.
4. **Central hypothyroidism:** This results from various pituitary or hypothalamic disorders, including neoplastic, infiltrative, inflammatory, genetic, or iatrogenic factors.

Evaluation for persistent symptoms of hypothyroidism

Even after years of levothyroxine monotherapy, some patients believe that they still have impaired quality of life. Patients with persistent symptoms despite optimum levothyroxine replacement therapy should be assessed for other underlying diseases (Table 1).

Table 1: Assessment for patients with persistent symptoms despite normal TSH While on LT4 [3]

Medical history and physical examination
Laboratory investigations
TSH
FT4 or Total T4
TPO antibodies (if available)
Interpretation
Overt hypothyroidism-TSH elevated with low FT4 or T4 levels
Subclinical hypothyroidism-TSH elevated with normal FT4 or T4 levels
Complete blood cell count
Erythrocyte sedimentation rate
Other Endocrine laboratory evaluation
25-Hydroxyvitamin D
Serum cortisol
Other pituitary profile-Imaging of Sella
USG neck, nuclear imaging (Not a must, if Abnormal do not delay treatment)

TSH, thyroid stimulating hormone; FT4, free thyroxine; T4, thyroxine; USG, ultrasonogra

Need for addition of liothyronine to levothyroxine in patients with uncontrolled symptoms despite compliant lt4 therapy

Levothyroxine (LT4), the pill form of T4, remains the mainstay of treatment for hypothyroidism. The LT4 formulations available have a half-life of six days and provide fairly stable blood levels of T4 after ingestion of an oral daily dose [10]. About 80% of thyroid hormones secreted by the thyroid are in the form of T4, with the rest secreted as T3. In principle, therefore, co-administering T4 and T3 might provide a mechanism to simulate the physiological euthyroid state in patients with hypothyroidism. A substantial group of LT4-treated patients with hypothyroidism still report symptoms typical of this condition (e.g. fatigue, weakness, feeling cold, gastrointestinal disturbances, and constipation), despite successful normalization of TSH [11]. There is mounting evidence for T4+T3 therapy, specifically because it might potentially resolve persistent symptoms that occur in 5% to 15% of hypothyroid patients despite treatment with LT4 along with normal TSH values [12].

Treatment of hypothyroidism involves thyroid hormone replacement in quantities sufficient to relieve symptoms and normalize serum TSH levels. There are three approaches to utilizing different preparations of thyroid hormones, T3, and/or T4 (Table 2). First, standard treatment with LT4 is recommended to be administered as a single daily dose, half-an-hour to one hour before breakfast to reach an age-adjusted TSH target. The dose must be titrated periodically [2]. T3 is known to be the main metabolically active thyroid hormone that binds to thyroid hormone receptors and produces thyroid hormone effects at the tissue level. In theory it is effective, but its main disadvantage is its short half-life. T3 can be used for initiation as well as intensification of therapy in supplementing therapy with T4. The 2021 ETA consensus established evidence-based recommendations and patient criteria for LT3 + LT4 supplementary therapy in hypothyroidism. After excluding other causes of persistent symptoms, patients who do not report clinical improvement with a dose of at least 1.9 µg/kg/day of LT4 should be considered for additional LT3 therapy. Likewise, those with low baseline serum total T3 levels while taking LT4 monotherapy should also be included. Also, future trials on therapy with LT3 as a supplement to LT4 should consider including polymorphism genotyping [16].

Guideline recommendations

The 2012 European Thyroid Association (ETA) guidelines were introduced with a specific focus on improving safety and addressing the indiscriminate use of T4+T3 combination therapy. The guidelines suggest that this approach should be considered as an experimental option for hypothyroid patients who are compliant with LT4 treatment, continue to experience symptoms despite having serum TSH values within the reference range, and have previously received guidance to manage the chronic nature of their condition. Additionally, these patients should have undergone evaluations to rule out associated autoimmune diseases [13]. T4 is the body's native thyroxine hormone, whereas LT4 is its pharmaceutical substitute, levothyroxine. Similarly, T3 is the endogenous triiodothyronine hormone, and LT3 is its pharmaceutical equivalent, liothyronine [13]. The 2012 ETA guidelines recommended excluding

comorbidities before administering T₄+T₃ combination therapy. The ETA also offered a second-line approach for these symptomatic individuals using LT₄+LT₃ combination therapy for these select individuals. The guidelines state that if LT₄+LT₃ combination therapy is effective and well tolerated, it may be continued beyond the trial period of 3 months.

The American Thyroid Association (ATA), ETA, and the American Association for Clinical Endocrinology (AACE) recommend T₄ as first-line therapy for hypothyroid patients, perceiving the lack of randomized clinical trial data on both the efficacy and safety of combining therapies of levothyroxine and liothyronine and formulations of T₃ that reflect thyroid hormone physiology. However, the guidelines recommend combination therapy in hypothyroid patients who report poor quality of life on T₄ compliant therapy. The British Thyroid Association likewise recommended a therapeutic trial of LT₄+LT₃ therapy to 'restore physical and psychological well-being'. Despite consensus from these societies that LT₄ remains the first-line treatment and preferred mode of providing thyroid hormone replacement, a recent survey found that at least 58% of clinicians would prescribe a trial of supplementing liothyronine to levothyroxine therapy for specific clinical scenarios in which LT₄-treated patients with normal serum TSH exhibited residual symptoms^[14].

In 2021, the ATA, BTA, and ETA developed a consensus statement in which they reviewed the latest evidence on hypothyroidism treatment with LT₄/LT₃ and developed recommendations for future clinical trials. The recent scientific developments proposed that the design of future studies may represent a substantial advancement in achieving a fair assessment of the potential benefits of 'physiological thyroid hormone replacement' by adding LT₃ TO LT₄, with a focus on assessment of its effects on patient-centered outcomes/patient-reported outcomes (PROs)^[15].

Treatment of hypothyroidism involves thyroid hormone replacement in quantities sufficient to relieve symptoms and normalize serum TSH levels. There are three approaches to utilizing different preparations of thyroid hormones, T₃, and/or T₄ (Table 2). First, standard treatment with LT₄ is recommended to be administered as a single daily dose, half-an-hour to one hour before breakfast to reach an age-adjusted TSH target. The dose must be titrated periodically^[2]. T₃ is known to be the main metabolically active thyroid hormone that binds to thyroid hormone receptors and produces thyroid hormone effects at the tissue level. In theory it is effective, but its main disadvantage is its short half-life. T₃ can be used for initiation as well as intensification of therapy in supplementing therapy with T₄. The 2021 ETA consensus established evidence-based recommendations and patient criteria for LT₃+LT₄ supplementary therapy in hypothyroidism. After excluding other causes of persistent symptoms, patients who do not report clinical improvement with a dose of at least 1.9 µg/kg/day of LT₄ should be considered for additional LT₃ therapy. Likewise, those with low baseline serum total T₃ levels while taking LT₄ monotherapy should also be included. Also, future trials on therapy with LT₃ as a supplement to LT₄ should consider including polymorphism genotyping^[16].

Challenges Faced with Addition of T₃ to T₄ Treatment^[18]

In certain reports, a consistent LT₄ dose (typically 50 µg) was exchanged for varying amounts of LT₃ (ranging from 7.5 to 20 µg), leading to inconsistent T₄/T₃ ratios. This approach often failed to achieve the optimal ratio and might have obscured any potential clinical improvements due to subclinical hypo or hyperthyroidism states during LT₄ therapy.

In other LT₄+LT₃ therapy trials, specific T₄/T₃ ratios were used, such as 3:1, 5:1, 10:1, 14:1, and 15:1. However, like previous studies, many of these trials did not achieve euthyroidism, resulting in overtreatment, as indicated by TSH suppression, elevated FT₃ levels, and peripheral markers of thyroid hormone action in the thyrotoxic range. This was accompanied by hyperthyroid symptoms, including atrial arrhythmias, weight loss, and increased bone turnover.

Most studies investigating combined T₃ and T₄ therapy utilized one or two daily doses of T₃. This dosing regimen led to fluctuations in serum T₃ levels, which could negate potential tissue-related benefits.

To adequately address the potential benefits of combined therapy, large-scale trials are necessary. These trials should use the appropriate T₄/T₃ ratio and formulations to maintain steady-state hormone concentrations. This approach aligns with the natural thyroid hormone secretion ratio of approximately 14:1.

Table 2: Approach to patients with persistent symptoms despite normal TSH While on LT₄^[19]

A well-balanced diet with adequate amounts of fruits, vegetables, and high-value protein
Healthy snacking
Regular exercise, combination of aerobic and resistance work
Stress management with relaxation, meditation, yoga, counselling
Depression management
Medical illness management
Treating subclinical hypothyroidism in presence of large goitre/positive TPO antibody/ASCVD /heart failure/ dyslipidemia/infertility /depression/refractory anemia/ personal or family history of autoimmune disease
Optimize levothyroxine therapy. Titrate based on TSH levels, once in 3 to 6 months initially, once stable dose is achieved, annual follow up
Switch to another levothyroxine brand: be aware of different formulations
Consider supplementing levothyroxine therapy with liothyronine therapy

ASCVD, atherosclerotic cardiovascular disease; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Patient-reported outcomes during Supplementation of LT₄ Treatment with LT₃

There are cases describing unexplained persistent symptoms in levothyroxine-treated patients despite their TSH levels being within the normal reference range. As in most cases, hypothyroidism is a permanent condition, in which affected patients rely on life-long replacement therapy. For many patients, such therapy, usually provided as synthetic LT₄, is entirely satisfactory and fully resolves the symptoms of untreated hypothyroidism. However, some patients do not

feel that they are returned to full health, and note decreased quality of life, often dating from their diagnosis of hypothyroidism. Some patients may feel better while taking therapy consisting of both LT4 and liothyronine (LT3)^[16].

Hypothyroidism is considered refractory to levothyroxine replacement, when there is elevation of serum TSH or clinical evidence of hypothyroidism, despite increasing dosages of levothyroxine beyond 1.9 µg/kg daily. In these circumstances, further increments in the dosage of levothyroxine may not be the most appropriate intervention. In such a situation, physicians need to identify the causes of decreased absorption of levothyroxine or increased demand for thyroxine^[16].

The 2012 ETA guidelines suggest LT4+LT3 combination therapy as an experimental option for certain hypothyroid patients. Patients eligible for this approach comply with LT4 treatment, experience persistent symptoms despite normal TSH levels, have received support for managing their condition, and ruled out associated autoimmune diseases. This addition of LT3 to LT4 therapy is not recommended for pregnant women or patients with cardiac arrhythmias. The Italian and British Thyroid Associations have adopted these guidelines, while the ATA maintains a more neutral position^[20].

The guidelines also suggest that if no improvement is observed after three months of supplementing therapy, it should be discontinued. There are lingering concerns about the long-term safety of T₄+T₃ additional therapy, but a 17-year observational population-based study conducted in Scotland on liothyronine (T₃) use provides some reassurance. The study found that patients using LT3, either alone or with LT4, did not exhibit an increased risk of cardiovascular disease, atrial fibrillation, or fractures when compared to those solely taking LT4 after adjusting for age.

In this review, we discussed the challenges in relating symptoms to biochemical diagnosis and treatment of hypothyroidism. Thyroid-related symptoms are mainly non-specific and noted in the euthyroid population. After treatment with LT4, a considerable number of patients report suboptimal symptom relief. Future clinical trials must be carried out; in addition, the systematic use of PROs to enhance communication with patients, further development of innovative monitoring tools including free triiodothyronine (FT3) and functional brain imaging, and better adherence to international guidelines should be ensured.

We emphasize that more studies are needed to identify the subgroup of hypothyroid patients that may benefit from the use of liothyronine, in addition to levothyroxine, probably through the identification of new biomarkers or genetic polymorphisms^[16].

Conclusion

Hypothyroidism is a global health concern, with significant prevalence in India, where it affects approximately 11% of adults. A small subset of hypothyroid patients on adequate levothyroxine therapy continue to present with residual symptoms of hypothyroidism including brain fog, lethargy, depression and inability to lose weight. Patient reported outcome scales report poor quality of life in such patients. Addition of LT3 in small doses to the existing LT4 therapy has been proven to improve quality of life in such patients with improvement in the residual symptoms of hypothyroidism. As T₃ represents the final effector phase of

thyroid hormones at the tissue level, supplementing with LT3 in such patients may compensate for ineffective conversion of LT4 to LT3 in peripheral tissues due to decreased activity of deiodinase enzymes.

As we move forward, increasing awareness, targeted screening, and effective management will be essential in India's efforts to tackle hypothyroidism, while also working to fine-tune treatment approaches based on individual patient needs. Further research is required to better identify the subset of patients who would benefit most from supplementing existing levothyroxine therapy with liothyronine.

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