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Liothyronine Therapy in Hypothyroidism

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Abstract

Hypothyroidism is a clinical condition characterized by reduced production of thyroid hormones and is among the most common endocrine disorders, affecting about 3% of the general population, with a higher prevalence in women (5.1%) than in men (0.9%). In Indonesia, the prevalence of hypothyroidism is estimated at 5-10%. Despite achieving normal thyroid stimulating hormone (TSH) levels with levothyroxine (LT4) therapy, many patients continue to experience symptoms like fatigue, depression, and cognitive impairment, which impact their quality of life. A study of 969 hypothyroid patients found that 77.6% were dissatisfied with their treatment and reported low quality of life scores. Although LT4 has been the standard therapy for nearly 50 years due to its stability and the peripheral conversion of thyroxine (T4) to triiodothyronine (T3), recent recommendations from experts in developed countries suggest using liothyronine (LT3) monotherapy or a combination of LT3 and LT4 in selected cases.

Keywords: Hypothyroidism, liothyronine.

Abstrak

Hipotiroidisme adalah kondisi klinis yang ditandai dengan berkurangnya produksi hormon tiroid dan merupakan salah satu gangguan endokrin yang paling umum, mempengaruhi sekitar 3% dari populasi umum, dengan prevalensi lebih tinggi pada wanita (5,1%) dibandingkan pada pria (0,9%). Di Indonesia, prevalensi hipotiroidisme diperkirakan 5-10%. Meskipun mencapai kadar hormon perangsang tiroid (TSH) normal dengan terapi levotiroksin (LT4), banyak pasien terus mengalami gejala seperti kelelahan, depresi, dan gangguan kognitif, yang memengaruhi kualitas hidup mereka. Sebuah studi terhadap 969 pasien hipotiroid menemukan bahwa 77,6% tidak puas dengan pengobatan mereka dan melaporkan skor kualitas hidup yang rendah. Meskipun LT4 telah menjadi terapi standar selama hampir 50 tahun karena stabilitasnya dan konversi perifer tiroksin (T4) menjadi triiodotironin (T3), rekomendasi terbaru dari para ahli di negara-negara maju menyarankan penggunaan monoterapi liotironin (LT3) atau kombinasi LT3 dan LT4 pada kasus-kasus tertentu.

***Kata kunci**: Hipotiroidisme, liotironin*

I. INTRODUCTION

Hypothyroidism is a clinical condition resulting from reduced thyroid hormone production. In Indonesia, according to the 2007 Basic Health Research, 2.7% of men and 2.2% of women were found to have elevated TSH levels, indicating potential hypothyroid disorders. In the United States, hypothyroidism affects 4.3-8.5% of the population, which can lead to myxedema coma in severe cases, a life-threatening condition with high mortality rates.[1] Prior to the 1970s, combination therapy with LT3 and LT4 was widely used. However, after it was discovered that T4 is largely converted to T3 in tissues, LT4 became the standard therapy for nearly 50 years.[2-4]

Approximately 5-10% of patients with normal TSH levels following LT4 therapy continue to experience symptoms such as fatigue, depression, and cognitive impairment. A study by Saravanan et al. (2018-2019) involving 969 patients found that 77.6% were dissatisfied with their treatment and reported low quality of life. Patients receiving combined LT4 and LT3 therapy reported better quality of life compared to LT4 monotherapy. Similarly, a survey by Peterson et al. (2018) of 12,146 patients found higher satisfaction levels among those treated with LT4 and LT3 combination therapy.[4-6]

Research by Celi et al. (2011) demonstrated that LT3 has a more favorable impact on lipid profiles and weight loss compared to LT4, particularly in patients with comorbidities such as cardiovascular disease and obesity.37 However, LT3 requires more frequent dosing and is more expensive, necessitating careful patient selection.[1,7] LT3 therapy, either as monotherapy or in combination with LT4, can be considered as an alternative treatment, particularly in Indonesia.[8]

II. DEFINITION

Hypothyroidism is caused by reduced thyroid hormone production. Clinical hypothyroidism is marked by elevated TSH and low FT4, while subclinical cases show high TSH but normal FT4. Untreated, it can lead to serious effects on multiple organ systems. Most adults with hypothyroidism have acquired the condition, primarily due to thyroid gland dysfunction (primary hypothyroidism) or issues in the pituitary or hypothalamus (central hypothyroidism).[9]

III. EPIDEMIOLOGY

The prevalence of primary hypothyroidism is 0%-4% in the U.S. and 0%-3% in Europe, with 5%-6% of cases undiagnosed. Iodine levels significantly impact hypothyroidism risk, with both excess and deficiency increasing TSH levels. It is more common in women, the elderly (over 65), and white populations, and is frequently seen in those with autoimmune conditions like type I diabetes or celiac disease, as well as Down or Turner syndromes. Smoking and moderate alcohol consumption may reduce hypothyroidism risk. Genetics play a key role, with TSH levels having a 60% inheritance likelihood, and genome studies have linked loci to autoimmunity. Monogenic congenital hypothyroidism is rare and often involves TSH resistance.[10,11]

IV. CLASSIFICATION AND ETIOLOGY

Hypothyroidism is classified into primary, secondary, tertiary, and peripheral types. Primary hypothyroidism results from T4 deficiency, secondary from TSH deficiency, and peripheral from TRH deficiency. The causes and mechanisms are outlined in Table 1.[12]

TABLE 1. ETIOLOGY OF HYPOTHYROIDISM AND PATHOGENETIC MECHANISMS[9]

Etiology	Mechanism/Pathophysiology
Chronic Autoimmune Thyroiditis (Hashimoto Thyroiditis)	T-cell mediated inflammatory response failure, cytokine release, thyroid infiltration by lymphocytes, and fibrosis cause development in the thyroid.
Iodine Metabolism Disorders	Iodine deficiency reduces thyroid hormone production. Excess iodine causes hypothyroidism in patients with primary thyroid disease.
Glandular Destruction (Infiltrative Disorders, Infections, and/or Inflammation)	Thyroid cell infiltration. Loss of function; pathogenic variants. Infiltration with various cells or substances (e.g., granuloma formation, fibrosis, glycosaminoglycans). Thyroid cell destruction (e.g., recent COVID-19 infection).
Infections and/or Inflammation	Uncertain increase in intrathyroidal content, reduced peroxidase activity, or autoantigen release-induced autoimmunity. Infection leading to destruction of follicles, inducing primary hypothyroidism.
Medications	Various drugs inhibit thyroid hormone production, cause thyrocyte destruction, or impair iodine uptake.
Environmental and Industrial Agents	Disruption of various hypothalamic-pituitary-thyroidal steps.
Hypothalamic or Pituitary Damage and/or Disease	Interruption in hypothalamic or pituitary function or elasticity involving key regulatory hormones (e.g., TSH and TRH). Secondary hypothyroidism due to head trauma, tumors, or infiltrative disease.
Infiltrative and/or Infections in Hypothalamic-Pituitary Axis	Infectious causes (e.g., tuberculosis) or primary causes (e.g., sarcoidosis, hemochromatosis) disrupting regulatory pathways.
Congenital	Malformations, mutations, lack of thyroid gland formation. Defective hormone synthesis pathways (e.g., TSH receptor mutations, POU1F1 deficiency).
Consumptive Hypothyroidism	Increased type 3 iodothyronine deiodinase expression (e.g., by tumor cells).
Autoimmune	Tissue-specific hypothyroidism due to reduced sensitivity to thyroid hormones (e.g., mutations in MCT8, TSHR, or TRβ).

V. PATHOPHYSIOLOGY

The hypothalamic-pituitary-thyroid (HPT) axis regulates thyroid hormone production. TRH from the hypothalamus controls TSH release from the anterior pituitary, which stimulates thyroid follicular cells to produce T4 (80%) and T3 (20%). Negative feedback from thyroid hormones regulates TSH and TRH production. T3 binds to nuclear thyroid receptors, while T4 is converted to T3 by deiodinases, accounting for 80% of T3 production in euthyroid individuals. Deiodination, catalyzed by selenoenzymes (D1, D2, D3), helps regulate T3 production in the liver, kidneys, and thyroid, with D2 converting T4 to T3 in the hypothalamus and pituitary (Table 2).[13-15]

TABLE 2. KEY CHARACTERISTICS OF TYPE 1, 2, AND 3 DEIODINASES

Characteristic	D1	D2	D3
Preferred Substrate	T_4	T_4	T_3
Tissue Localization	Liver, kidneys, thyroid	Pituitary, CNS, brown adipose tissue, heart	CNS, skin, placenta
Cellular Localization	Plasma membrane	Endoplasmic reticulum	Plasma membrane
Hyperthyroidism	↑	↑	↓

Characteristic	D1	D2	D3
Hypothyroidism	↓	↓	↑
Selective Activators	None	cAMP	Hypoxia
Selective Inhibitors	Propylthiouracil	None	None
Clinical Relevance	Responsible for 20% of extrathyroidal T_3 production	Responsible for 80% of extrathyroidal T_3 production	Plays a role in primary T_3 clearance

T4 enters cells via membrane transporters and is converted to T3 by D1 or D2, supplying both systemic and local T3. Cytosolic T3 binds to chromatin-binding proteins, primarily thyroid hormone receptor b2. D2 rapidly converts T4 to T3, increasing cytosolic T3, while D3 inactivates T3, protecting the fetus from maternal thyroid hormones during development.[9,16,17]

Primary hypothyroidism is mainly due to thyrocyte dysfunction, with chronic autoimmune thyroiditis (Hashimoto's) being the most common cause. Contributing factors include genetics, environmental factors, micronutrient deficiencies (iodine, selenium), medications, infections, and immune dysfunction (Figure 1).[9]

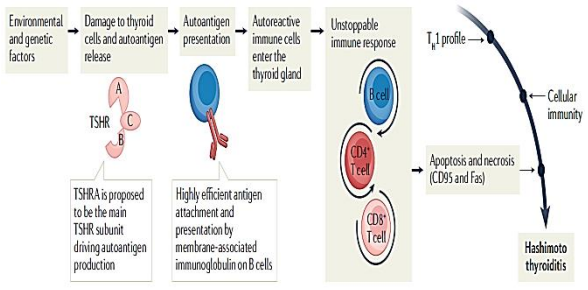

Figure 1. Mechanism of hashimoto's thyroiditis pathogenesis.[9]

Hashimoto's thyroiditis is characterized by an increase in TSH levels and a decrease in FT4 levels. The three commonly tested antibodies are Thyrotropin Receptor Antibody (TRAb), anti-TPO antibody (TPOAb), and anti-Tg antibody (TgAb/ATA), although these autoantibodies are not always detectable in the serum of patients with autoimmune thyroid disease.[18]

High levels of anti-TPO antibodies are found in most patients and 10% of the euthyroid population. During pregnancy, 2–17% of women test positive for TPOAb, which may be linked to elevated TSH in the first trimester. Chronic thyroiditis involves a T cell-mediated inflammatory response, with TH1 lymphocytes affecting thyroid cells through cytokines like IL-1, TNF, and IFNγ.[9]

VI. Clinical Manifestations

Hypothyroidism affects multiple organs, with symptoms ranging from fatigue, cold intolerance, bradycardia, and weight gain to coarse hair and hoarseness, due to decreased metabolism or glycosaminoglycan buildup. Symptoms can be mild, as in subclinical cases, or severe, like myxedema coma.[19]

Gradual onset makes symptoms less apparent, complicating diagnosis. Common issues include fatigue, dry skin, weight gain, constipation, and mild liver dysfunction. Hypothyroidism is also linked to non-alcoholic fatty liver disease, entrapment neuropathies, memory issues, sleep apnea, and depression. Severe cases can lead to cardiovascular problems, including hypertension, dyslipidemia, and myocardial injury.[9,19]

VII. Diagnosis

Before biochemical thyroid tests, hypothyroid diagnosis relied on symptoms like delayed ankle reflexes, low basal metabolic rate, and bradycardia, though milder forms were often missed. The introduction of tests for circulating thyroid hormone levels in the 1950s and TSH in the 1960s allowed for earlier detection and more precise treatment.[20]

Today, biochemical testing, particularly third-generation immunoassays for serum TSH, is crucial for diagnosing thyroid dysfunction, provided pituitary disease is excluded. There is a log-linear relationship between TSH and FT4, where halving FT4 leads to a 100-fold rise in TSH, though factors like age, sex, and TPOAb status can affect this. Abnormal TSH levels indicate early thyroid dysfunction, and testing for autoimmune markers (TPOAb or anti-thyroglobulin antibodies) can help confirm autoimmunity as the cause (Figure 2).[21,22]

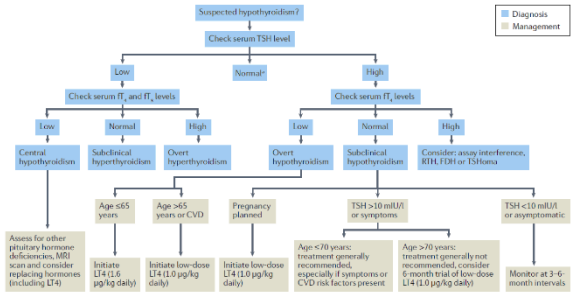

Figure 2. Diagnosis and management algorithm for hypothyroidism.[9]

VIII. THERAPY

Thyroid hormone replacement therapy

LT4 is the preferred treatment for thyroid hormone replacement due to its stable potency and long duration of action. It is converted to T3 by D1 and D2, maintaining stable serum FT3 levels. The average adult LT4 dose is 1.7 µg/kg body weight, aimed at normalizing serum TSH (for primary hypothyroidism) or FT4 (for secondary/tertiary hypothyroidism). Lower initial doses are recommended for patients over 60 or with heart disease, increasing gradually. Studies suggest no significant benefit of LT4-LT3 combination therapy over LT4 alone, though some patients report feeling better on combination therapy. LT4 monotherapy remains the standard due to its close mimicry of normal physiology. Side effects often result from overtreatment and include risks like atrial fibrillation and osteoporosis.[23]

Liothyronine (LT3) is rapidly absorbed and used in cases requiring fast effects, such as myxedema coma. However, it is less preferred for chronic use due to its short half-life and temporary serum T3 spikes, requiring multiple daily doses. LT3 acts by interacting with thyroid hormone receptors to alter gene transcription and signaling pathways, affecting various systems, with minimal excess linked to symptoms like palpitations or sweating.[24]

Studies on LT3 therapy show that single doses (10 or 50 mcg) can significantly increase serum T3 levels without major adverse effects in healthy adults. Long-term LT3 administration has shown benefits like weight loss and increased energy expenditure, though caution is advised in older patients.[25,26]

Most research on thyroid hormone replacement focuses on patients with stable elevated T4/T3 or suppressed TSH levels, as seen in hyperthyroidism. Lower serum TSH has been linked to increased risks of atrial fibrillation and osteoporosis. However, transient T3 increases from LT3 therapy within normal TSH ranges have not been conclusively shown to increase these risks, though further research is needed.[24,27]

Comparison of liothyronine therapy with levothyroxine

To date, there remains limited data supporting the use of LT3 in hypothyroid treatment. However, LT3 may offer benefits in specific cases. For example, hypothyroid patients with type 2 deiodinase polymorphism may continue to experience symptoms despite achieving target TSH levels. In thyroid cancer patients, LT3 can be used temporarily for 3-4 weeks before radioactive iodine treatment to shorten the duration of hypothyroidism. LT3 monotherapy has shown metabolic benefits such as improved weight, LDL cholesterol, mood, and psychometric function, and may

be better tolerated in high-risk groups with dyslipidemia and obesity.[15]

Studies indicate that patients on LT4 replacement therapy with normal serum TSH levels tend to have higher total T4 and FT4 concentrations and lower total T3 and FT3 levels compared to healthy controls. Around 15% of hypothyroid patients on LT4 exhibit FT3 levels below the lower normal limit, raising the question of whether low serum T3 levels contribute to persistent patient discomfort, requiring higher LT4 doses to normalize T3 levels.[7]

Deiodinase enzymes (D1 and D2) play critical roles in TSH feedback mechanisms. In thyroidectomized patients on LT4 therapy to normalize serum TSH, D2 accounts for about 80% of circulating T3. Animal studies show that T4 is taken up by tanycytes in the hypothalamus and thyrotropes in the pituitary, locally converted to T3 by D2, which then lowers TSH secretion.[7]

When LT4 doses are increased to treat hypothyroidism, serum TSH normalizes before full normalization of serum T3 levels. D1 plays a secondary role, with lower affinity for T4 than D2, and its expression is positively regulated by plasma T3. Thus, D1 activity remains suboptimal in hypothyroid rats treated with LT4, while combined LT4 and LT3 therapy restores normal serum T3 levels. Therefore, higher LT4 doses are required to achieve normal serum T3 concentrations, which often suppress serum TSH, prompting the addition of LT3.[28,29]

Animal studies suggest combined LT4 and LT3 therapy is necessary to reach physiological tissue concentrations. However, similar human studies have not shown improvements in patient-reported outcomes. Serum T4 and T3 concentrations do not differ between LT3 responders and non-responders, likely due to intracellular T3 levels depending on various factors such as membrane transport proteins, deiodinase activity, nuclear protein binding (retinoid X receptors), and thyroid hormone receptors, which are regulated by serum hormone levels. A meta-analysis comparing LT3 or LT3-LT4 combination therapy with LT4 alone found no consistent benefit in LT3 use and no difference in side effects. Current oral LT3 formulations cause temporary, non-physiological T3 serum spikes after dosing, which are not associated with low serum TSH but may still pose risks. The introduction of flexible 5-µg LT3 tablets allows for easier and potentially safer dosing by reducing the risk of elevated T3 levels.[30]

LT3 monotherapy seems more advantageous for patients with dyslipidemia and obesity, but there is insufficient evidence of its superiority over standard LT4 therapy. This is mainly due to the need for strict compliance with dosing schedules, the risk of overdose or underdose, and potential heart and bone toxicity. Careful and judicious LT3 use may be indicated for certain patients reporting persistent worsening symptoms not attributable to other causes.[31]

Comparison of combination therapy (liothyronine and levothyroxine) with levothyroxine monotherapy

LT4 monotherapy aims to restore T3 levels via D1 and D2 conversion of T4 to T3, but in hypothyroid rats, it does not normalize serum or tissue T3 levels. Combination therapy with LT4 and LT3 normalizes thyroid hormone levels in tissues, restores serum TSH, and improves peripheral T3 deficiency. This raises concerns about LT4 monotherapy in humans, as it may not achieve euthyroidism across all tissues.[15,32]

In a study, hypothyroid patients were randomized to receive either standard LT4 or LT4 with 20 µg LT3. The combination therapy led to lower T4 and higher T3 serum levels than LT4 alone, with levels closer to normal controls. Extrathyroidal T3 production during LT4 monotherapy may not

fully compensate for the absence of thyroidal T3 secretion. High T4 levels inhibit D2, reducing tissue T3, especially in the brain. Serum TSH may normalize with elevated FT4, but tissue and serum T3 levels may remain low (Table 3).[33]

Table 3. Serum tsh, t4, and t3 levels before and after lt4 monotherapy or lt4 and lt3 combination therapy[33]

Parameter	Baseline	LT_4 Monotherapy	LT_4 & LT_3 Combination
TSH	1.10 (0.5–2.2)	0.99 (0.6–1.9)	0.76 (0.2–1.8)
T_4	124 ± 29	123 ± 30	77 ± 32
T_3	1.6 ± 0.4	1.7 ± 0.6	2.4 ± 1.0

Combination therapy with LT4 and LT3 produces FT3, FT4, and FT3/FT4 ratios closer to healthy individuals. This was seen in five randomized trials, but despite near-normal FT3/FT4 ratios, combination therapy showed no clear advantage over LT4 monotherapy. A Danish study of 37 patients on combination therapy found no link between serum T3 levels and symptom improvement, as 65% were responders and 35% non-responders, with no correlation between T3 levels and response. Similarly, in thyroid cancer patients treated with LT4, hormone levels did not relate to quality of life or fatigue.[33]

To date, 13 randomized controlled trials have compared LT4/LT3 combination therapy with LT4 monotherapy. Four meta-analyses found no clear benefit in mood, quality of life, or cognitive function, suggesting no population-level advantage of combination therapy. However, long-term studies are still needed before ruling out benefits. Current guidelines maintain LT4 monotherapy as the preferred treatment for hypothyroid patients.[2,34]

Dosing, monitoring, and formulations of combination therapy with liothyronine and levothyroxine

Various LT3 formulations are available in tablet concentrations ranging from 5 to 50 µg. The European Thyroid Association (ETA) recommends an initial LT4:LT3 ratio of 13:1 to 20:1, equating to 5 or 10 µg LT3 for patients on 100–200 µg LT4. Tablets can be split for twice-daily dosing, such as 2.5 µg twice daily. Typically, the LT4 dose is reduced by 12.5 or 25 µg to accommodate LT3 addition. A therapeutic substitution ratio of 1:3 (LT3:LT4) is used. A simple method (Table 4) for adjusting the LT4:LT3 dose is: Let "x" be the daily LT4 dose in µg. The required daily LT3 dose "y" in µg is given by y = x:20, and the adjusted LT4 dose "z" is z = x−3y. While LT4 is administered once daily, LT3 should ideally be divided into two doses, with one before breakfast and the larger one before bed. This is due to LT3's shorter half-life, peaking 2–4 hours post-consumption, and the diurnal variation in T3, which peaks around 4 a.m. and is lowest between 3 and 5 p.m.[7,35]

Table 4. Practical methods for calculating combination doses of liothyronine (LT3) and levothyroxine (LT4)

Doses of LT_4 for Normalizing TSH	X = 50 µg	X = 100 µg	X = 150 µg
Doses of LT_3 = Y			
Formula: Y = X/20	2.5 µg	5 µg	7.5 µg
Doses of LT_4 = Z			
Formula: Z = X - 3Y	42.5 µg	85 µg	127.5 µg
Rounded LT_4 Dose	50 µg	88 µg	125 µg
LT_4/LT_3 Ratio	17:1	17:1	17:1

The ETA (2012) guidelines recommend using LT4 tablets separately from LT3 due to the dosing ratios in combination tablets (4:1, 5:1, and 10:1) differing significantly from the recommended 13:1–20:1. For dose adjustments, it is preferable to modify LT3. Evidence on the duration of combination therapy is limited, with RCTs ranging from 5 to 52 weeks; the consensus suggests a minimum of 1 year for trials, with assessments at 3 and 6 months. Long-term agreements with patients should clarify that LT4 monotherapy will be the primary

treatment if no significant benefits are observed.[34]

Monitoring is complicated by serum T3 level variations. Safe doses are indicated by serum T3 peaks (2-4 hours post-dose) within reference values and non-suppressed TSH, though patient satisfaction may vary. The goal is to achieve a physiological LT4 ratio. For those on long-term LT3 treatment, monitoring pulse regularity and conducting ECGs at each visit are recommended, along with bone density assessments for postmenopausal women every 3 years. Patient-reported improvements are typically used for response assessment, although some physicians may use questionnaires like ThyPRO. Regular assessments are crucial to discontinue treatment if ineffective or if effects wane over time.[7,35]

IX. CONCLUSION

Liothyronine (LT3) and levothyroxine (LT4) are used for hormone replacement therapy in hypothyroidism, with increasing recommendations for LT3 monotherapy or LT3-LT4 combination therapy. LT3 is beneficial for patients who still experience symptoms despite normal TSH levels and is recommended for specific conditions like myxedema coma or post-thyroidectomy. The combination therapy can improve weight loss and lipid profiles, particularly in those with metabolic syndrome. However, it requires careful dose calculations and strict monitoring for side effects. More research is needed to validate the use of LT3 in hypothyroidism.

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