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LEVOTHYROXINE AND LIOTHYRONINE IN HYPOTHYROIDISM: A COMPARATIVE REVIEW OF SAFETY AND EFFICACY

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ABSTRACT

Hypothyroidism is one of the most prevalent endocrine disorders worldwide and represents a major clinical and public health challenge due to its diverse systemic manifestations. Epidemiological data from the National Health and Nutrition Examination Survey indicate that approximately 4.6%of the United States population is affected. With higher prevalence among women and the elderly. [1,2] The condition arises from deficient production of thyroid hormones and is regulated through the hypothalamic-pituitary-thyroid (HPT)axis, involving coordinated secretion of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the peripheral conversion of thyroxine (T4) to the biologically active triiodothyronine (T3).[3,4] Thyroid hormone plays a crucial role in maintaining basal metabolic rate, cardiovascular function, thermoregulation, lipid and carbohydrate metabolism, and neurodevelopment. Levothyroxine (LT4) monotherapy remains the standard of care and is effective in achieving biochemical euthyroidism in the majority of patients.[6] However, a subset of individuals continues to experience persistent symptoms despite normalized thyroid function test, leading to interest in alternative therapeutic strategies. Combination therapy with LT4 and liothyronine (LT3) has been investigated in multiple clinical trials, with mixed results regarding symptomatic improvement and quality of life. At

present, such combination therapy is considered experimental and has not been approved by the US Food and Drug Administration. This review summarizes the epidemiology, physiologic basis, clinical manifestation, and current management strategies of hypothyroidism, with particular emphasis on emerging evidence surrounding combination hormone therapy and its potential role in selected patient populations.[12]

INTRODUCTION

Hypothyroidism is a condition where the body doesn’t produce enough thyroid hormones to meet its metabolic needs. If left untreated, it leads to serious health issues such as high blood pressure, abnormal lipid levels, infertility, reduced cognitive function, and muscle problems. According to NHANES III data, about 1 in 300 people in the United States have hypothyroidism. It is more common in women and older adults and often goes unnoticed, with nearly 13 million Americans estimated to have undiagnosed cases.[2] The most common type is primary hypothyroidism, which happens due to failure of the thyroid gland itself. The main cause is autoimmune destruction, especially Hashimoto’s thyroiditis. Other causes include congenital thyroid disorders, iodine deficiency, infiltrative diseases like sarcoidosis or amyloidosis, and medical interventions such as thyroid surgery, radioiodine ablation, and neck radiation. Transient hypothyroidism can occur in conditions like postpartum thyroiditis, subacute thyroiditis, silent thyroiditis, or from blocking antibodies affecting TSH receptors. Central hypothyroidism results from issues in the pituitary gland and hypothalamus. It is marked by low. This condition often relates to a brain tumour, neurosurgery, or radiation to the head. Additionally, some medications like lithium, amiodarone, interferon-α, Interleukin-2, and tyrosine kinase inhibitors are known to cause drug-induced hypothyroidism.[3,6] Hypothyroidism often shows up with vague symptoms such as fatigue, weight gain, and feeling cold, especially in older adults, making it hard to diagnose. The most effective initial test is the serum thyroid-stimulating hormone (TSH), particularly for primary hypothyroidism. However, routine screening of asymptomatic adults hasn’t conclusively proven to lower negative outcomes.[16]

Thyroid Hormones and Brain Functions: A Clinical Perspective

Thyroid hormones are essential for brain development and continue to manage metabolic functions in the adult brain. In addition to their traditional roles, they are now seen as important for mood, thinking, and brain structure. New imaging techniques like functional MRI and quantitative MRI have greatly improved our understanding of how thyroid problems impact brain networks.[14] Hypothyroidism is prevalent among adults, with an overall rate of the gland to nearby areas, which allows it to move during swallowing. At the back, the thyroid is closely related to important structures like the recurrent laryngeal nerve and the parathyroid glands. This makes understanding its anatomy crucial for surgery. It receives a rich blood supply from the superior thyroid artery, a branch of the external carotid artery, and the inferior artery from the thyrocervical trunk. Venous drainage occurs through the superior, middle, and inferior thyroid veins. Under a microscope, the thyroid gland is made up of many spherical follicles lined by cuboidal to columnar follicular epithelial cells. These cells surround a central lumen filled with colloid containing thyroglobulin, which is the storage form of thyroid hormones. The follicular cells also synthesize and secrete triiodothyronine (T3) and thyroxine (T4). Scattered between the follicles are parafollicular or C cells, which release calcitonin and help regulate calcium metabolism. This special follicular arrangement allows the thyroid gland to store a large number of hormones outside the cells. This feature sets it apart from other endocrine glands and lets it release hormones according to the body's metabolic needs, about 9.4%. Overt hypothyroidism represents about 0.4%, while subclinical hypothyroidism, marked by high TSH along with low T3 and T4 levels. Thyroid dysfunction can significantly impact the brain, leading to functional and structural changes that are similar to those seen in major depressive disorder. Notably, about 15% of patients with depression have hypothyroidism, and 25-30% show abnormal responses of thyrotropin-releasing hormone, indicating hidden thyroid issues. Preclinical and animal research links hypothyroidism to problems with myelination, lower microvascular density, reduced neurogenesis, and changes in brain network function. The relevance of these findings for humans is still being explored. Modern imaging techniques hold promise for assessing how hypothyroidism affects the brain, tracking responses to hormone replacement therapy, and understanding the connection between hormone deficiency and symptoms related to thinking or mood.[14]

Therapeutic Use of Thyroid Hormones in Mood Disorders

Thyroid hormones have proven roles in treating mood disorders. Triiodothyronine (T3, Liothyronine) is used to enhance and speed up the effects of antidepressants, especially tricyclic antidepressants and selective serotonin reuptake inhibitors. High doses of thyroxine (T4, Levothyroxine), sometimes reaching up to 600 µg/day, have demonstrated effectiveness in treating resistant depression and bipolar disorder, with long-term safety shown in controlled studies. Notably, thyroid hormone therapy can improve the effect of antidepressants and lower the risk of relapse even in patients with resistant mood disorders who have a normal thyroid function.[15]

ANATOMY

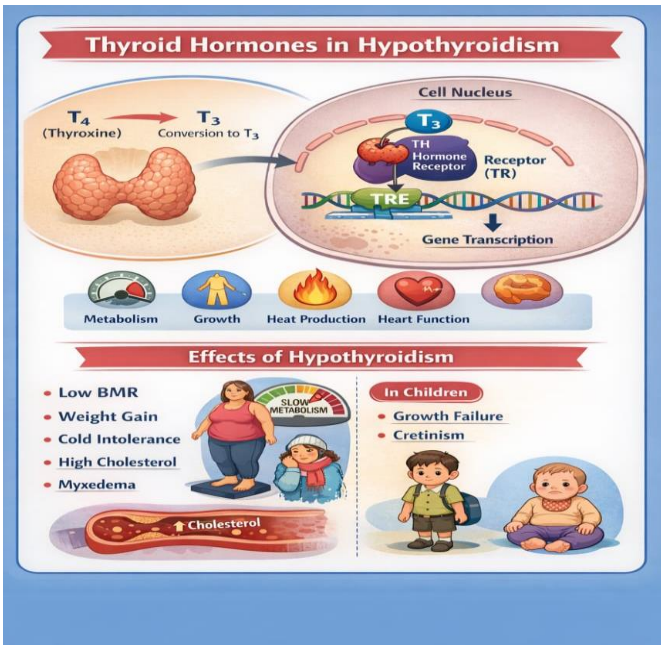
The thyroid gland is a butterfly-shaped endocrine gland located at the front of the neck, below the larynx and in front of the neck, below the larynx and in front of the upper trachea. It usually extends from the level of the fifth cervical vertebrae to the first thoracic vertebrae. The gland has two lateral lobes, the right and the left, connected in the middle by a narrow isthmus, typically lying over the second to fourth tracheal rings. In some people, a pyramidal lobe can extend upward from the isthmus as a remnant of the thyroglossal duct.[3] The thyroid is soft, reddish-brown, and filled with blood vessels. It weighs on average 15 and 25 grams in adults. The gland is enclosed by a true fibrous capsule and a false capsule from the pretracheal fascia. This structure anchors the gland to nearby structures and allows it to move during swallowing. At the back, the thyroid is closely related to important structures like the recurrent laryngeal nerve and the parathyroid glands. This makes understanding its anatomy crucial for surgery.

It receives a rich blood supply from the superior thyroid artery and the inferior thyroid artery from the thyrocervical trunk. Venous drainage occurs through the superior, middle, and inferior thyroid veins. Under a microscope, the thyroid gland is made up of many spherical follicles lined by cuboidal to columnar follicular epithelial cells. These cells surround a central lumen filled with colloid containing thyroglobulin, which is the storage form of thyroid hormones. The follicular cells also synthesize and secrete triiodothyronine (T3) and thyroxine (T4). Scattered between the follicles are parafollicular or C cells, which release calcitonin and help regulate calcium metabolism. This special follicular arrangement allows the thyroid gland to store large amounts of hormone outside the cells. This feature sets it apart from other endocrine glands and lets it release hormones according to the body’s metabolic needs.

Hormones produced by the thyroid gland: The thyroid gland produces three important hormones: thyroxine (T4), triiodothyronine (T3), and calcitonin. Each hormone has its own origin and function. Thyroxine (T4) is the main hormone secreted by the follicular cells of the thyroid gland and makes up about 90% of total thyroid hormone output. While it has relatively low biological activity, its primary role is to act as a peripheral tissue, such as the liver, kidney, and muscles into the more active triiodothyronine (T3). Triiodothyronine (T3) is also produced in small amounts directly by the thyroid gland. It has a much stronger affinity for the nuclear thyroid hormone receptors and is responsible for most of the actions of thyroid hormones. These actions include regulating the basal metabolic rate, oxygen consumption, heat production, protein synthesis, and carbohydrate metabolism. T3 also plays a role in growth and the development of the central nervous system. Both T3 and T4 are made from the amino acid tyrosine and iodine. They are stored in the follicular colloid as thyroglobulin and released into the blood under the control of thyroid-stimulating hormone (TSH) from the anterior pituitary. In addition to these hormones, the thyroid gland releases calcitonin from the parafollicular cells. Calcitonin helps maintain calcium and phosphate balance by lowering blood calcium levels. It does this by inhibiting osteoclastic bone resorption and acts as a counterbalance to parathyroid hormone.[13]

PHYSIOLOGY OF HORMONES

Mechanism of action and metabolic role of T3 and T4 in hypothyroidism (exam-oriented): Thyroid hormones work through nuclear hormone receptors (TRs) found in the cell nucleus. T3 (triiodothyronine) is the active hormone and has a much stronger affinity for the receptor than T4 (thyroxine). T4 is mostly converted to T3 inside target cells. T3 binds to the TR to form a hormone-receptor complex, which attaches to specific DNA sequences known as thyroid hormone response elements (TREs) using zinc-finger domains. This process regulates gene transcription. These genes control metabolism, growth, heat production, and heart function. In hypothyroidism, a lack of T3 and T4 leads to reduced gene transcription and a general decline in metabolic activity. This results in a lower basal metabolic rate, decreased carbohydrate, lipid, and protein metabolism, less heat production, weight gain, high cholesterol, cold intolerance, and myxoedema.[13] In children, severe deficiency can cause growth failure and neurodevelopmental issues like cretinism.



PHARMACOLOGY PROFILE OF THYROID HORMONES

Levothyroxine (LT4) therapy has been the standard treatment for hypothyroidism for over five decades. It continues to be the primary approach used worldwide. LT4 is safe, easy to give, and very effective in restoring normal thyroid function in most patients. This allows for long-term follow-up by non-specialists with little input from endocrinologists. The use of LT4 became popular because peripheral tissues can convert T4 to the active hormone. The ability to measure serum TSH levels made it possible to fine-tune doses accurately.[6]

However, even when TSH levels are normal, 10-20% of patients still report ongoing symptoms. These can include cognitive issues, lower quality of life, weight gain, and abnormal lipid levels. This has sparked renewed interest in liothyronine (T3) therapy, used alone or with LT4. Current evidence from trials and meta-analyses does not show a clear overall advantage of T3 supplementation compared to LT4 alone. Still, some patients prefer T3, and there are slight benefits to weight or lipid profiles that may indicate a responsive group.[8] Safety data looks good when TSH levels are kept within the normal range, but there are still concerns about unnatural spikes in T3. Therefore, while LT4 remains the first treatment option, carefully monitored T3 use might be considered for certain patients under specialist care. This underscores the need for better biomarkers and larger studies to tailor treatment to individual needs.[12]

METHODS OF DOSE CALCULATION

They are based on the current LT4 dose, which keeps TSH in the desired range. Replacing part of that LT4 dose with LT3. Using a 3:1 potency ratio (i.e., 3 mcg T4 ~1 mcg T3) derived from measurements in thyroidectomized patients. Target T4:T3 Ratios: The three approaches proposed by Weirding give a T4:T3 therapy. All these studies used fixed replacement ratios (for example, 10 mcg T3 for 50 mcg T4 equals a 5:1 ratio), which led to higher T3 dosing than what is natural. Comparison to Animal Thyroid Extracts: Desiccated animal thyroid has a T4:T3 ratio of about 4:1, which has much more T3 than human thyroid production. This suggests that these extracts are likely over-replacing T3. Practical limitation: In a patient who has previously taken 100 mcg of LT4 daily, such an approach would suggest only an increase of 4 to 6 mcg of T3 per day. However, there isn't a ready-made preparation of T3 (usually 5 mcg or 10 mcg tablets) that enables even low-dose, split dosing-especially with two doses per day to mimic natural variation. Last-Minute Takeaway:[8] Wiersema's methods suggest more natural T4:T3 dosing (13:1 to 20:1) than most studies or animal extracts. But in real-world practice, low-dose T3 delivery remains difficult due to tablet size and dosing schedules.

DIAGNOSIS

The diagnosis of thyroid disorders involves a mix of clinical evaluation, lab tests, and imaging studies. These methods help assess how the thyroid works and its structure. Clinically, doctors check for symptoms and signs of hypo- or hyperthyroidism. These symptoms include weight changes, intolerance to heat or cold, palpitation, fatigue, neck swelling, and changes in skin and hair, or bowel habits.

Lab test or crucial for diagnosis, with serum thyroid-stimulating hormone (TSH) being the most sensitive initial test. High TSH levels indicate primary hypothyroidism, while low TSH levels suggest hyperthyroidism. Measuring free thyroxine (FT4) and free triiodothyronine (FT3) helps determine the severity and type of thyroid dysfunctions and separates overt disease from subclinical cases.

Autoimmune thyroid disorders are identified by checking for thyroid autoantibodies. This includes anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies in hypothyroidism and TSH receptor antibodies in hyperthyroidism. Imaging studies also support the diagnosis, especially for patients with goitre or nodules. Ultrasonography is the preferred first imaging method to evaluate the size, echotexture, and presence of nodules in the thyroid. A radionuclide thyroid uptake and scan assesses functional activity and helps identify the causes of hyperthyroidism.[6] In cases of thyroid nodules with concerning features, fine needle aspiration cytology (FNAC) is done to check for cancer. In summary, combining clinical findings, lab tests, and imaging ensures a precise diagnosis and suitable management of thyroid disorders.

EXCLUDE CO-MORBID ILLNESSES BEFORE COMBINATION THERAPY

Nonspecific signs of hypothyroidism, such as fatigue, low mood, and mental fog, can overlap with or be caused by other diseases. Hypothyroidism is relatively common, so it may occur alongside other conditions, making diagnosis and management tricky.

Differential Conditions That Mimic or Co-exist with Hypothyroidism

- ✓ Depression
- ✓ Chronic Fatigue Syndrome (CFS)
- ✓ Fibromyalgia's.

Autoimmune Connection: Most cases of hypothyroidism are autoimmune, such as Hashimoto's. Other autoimmune diseases, like rheumatoid arthritis and celiac disease, are also common in these patients. Therefore, it is crucial to.

- Take a full history
- Perform a targeted physical examination
- Have some investigations in mind.

Does Autoimmunity Alone Cause Symptoms? Inconsistent Evidence: A large Norwegian study found no convincing link between thyroid antibodies and symptoms. Two small studies suggest that some symptoms are related to thyroid autoimmunity, even if hormone levels are normal. Implication: If symptoms are due to autoimmunity, combination therapy (T4/T3) will not help. Symptoms will only improve as antibody levels decrease, not because of T3 use. Thyroid antibody levels should not guide decisions about combination therapy. Physiological Comorbidities: depression, anxiety, and other mental health issues can show thyroid-like symptoms of hypothyroidism. They can interfere with treatment response and may even worsen with LT3, especially anxiety. Important Takeaways: Do not assume that ongoing symptoms mean T4 therapy is failing. Always check for other diagnoses, especially psychological and autoimmune overlap syndromes. Be cautious when using LT3 in individuals with psychiatric conditions. Avoid Interpretation of Thyroid Function Tests (TFTs).

INTERPRETING THYROID FUNCTION TESTS

Interpreting thyroid function tests is based on the physiology of the Hypothalamic-Pituitary-Thyroid (HPT) axis. This system keeps thyroid hormone levels stable through a regulated negative feedback process. In this axis, the pituitary gland releases thyroid-stimulating hormone (TSH). TSH prompts the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). Higher levels of T3 and T4 then reduce TSH release. TSH is the most sensitive and reliable marker for thyroid issues. It is usually assessed along with free T4 to differentiate between subclinical and overt disease. More than 99% of thyroid hormones circulate bound to plasma proteins, such as thyroxine-binding globulin. Only the free hormone fraction is biologically active, so measuring free hormones is more meaningful than total hormone levels. Specific biochemical patterns aid in diagnosis. Elevated TSH with normal T4 indicates subclinical hypothyroidism, elevated TSH with low T4 indicates overt hypothyroidism, and low TSH suggests subclinical hyperthyroidism. However, interpretation can be complex. Factors include assay interferences, biotin supplementation, altered binding proteins, medications affecting hormone production or absorption, non-thyroidal illness, and central disorders affecting the pituitary or hypothalamus. All these aspects must be carefully reviewed for accurate diagnosis and proper clinical management.[15]

Biochemical patterns in the interpretation of thyroid function tests

Interpreting thyroid function tests relies on recognizing specific biochemical patterns between thyroid-stimulating hormone (TSH), T4, and T3 within the hypothalamic-pituitary-thyroid-thyroid (HPT) axis, which generally works through a negative feedback mechanism. Normally, a drop in thyroid hormones leads to a rise in TSH, while excess thyroid hormones lower TSH levels. Disruption of this balance creates diagnostic patterns that classify thyroid hormones. Subclinical hypothyroidism typically shows mildly elevated TSH (4.5-10mIU/L) and normal T4. Over-hypothyroidism is marked by significantly elevated TSH (≥10 mIU/L) with low or normal T4. In contrast, sublingual hyperthyroidism presents with low TSH and normal thyroid hormone levels, while overt hyperthyroidism shows low TSH with elevated T4 and/or T3. Some unusual patterns need special attention, such as high TSH with elevated T4/T3, which can occur in rare cases like TSH-secreting pituitary adenoma or thyroid hormone resistance. Low TSH with T4/T3 may indicate central hypothyroidism due to pituitary or hypothalamic issues. A normal TSH with elevated thyroid hormones often is not a concern and can arise from biotin interference, excess thyroxine-binding globulin, or familial dys albuminaemia. In patients on thyroxine therapy, abnormal TSH patterns may indicate poor adherence, malabsorption, dietary or drug interference, excessive dosing, aging, or hormonal changes like estrogen withdrawal. Clinicians should also watch for assay interferences, such as biotin causing falsely low TSH, macro-TSH leading to falsely high TSH, and changes in binding proteins due to medications.[13] Therefore, accurately interpreting TFTs calls for correlating biochemical patterns with the clinical context, treatment history, and possible lab artifacts.

HERITABILITY OF THYROID HORMONES

It has long been understood that the levels of thyroid-stimulating hormone (TSH), free thyroxine (free T4), and free triiodothyronine (free T3) vary more between individuals than they do for the same. Person over time. Andersen et al. Showed that an individual's 95% confidence interval for these hormones is about half that of the whole study population. This means that, even with wide reference ranges for the population, each person has a narrower, genetically set point for thyroid hormones.

This idea has important clinical implications. Even small changes in thyroid function within the population reference range can affect different traits, such as serum cholesterol levels, mood, and longevity. Therefore, knowing where an individual falls within this range is crucial for deciding if changes in thyroid function could lead to significant health issues.[9] Several studies have tried to measure how much genetic and environmental factors affect individual thyroid hormone set points, using twin and family study designs. Twin studies look at the differences between identical and fraternal twins. A higher similarity between identical twins' points to a stronger genetic influence. Family studies involve larger family trees and inheritance models to estimate heritability. Estimates of thyroid function heritability have varied widely across research. This variation likely comes from differences in population size, ethnicity, and how studies are designed. However, larger and more reliable studies indicate a strong genetic contribution, especially for TSH levels at about 65%. There is also a moderate genetic effect on free T4 and free T3 levels, which is around 40-50%. These results show that individual thyroid hormone set points are mostly set by genetics, but the specific genes involved have only recently started to be identified.

SAFETY AND EFFICACY OF T4/T3 COMBINATION THERAPY

This long-term U.S. study is one of the few to assess the safety and effectiveness of combination therapy using levothyroxine (T4) and liothyronine (T3) for patients with hypothyroidism. The study showed significant improvement in symptoms and quality of life for patients on combination therapy, without an increase in hyperthyroidism. The researchers observed a temporary drop in TSH and raised levels of FT4 and FT3. These were effectively managed with personalized dose adjustments and regular check-ins with an endocrinologist. Importantly, there were no serious adverse outcomes such as atrial fibrillation, cardiac death, or hospitalization. Only a small number of patients reported mild palpitations or anxiety.[11]

ADVERSE EFFECTS

This randomized, double -blind, crossover clinical trial compared standard levothyroxine (LT4) monotherapy with combined LT4 and liothyronine (LT3) therapy in adults with hypothyroidism. Each treatment phase lasted eight weeks and included LT4 100µg/day, LT4 75 µg plus LT3 5 µg/day, and a final combination of LT4 87.5 µg plus LT3 7.5µg/day. This was designed to achieve a physiological LT4:LT3 ratio of about 14:1. Participants received two daily tablets dispensed in opaque colour-coded boxes to maintain blinding: a fixed 50 µg LT4 tablet (Euthyrox: Merck KGaA) and a second tablet that varied by study phase (Levothyroid Novothyral Mite, or Novothyral 75). This ensured consistent dosing and preserved the double-blind design.[4]

SPECIAL POPULATION: OLDER PATIENTS

As populations age, thyroid dysfunction has become more significant in older adults. By 2040, nearly one in seven people in the United Kingdom is expected to be 75 years or older. This will bring a rising burden of age-related conditions such as dementia, type 2 diabetes mellitus, and cardiovascular disease. Thyroid dysfunction, which affects about 3-21% of the population, is more common in women and the elderly.[17] Diagnosing I is difficult due to nonspecific symptoms that overlap with normal aging and other health issues. Assessment mainly relies on biochemical testing, especially serum TSH. However, age-related increases in TSH can lead to overdiagnosis and overtreatment when uniform reference ranges are used. As thyroid hormone needs decrease with age, older patients are more likely to experience negative effects from excess therapy, such as atrial fibrillation and osteoporosis. This underscores the need for careful, individualized management and age-appropriate interpretation of thyroid function tests.[18]

Pregnancy results in significant changes to thyroid function. .it increases iodine needs from about 150 micrograms in non-pregnant women to around 350 micrograms. Thyroid disorders, particularly autoimmune conditions, are common during pregnancy. Hypothyroidism is usually due to Hashimoto’s thyroiditis, while hyperthyroidism is often linked to Graves' disease. Understanding thyroid function tests is complicated. Estrogen raises thyroid binding globulin, and the placenta's human chorionic gonadotropin lowers TSH, especially in the first trimester. This situation requires reference ranges specific to each trimester both overt and subclinical hypothyroidism are diagnosed using trimester-adjusted TSH and free T4 levels. They need treatment with levothyroxine, which includes careful monitoring during pregnancy, adjusting the dose after conception, and reevaluating after childbirth.

CONCLUSION

Levothyroxine (LT4) monotherapy is the standard treatment for hypothyroidism and works well for most patients. However, 10 to 20 % of patients still have persistent symptoms, even with normal lab results. Adding liothyronine (LT3) to LT4 has not shown clear benefits for the general population, but some patients seem to do better with the combination. This may be because of issues with converting T4to T3 in the body. Evidence from several randomized controlled trials and retrospective studies indicated that LT4 +LT3 therapy can be safe and effective for certain individuals. Future progress relies on large, well-designed trials focusing on the right patient groups. Meanwhile, new developments like slow-release and rapid-acting LT3 formulations, along with experimental synthetic thyroid tissue, could help tailor and improve hypothyroidism treatment.[7]

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