S Afr Gen Pract. 2025;6(2):65-70
https://doi.org/10.36303/SAPJ.3267

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621

REVIEW

Advances in hypothyroidism management: rethinking therapy beyond levothyroxine

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Hypothyroidism, a prevalent neuroendocrine disorder characterised by insufficient thyroid hormone production and a wide spectrum of clinical manifestations, affects approximately 5% of the population, with an additional 5% remaining undiagnosed. While levothyroxine remains the golden standard of care, its inability to resolve persistent symptoms in a subset of patients highlights the need for alternative approaches. Combination levothyroxine+liothyronine therapy, though unpopular and underutilised by most physicians, offers potential benefits, particularly when tailored to mimic natural thyroid hormone ratios. Furthermore, emerging therapies show promise in reducing pharmacokinetic fluctuations that limit current advances in hypothyroidism therapy. By addressing the shortcomings of traditional therapies, these innovative approaches aim to improve the quality of life and clinical outcomes for patients with hypothyroidism, especially when the golden standard fails. This review highlights current viable options and explores emerging therapeutic strategies that could potentially optimise current treatment and quality of life, catering for all hypothyroidism patients.

Keywords: hypothyroidism, levothyroxine, liothyronine, novel thyroid hormone formulations, T4/T3 combination therapy

Republished from: *S Afr Pharm J.* 2025;92(4):50-54. https://doi.org/10.36303/SAPJ.3267

Introduction

Hypothyroidism is the most common hormone deficiency disorder[1] affecting approximately 5% of the general population, with an additional 5% estimated to be undiagnosed.[2] Despite its global prevalence, epidemiological data highlighting the prevalence of hypothyroidism in South Africa is currently very limited. However, it is well established that women are five to ten times more likely to develop hypothyroidism than men, with the likelihood increasing with age, during pregnancy, postpartum, and menopause.[3] Hypothyroidism occurs when there is insufficient production of thyroid hormone to meet the body's requirements,[2] which can result in a range of subtle to life-threatening symptoms, if not adequately treated and monitored.[2] The thyroid gland, located in the neck, is responsible for the production of the prohormone thyroxine/tetraiodothyronine (T4) and its activation to form its biologically active counterpart, triiodothyronine (T3) (Figure 1).[2-3] Both T3 and T4 are collectively termed thyroid hormone.[2] Conversion of T4 to T3 occurs through a process called deiodination by 5' deiodinase enzymes, which remove an iodine atom from T4.[4] Deiodinase is also responsible for producing metabolically inactive T3 known as reverse T3.[4]

Hypothyroidism pathophysiology

Secretion and production of thyroid hormone are under the control of a self-regulatory circuit known as the hypothalamic-pituitary-thyroid (HPT) axis (Figure 2).[6] This neuroendocrine system regulates the production and secretion of thyroid hormone.[6] In this system, the thyroid releasing hormone (TRH) is produced by the neurons of the hypothalamus known as the paraventricular nuclei.[7] This stimulates the secretion of thyroid stimulating hormone (TSH), also known as thyrotropin, by the

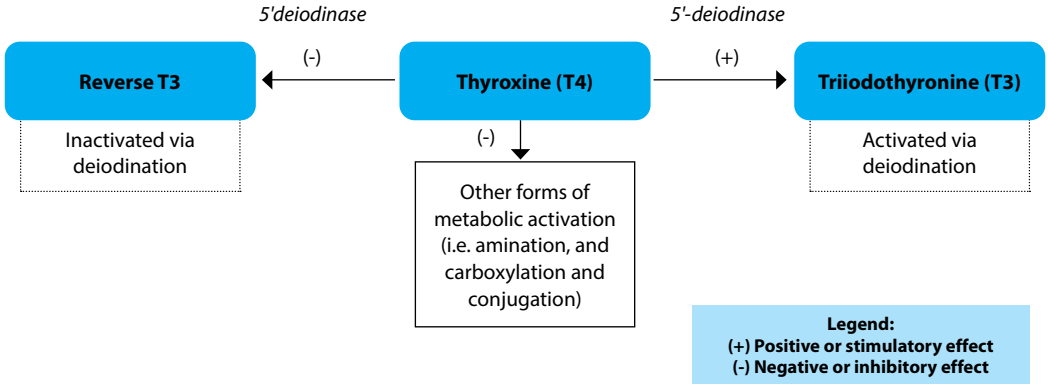

Figure 1: The metabolic pathways of thyroxine (T4)[5]

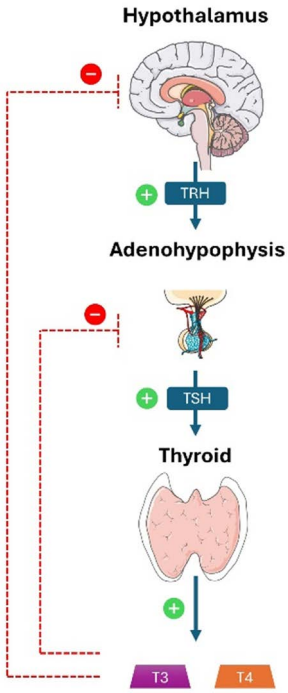

Figure 2: A visual representation of the hypothalamus-pituitary-thyroid (HPT) axis.[7] Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce and release triiodothyronine (T3) and thyroxine (T4).

pituitary gland, which binds to its membrane receptor on the thyroid, facilitating the release of T4 and T3.[7] Iodine is the main micronutrient required for this process, serving as a component of T4 and T3.[8] When there is a high concentration of thyroid hormone (T4 + T3) in the blood, a negative feedback mechanism is activated to inhibit the further secretion of the hormone by the pituitary gland, ensuring that homeostasis is maintained.[6-7] A disruption in the function of any of the three components of the HPT axis (hypothalamus, pituitary gland or thyroid gland) can lead to insufficient production of thyroid hormone and thus hypothyroidism.[9] Depending on the origin of the disruption, hypothyroidism can be classified into various types.

Classifications of hypothyroidism and their causes

Hypothyroidism can be classified into primary, secondary, and tertiary types.[10] While over 99% of hypothyroidism cases are due to failure of the thyroid gland (primary), causes of hypothyroidism may alternatively be due to insufficient TSH from the pituitary gland (secondary) or insufficient TRH from the hypothalamus (tertiary).[2] Secondary and tertiary hypothyroidism are rare and often present with the same clinical manifestations,[10] consequently, they are collectively termed central hypothyroidism.[2,10]

Primary hypothyroidism

Primary hypothyroidism is mainly caused by iodine irregularities or autoimmune thyroiditis, commonly referred to as Hashimoto's disease. In addition to this, there are many other causes which are highlighted in Table I.[11-12] Both excess iodine and the deficiency thereof can induce hypothyroidism.[13] Excess iodine can result from external radiation, radioactive iodine, and certain medications, such as amiodarone and lithium, which can affect thyroid function and subsequently hormone production.[3] Additionally, medications like β-blockers and corticosteroids inhibit 5′-deiodinase activity, critical for the conversion of T4 to T3, further impairing thyroid hormone synthesis. Both excess iodine and the deficiency thereof can induce hypothyroidism.[13] Excess iodine can result from external radiation, radioactive iodine, and certain medications, such as amiodarone and lithium, which can affect thyroid function and subsequently hormone production.[3] Additionally, medications like β-blockers and corticosteroids inhibit 5′-deiodinase activity, critical for the conversion of T4 to T3, further impairing thyroid hormone synthesis.[14]

Nevertheless, environmental iodine deficiency is the most common cause of hypothyroidism.[2] Reduced iodine content in soil across many regions results in crops with insufficient iodine levels, leading to dietary intake below the daily requirement for synthesising thyroid hormones, particularly T4.[15] To address this, many countries, including South Africa, have implemented iodine fortification programmes, such as iodising salt and

Table I: Causes of hypothyroidism[12-13]

Primary Hypothyroidism	Central Hypothyroidism
Loss of functional thyroid tissue	Pituitary or hypothalamic neoplasms
Hashimoto's thyroiditis	Trauma (surgery, head injury)
Surgical removal of the thyroid	Radiation ischaemic necrosis (postpartum pituitary infarction/
Radioiodine ablation, external irradiation of the thyroid	Sheehan's syndrome, severe shock, diabetes mellitus)
Silent and postpartum thyroiditis	Vascular (haemorrhage, aneurysm of the internal carotid artery)
Cytokine-induced thyroiditis	Infections (abscess, tuberculosis, syphilis, toxoplasmosis)
Invasive fibrous thyroiditis	Infiltrative disorders (sarcoidosis, histiocytosis, haemochromatosis)
Thyroid infiltration (amyloidosis, haemochromatosis, sarcoidosis, scleroderma,	Lymphocytic hypophysitis
cystinosis, primary thyroid lymphoma)	Drugs (bexarotene)
Thyroid dysgenesis	Set point diseases (infants born to mothers with poorly controlled
Functional defects in thyroid hormone biosynthesis and release	Graves' disease)
Iodine deficiency and iodine excess	Genetic mutations
Thyroid hormone biosynthetic defect	Idiopathic
Drugs: antithyroid agents, lithium, amiodarone, tyrosine kinase inhibitors	
(e.g. sunitinib), ethionamide, sulphonamides, goitrogenic chemicals, thalidomide	
Peripheral (extrathyroidal) hypothyroidism	
Large haemangioma	
Thyroid hormone resistance	

common food items, to reduce the prevalence of iodine-deficiency-induced hypothyroidism.[13] In areas with sufficient iodine, Hashimoto's disease is the most common cause of hypothyroidism.[2] This disease occurs due to an immune-mediated destruction of the thyroid gland by cytotoxic T-lymphocytes and autoantibodies.[6] As a result, fibrosis may reduce thyroid gland size and lead to hypothyroidism.[6] While the precise mechanisms underlying Hashimoto's disease remain unclear, it is believed that genetic and environmental factors play a causative role.[13]

Central hypothyroidism

Central hypothyroidism is caused by impaired production of TSH from the pituitary gland, leading to inadequate stimulation of an otherwise normal thyroid gland to produce thyroid hormone.[1,16] Since the pituitary is stimulated by TRH, which is released by the hypothalamus, hypothyroid impairments are frequently linked to the hypothalamus as well.[13] As a result, secondary hypothyroidism, which arises from the pituitary gland, and tertiary hypothyroidism, which originates in the hypothalamus, are collectively referred to as central hypothyroidism.[13,16] Secondary and tertiary hypothyroidism are uncommon, occurring in less than 1% of hypothyroidism cases.[1] Contrary to primary hypothyroidism, central hypothyroidism has a uniform prevalence in both sexes.[1,13] The causes of central hypothyroidism are listed in Table I[13] and include pituitary adenomas, head trauma, radiation, various surgical procedures and genetics.[13]

Signs and symptoms of hypothyroidism

The thyroid hormone impacts nearly every organ system in the body, including the heart, nervous system, bones, and gastrointestinal tract.[6] This is because thyroid hormone plays diverse roles in the regulation of metabolism, growth, neural differentiation and normal development of mammals, resulting in a range of symptoms when production is disturbed.[17] Table II provides a broad overview of the effects of thyroid hormone, emphasising its diverse roles and impact on bodily functions.[6] Thyroid hormone production is particularly vital during pregnancy, as it supports foetal development, placing an increased demand on the mother's thyroid gland to meet the needs of both mother and foetus.[18] In infants, conditions of hypothyroidism during development manifest as significant neurological deficits and growth retardation.[17] In contrast, symptoms in adults range from subtle[17] to life-threatening, with subtle symptoms including fatigue, depression, weight gain, voice changes, dry skin, lethargy, constipation, sleep disorders, muscle cramps, oedema, and cold intolerance, while the most serious symptom is myxoedema coma.[19] Hypothyroidism typically presents with numerous symptoms that are normal to ageing and easily attributable to other disorders, making clinical manifestations an unreliable method for diagnosis.[3]

Diagnosis

Diagnosis of hypothyroidism may begin with a physical examination for course skin, delayed ankle reflex, and other common symptoms.[3] However, due to low specificity of these signs, a clinical evaluation should be accompanied with a diagnostic work up.[3] Blood tests to assess TSH and free T4 levels are essential for confirming the diagnosis.[19] Primary hypothyroidism is characterised by reduced free T4 and elevated TSH levels, while central hypothyroidism may present with normal/low TSH levels and low free T4 levels.[19] Additional testing that reveals elevated thyroid peroxidase antibodies supports the diagnosis of autoimmune hypothyroidism.[19]

Blood test levels of T4 and TSH are further classified into two diagnostic categories that guide treatment: subclinical hypothyroidism and overt hypothyroidism.[12] Subclinical hypothyroidism is a mild form of hypothyroidism, biochemically diagnosed when there are elevated TSH concentrations while free T4 and T3 serum concentrations remain within the normal range.[12] This grade of hypothyroidism is usually an indicator that the thyroid is starting to underperform, but is still maintaining normal thyroid hormone production.[12] Patients are usually treated when TSH levels rise above 10 mIU/L, as this threshold suggests a greater risk of progression or complications.[12] In pregnant women, however, most clinicians treat subclinical hypothyrodism even when TSH levels are below 10 mIU/L due to the risks that low thyroid hormone levels pose to foetal development.[12] In some cases, subclinical hypothyroidism can progress to overt hypothyroidism,[12] a more intense form of hypothyroidism characterised by elevated TSH accompanied by low serum free T4 concentrations.[20] Overt hypothyroidism

Table II: Organ and system involvement of thyroid hormone and its resulting effects[6,18]

Organ/system	Effect	Result
Heart	Increased β-receptor expression	Increased heart rate, stroke volume, cardiac output and contractility
Lungs	Stimulate respiratory centres	Increased perfusion and oxygenation
Skeletal muscle	Increased development of Type II (fast twitch) muscle fibres.	Increased capability for fast and powerful contractions
Metabolism	Increased Na+/K+ ATPase expression and basal metabolic rate	Increased oxygen consumption, respiration rate and body temperature
Growth during childhood	Induction of chondrocytes, osteoblasts and osteoclasts. Assist axonal growth and myelin sheath formation	Bone growth Brain maturation
Hypothalamic-pituitary gonadal axis	Regulates kisspeptin and gonadotropin-releasing hormone directly, and indirectly through prolactin and leptin. Affects the biological availability of sex steroids	Development and maintenance of the ovary, uterus and endometrium Regulates placental and foetal development during pregnancy

is particularly common in women who are of reproductive age and warrants treatment regardless of symptom severity.[20] This grade of hypothyroidism is mostly permanent and requires lifelong management and treatment.[12]

Treatment

Levothyroxine

Replacement therapy with levothyroxine (LT4) monotherapy currently serves as the standard of care for hypothyroidism.[21] Synthetically produced T4, LT4, is identical to the hormone secreted by the thyroid gland and can be converted to T3 when appropriately regulated by peripheral tissues (Figure 1). This results in the maintenance of a steady secretion of thyroid hormone to meet the body's requirements.[12] An advantage of LT4 therapy is its long half-life of seven days, allowing single daily doses and maintenance of patient safety in the case of omission or lack of compliance for a day.[12] The greatest challenge with LT4, however, lies in its low therapeutic index (TI) and the fact that normalising TSH levels does not always correspond with the normalisation of other markers of hypothyroidism.[21] Due to its narrow TI, precise dosing of LT4 is critical.[11] Typical dosages for women are 100–125 µg/day and 125–150 µg/day for men, with T4 requirements varying, depending on body weight and surface area, age, and pregnancy status.[11] Dosing in individuals with ischaemic heart disease or those over 60 should typically start with between a fourth and half of the expected dosage, while pregnant women require higher dosages due to increased hormone requirements.[3]

Side effects of levothyroxine therapy

Though LT4 is identical to thyroid-secreted T4, there are clinical consequences to excessive administration, and this is unfortunately common in clinical practice.[12] A notably high proportion (15–38%) of LT4 patients have been found to present with TSH levels dropping below reference range, indicative of over-replacement, thus highlighting the importance of close monitoring of TSH levels.[22] Furthermore, LT4 therapy presents with several adverse effects including reduction in bone density, especially in post-menopausal women,[12] increased risk of fracture, atrial fibrillation, stroke and bleeding.[11]

Limitations of current LT4 monotherapy

Standard hypothyroidism therapy has three main limitations.[23] Firstly, an estimated 10–20% of patients remain symptomatic despite the normalisation of TSH levels.[23] These patients experience the persistence of residual cognitive symptoms, difficulties managing body weight, and elevated cholesterol levels, all of which significantly reduce their quality of life and diminish the perceived benefits of treatment.[23]

Secondly, patients treated with LT4 may exhibit a relative and sometimes absolute deficiency of LT3.[24-25] This is because although LT4 effectively normalises pituitary TSH levels, it does not consistently restore T3 levels in peripheral tissues.[26-27] This discrepancy arises because T4 itself can inhibit the activity of Type 2 5′-deiodinase, thereby creating a localised T3 deficiency despite normal serum TSH levels.[26-27]

Lastly, the efficacy of LT4 therapy may also be influenced by genetic factors and comorbid conditions.[28] For instance, patients with polymorphisms such as Thr92Ala in the iodothyronine deiodinase 2 gene, which encodes Type 2 5′-deiodinase, often show improved outcomes with combination therapy compared to levothyroxine monotherapy.[29] These genetic variations reduce the catalytic activity of Type 2 5′-deiodinase, impairing the conversion of T4 to T3 in tissues (Figure 1).[29] Such genetic predispositions, combined with other comorbidities, help explain the persistence of symptoms in some patients, even when serum TSH levels are within the normal range.[12,30]

Combination LT4+LT3 therapy

In cases where persistent hypothyroidism symptoms occur despite normal TSH concentrations in patients treated with LT4, a combination of LT4 and LT3 therapy may be considered.[31] Currently, no combined formulation of T3 and T4 adequately mimics the relative concentrations of thyroid hormone produced naturally by the human thyroid.[12] Furthermore, no formulation allows the sustainable release of T4 and T3 as they would be released by the human thyroid.[12] As a result, and in many cases, combination therapy has been ruled out by many clinicians because there is no clear benefit when compared to LT4 monotherapy.[12]

Nevertheless, the limitations of LT4 therapy and the need for alternatives have driven the development of new therapeutic approaches, including transitioning patients to a combination of LT4 and LT3 in ratios designed to mimic the natural thyroid.[23] Clinical studies have tested multiple ratios, concluding that a range of 13:1 to 20:1 (T4:T3) effectively replicates the thyroid gland's output.[32-33] When administered at appropriate ratios, combination therapy is as effective as LT4 monotherapy in resolving hypothyroidism symptoms and normalising TSH levels.[23] Despite this evidence, many clinicians continue to view LT4 monotherapy as the gold standard, highlighting the need for greater awareness of combination therapy's potential benefits.[23]

While this approach has mainly been explored in other countries, it is readily applicable in South Africa as LT4 (commonly known as Levothyroxine)[34] and LT3 (commonly Liothyronine)[35] are available. Physicians can enhance treatment outcomes for patients on LT4 who continue to experience hypothyroidism symptoms by carefully titrating LT4 and LT3 doses to replicate physiological thyroid hormone release more closely.[32]

Liothyronine sodium monotherapy

Liothyronine is the synthetic form of T3 hormone produced by the body.[12] Unlike T4, it requires more than one daily dose due to its short half-life of one day.[12] In addition to its short half-life, LT3 gives rise to extremely high serum T3 levels (between 250–600%) in its absorption phase, resulting in adverse effects, commonly cardiovascular effects such as palpitations.[12] These pharmacokinetic fluctuations and associated cardiovascular risks have led many clinicians to question the benefits of LT3 therapy.[12,23] Despite these concerns, evidence suggests that T3-

containing therapies are as safe as LT4 therapy when serum TSH levels are maintained within the normal range.[23] This further highlights the efficacy of combination LT4+LT3 therapy.[23,36] Liothyronine monotherapy may also be considered in rare cases of LT4 malabsorption or in patients who struggle to metabolise LT4 to LT3.[12]

Novel approaches to current available hormone replacement therapy

New slow-release T3 formulations are under development to address the rapid absorption and metabolism of current LT3 formulations, which lead to rapid fluctuations in serum T3 levels.[23] While current evidence does not associate these fluctuations with adverse outcomes, especially when TSH levels are normalised, the goal remains to achieve stable serum T3 levels.[23] Current and emerging approaches for slow-release formulations include modified matrix systems made from components such as magnesium stearate, mannitol, or calcium phosphate, designed to slow LT3 release in the intestine.[37] Clinical trials with these capsules have shown slight reductions in intestinal LT3 release and lower serum peaks.[38] However, sustained serum T3 levels were not consistently observed,[39] highlighting challenges in identifying matrix combinations capable of reliably stabilising LT3.[38]

Another promising approach is T3-Sulphate (T3-S), which involves chemically modifying T3 by attaching a sulphate group.[40] This combination inactivates T3 while improving its water solubility.[40] The liver and certain gastrointestinal bacteria can reactivate T3-S by desulfation, slowly converting it back to active T3 and releasing it into circulation.[41] A recent phase II study in hypothyroid patients, where 25 µg of LT4 was replaced with 40 µg of T3-S, demonstrated significant reductions in mean T4 levels without fluctuations in T3 levels.[42] These results suggest that T3-S could help maintain stable T3 levels while preserving a physiological T4:T3 ratio.[42]

Lastly, a novel candidate molecule, poly-zinc-LT3, is a supramolecular complex with mucoadhesive properties and controlled hydrolysis behaviour.[40] Its muco-adhesion to the gastrointestinal tract, combined with gradual hydrolysis, enables sustained LT3 release and absorption.[43] A crossover randomised controlled trial in healthy volunteers showed a 30% reduction in C_{max} for poly-zinc-LT3, delayed by an hour, with an extended plateau lasting up to six hours.[44] At 24 hours, serum T3 remained above half of the C_{max}, demonstrating an improved pharmacokinetic profile.[44]

Conclusion

Millions of individuals worldwide are affected by hypothyroidism, a complex neuroendocrine disorder characterised by insufficient thyroid hormone production and, subsequently, a wide range of clinical manifestations. While LT4 monotherapy remains the standard treatment in most healthcare settings, limitations such as unresolved symptoms in some patients highlight the need for alternative approaches. Combination LT4+LT3 therapy, previously dismissed by many clinicians due to inconclusive evidence of its benefits, is now demonstrating renewed potential when tailored to mimic physiological thyroid hormone release. In South Africa, the availability of LT4 and LT3 provides a unique opportunity to explore combination therapy as a means to improve patient outcomes. Moreover, staying informed about global advancements in hypothyroidism management, including novel therapies, positions South Africa to integrate these innovations into clinical practice as they become accessible, ensuring improved care for patients in the future.

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