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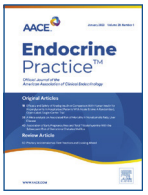

Review Article

Refractory Hypothyroidism: Unraveling the Complexities of Diagnosis and Management

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ABSTRACT

Introduction: Refractory hypothyroidism (RH) represents a challenge in the diagnosis and treatment within the field of thyroidology. It is defined as the inability to achieve disease control despite using levothyroxine (LT4) doses of 1.9 μg/kg/d or higher.
Methods: A comprehensive review, encompassing 103 articles, was conducted using the Scielo, Scopus, and EMBASE databases, providing an approach to evaluation and diagnosis of this condition.
Results: LT4 disintegrates and dissolves within an acidic gastric environment before being absorbed in the jejunum and ileum. It then extensively binds to serum transporter proteins and undergoes deiodination to yield tri-iodothyronine, the biologically active hormone. There are various nonpathological causes of RH, such as noncompliance with treatment, changes in the brand of LT4, food and drug interferences, as well as pregnancy. Pathological causes include lactose intolerance, *Helicobacter pylori* infection, giardiasis, among others. The diagnosis of RH involves conducting a thorough medical history and requesting relevant laboratory tests to rule out causes of treatment resistance. The LT4 absorption test allows for the identification of cases of malabsorption. The treatment of RH involves identifying and addressing the underlying causes of noncompliance or malabsorption. In cases of pseudomalabsorption, supervised and weekly administration of LT4 may be considered.
Discussion: Early recognition of RH and correction of its underlying cause are of utmost importance, as this avoids the use of excessive doses of LT4 and prevents cardiovascular and bone complications associated with this condition.

Introduction

The standard pharmacological treatment for patients with primary hypothyroidism is levothyroxine (LT4),[1] typically prescribed at an average daily dose of 1.6 to 1.8 μg/kg in most cases.[2,3] However, numerous challenges are encountered in LT4 therapy, including the management of patients who have thyroid-stimulating hormone (TSH) levels above the upper limit of the reference range despite receiving doses equal to or higher than 1.9 μg/kg/d of LT4, regardless of symptoms. This condition is known as refractory hypothyroidism (RH).[4,5]

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RH was first mentioned in 1956 when it was observed that some individuals with hypothyroidism had a poor response to thyroid hormone treatment, which at that time involved desiccated thyroid.[6]

The current definition of RH has been established exclusively considering primary hypothyroidism. However, it is also possible to occur in central hypothyroidism (CeH), which should be monitored by measuring free thyroxine (fT4), with the goal of maintaining it in the upper half of the reference range. In these cases, inadequate LT4 treatment is determined when fT4 is at or below the lower limit of the normal range, especially if hypothyroidism symptoms are present. The measurement of TSH alone is useful for indicating an insufficient LT4 dose in cases where it was within the normal range at the time of diagnosis and has not been successfully suppressed. Therefore, it would be prudent to consider the possibility of refractory CeH when symptoms associated with hypothyroidism persist, fT4 is at or below the lower limit of the normal range, or TSH suppression has not been achieved despite it being within the normal range at the time of diagnosis.[7-9]

Between 15% and 20% of patients receiving LT4 treatment develop RH.[10] In these cases, it is crucial to undergo an appropriate diagnostic approach to determine the underlying cause,[11] as the use of supratherapeutic doses of LT4, can result in cardiac and bone toxicity, as well as being associated with an increased risk of mortality.[12-14] In rare cases, RH may be associated with myxedema coma.[15]

Among the causes of RH, it is important to initially rule out nonpathological causes such as inadequate intake, change of brand, interaction with supplements or medications, misdiagnosis such as thyroid hormone resistance (THR) syndrome or pregnancy-related physiological increased demands,[16] immunoassay interferences, and non-adherence,[1,4,17] with the latter being the most common cause.[11] Pathological causes include obesity and gastrointestinal disorders responsible for LT4 malabsorption, as well as other rare conditions such as nephrotic syndrome, Addison's disease, and cystic fibrosis.[4,17]

The aim of this article is to provide an updated narrative review on the diagnosis and treatment of RH.

Highlights

Teaching points

- RH is the uncontrolled hypothyroidism despite using 1.9 μg/kg/d or higher LT4 dose.
- Most common causes of RH include pseudomalabsorption and gastrointestinal disorders.
- The LT4 absorption test is the gold standard exam to assess LT4 absorption.
- Appropriate management of RH reduces LT4 doses and the risk of complications.

Clinical Relevance

RH is observed in 15% to 20% of patients undergoing LT4 treatment, with the main causes being non-adherence to treatment and gastrointestinal disorders. Identification of RH, along with the prompt rectification of any underlying causes, is crucial, as long-term use of supratherapeutic doses is associated with heart and bone complications.

Methods

Systematic reviews, narrative reviews, meta-analysis, clinical trials, practice guidelines, case reports, retrospective studies, and cross-sectional studies that were pertinent to the research objective, were included. Correspondence, congress summaries and conference abstracts were excluded. The bibliographic research was conducted in the PubMed/Medline, EMBASE and Scielo databases focusing on the search terms “RH,” “LT4 treatment,” and “malabsorption syndromes” including 103 articles.

LT4 Pharmacology (Fig. 1)

The metabolism of LT4 tablets begins with its disintegration and dissolution in the stomach, a process that requires an acidic gastric pH (1.0-3.0) to remove the sodium ion and convert LT4 into a lipophilic molecule.[3,18]

LT4 is predominantly absorbed in the jejunum and ileum,[3] with absorption rates of 70% to 80% when taken on an empty stomach, and reaching its peak concentration in approximately 3 h, with a bioavailability of 70% to 80%.[19] The complete mechanism of LT4 transport across the intestinal mucosa is not fully understood, but it appears to involve the participation of transmembrane proteins, such as the organic anion transporters family, Na-taurocholate cotransporter, amino acid transporters type L 1 and 2, and monocarboxylate transporters 8 and 10, which are responsible for the entry and exit of thyroxine (T4).[20] There may also be a paracellular pathway that contributes to the absorption of LT4.[21]

After absorption, LT4 molecules are transported through the mesenteric and portal veins to the liver.[21] The metabolism of LT4 involves conjugation and deiodination processes.[22] In the liver, a portion of LT4 is conjugated by glucuronidation and sulfation, increasing its water solubility. Conjugated LT4 is secreted with bile into the intestine,[22] where it is broken down by intestinal microbiota and partially reabsorbed.[23] Deiodination involves type 1 and type 2 (D2) iodothyronine deiodinases, which convert T4 to triiodothyronine (T3) and degrade T3 to reverse T3 (rT3) and 3,3'-diiodothyronine (3,3'-T2), and type 3 (D3) enzyme, which degrades T4 to rT3 and then to 3,3'-T2.[22] T3 is the biologically active form, approximately five times more potent than T4, while rT3 has little effect in the body. The normal release ratio of T4:T3 by the thyroid gland is approximately 14:1.[24] Eighty percent of circulating T3 is derived from the deiodination of T4, and only the remaining 20% is directly released by the thyroid gland.[22,25]

Over 99% of the ingested LT4 that enters systemic circulation, as well as its biologically active metabolite, T3, bind to T4-binding globulin, albumin, and transthyretin1,19. These transporters facilitate the circulation of LT4 and prevent renal elimination. The average half-life of T4 is approximately 7.5 days, while that of T3 is approximately 1.4 days.[22,25] Thyroid hormones are primarily eliminated through the kidneys, with only 20% excreted in the feces.[26]

Our body does not distinguish between endogenous T4 and LT4, and both, along with T3, have a negative feedback effect on the hypothalamic-pituitary-thyroid axis. The release of TSH by the pituitary gland is a highly sensitive indicator of thyroid function, as its levels undergo significant changes in response to minimal variations in T4 levels.[27] This is not an inverse log-linear relationship but is composed of two overlapping negative sigmoid curves, and it varies with age and sex.[28]

However, TSH may not serve as the optimal indicator for monitoring hypothyroidism control. This potential limitation arises because it can be inadequate in accurately representing intracellular T3 levels within specific tissues, which exhibit distinct activities of deiodinases 2 and 3. Indeed, a reduction of the free T3

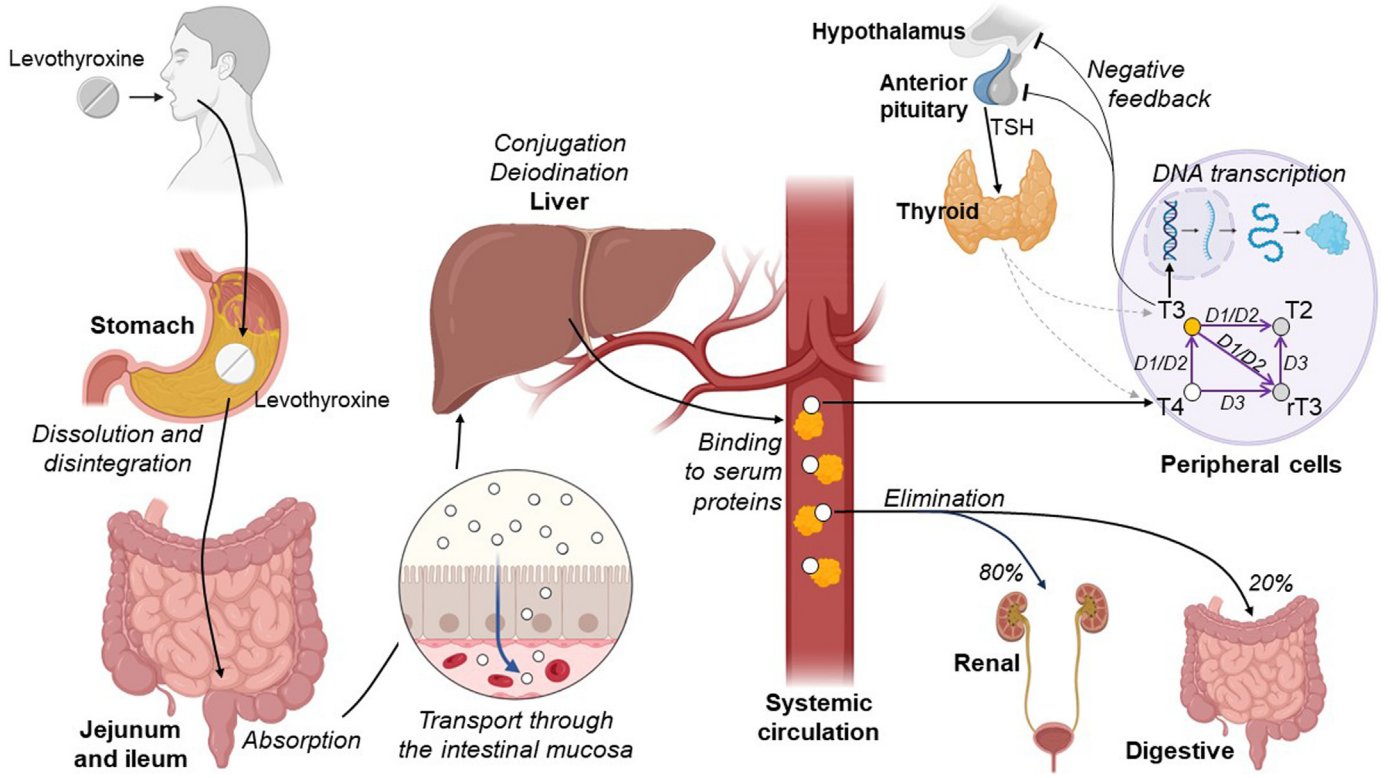

Figure 1. Pharmacokinetics and pharmacodynamics of levothyroxine. D1: type 1 iodothyronine deiodinase; D2: type 2 iodothyronine deiodinase; D3: type 3 iodothyronine deiodinase; DNA: deoxyribonucleic acid; LT4: levothyroxine; T2: di-iodothyronine; T3: tri-iodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.

(fT3):fT4 ratio is observed in numerous patients with hypothyroidism and normal TSH levels.[29] This might reflect an inability to achieve biochemical euthyroidism, as evidenced by subnormal levels of fT3, the unbound, biologically active hormone. It is important to underscore that this matter remains a topic of ongoing debate.

T3 binds to its nuclear receptors, influencing the transcription of genetic material and resulting in an increase in overall body metabolism by enhancing processes such as gluconeogenesis, protein synthesis, mobilization of glycogen stores, and other functions.[1] Thyroid hormones play a fundamental role in nearly all organs of the body, and their deficiency increases the risk of neurological, cardiovascular, myxedema, and osteoporosis-related problems.[1]

Etiology

In an observational study conducted in patients with primary hypothyroidism undergoing treatment, 28.2% had TSH levels above the reference range, and 85.4% did not take their medication properly, either due to incorrect timing or concurrent use with other medications.[30] Another study in patients with CeH treated with LT4 revealed that 38.9% of these patients had fT4 levels below the reference range despite taking LT4 as prescribed.[31] Failing to achieve euthyroidism has been associated with increased morbidity and mortality and poorer physical and emotional quality of life, highlighting the need to investigate and address the underlying factors.[1,32] In 2017, it was suggested to classify the main causes of RH as either pathological or nonpathological.[4] We will base our discussion on this classification to present the main causes.

Nonpathological Causes

1. **Inadequate intake**: Failing to observe a minimum interval of 30 min before having breakfast after administering the LT4 dose,[33] or consuming it not solely with water, but alongside another beverage,[34-37] are circumstances that may impede the absorption of LT4. The simultaneous utilization of additional medications has the potential to modulate LT4's pharmacokinetic profile[38,39]; however, this matter will be addressed subsequently.
2. **Poor adherence to treatment**: This can result from missing LT4 doses or improper use contrary to medical instructions,[4] and may arise because of potential adverse effects or insufficient availability of LT4.[10] There are instances pertaining to psychiatric conditions wherein patients denie their nonadherence to LT4 therapy.[40,41] A study demonstrated that 26% of patients with hypothyroidism had elevated TSH levels, and patients with low treatment adherence (31%) had even higher levels compared to adherent patients, highlighting treatment nonadherence as a major obstacle to achieving optimal TSH levels.[42] Another study in patients with hypothyroidism found that, over a 6-month period of LT4 treatment, 40.3% did not comply with the treatment for at least 20% of the days, and over 12 months, 51.9% of them were nonadherent to treatment.[43]
3. **Switching between different brands of LT4**: In 2004, with the introduction of generic LT4 and new commercial brands, the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society published a series of recommendations for patients switching from branded LT4 to generic and vice versa. They advised more frequent monitoring of TSH levels in these patients and recommended avoiding switches between different LT4 brands, as bioequivalence had

not been demonstrated among them.[44] In a study conducted in patients using continuous Thyrax and those who switched from Thyrax to generic LT4, it was found that 19% of patients using less than 100 μg daily of Thyrax and 24% of patients using an equivalent dose of generic LT4 did not achieve optimal TSH levels at 6 weeks. This difference was even greater in patients with doses above 100 μg/d, where 24% of Thyrax users and 63% of those who switched to generic LT4 failed to reach the TSH target.[45] For these reasons, the European Thyroid Association proposed an induction protocol when a brand switch occurs and the assessment of the bioavailability of different LT4 formulations using alternative methods.[46] In 2010, American Thyroid Association, American Association of Clinical Endocrinologists, and Endocrine Society conducted another study and again found that the use of LT4 was associated with adverse outcomes, mainly when there were switches between different formulations of the medication.[47]

Conversely, in 2022, a study evaluating 15 829 hypothyroid patients undergoing LT4 treatment was published, covering the period from 2008 to 2019. This investigation elucidated that switching between disparate generic LT4 products did not yield clinically significant variations in TSH levels. This finding presents a counterpoint to prevailing guidelines that forewarn health care practitioners about potential fluctuations in TSH levels ensuing from such therapeutic transitions.[48] This discrepancy may plausibly emanate from enhancements in manufacturing practices; nevertheless, a more extensive inquiry is indispensable to definitively ascertain the necessity of upholding the previously established therapeutic recommendation.

4. **Dietary interferences** (Table 1): Since the absorption of LT4 occurs in the jejunum and ileum, it can be affected by food or nutritional supplements.[4]
   - A systematic review found that high dietary fiber intake may result in LT4 malabsorption due to LT4 adsorption to fiber and increased bowel movements, suggesting monitoring of TSH levels.[34]
   - Regarding soy consumption, a systematic review found no relationship between isoflavone intake and TSH nonresponse to LT4 treatment, but did observe a slight increase in TSH levels in patients exposed to higher soy consumption.[49]
   - Milk and coffee interfere with LT4 absorption when consumed together with the medication, although the exact time interval for adequate absorption remains unknown.[34]
   - Additionally, consuming grapefruit juice 1 h before or after LT4 ingestion decreases its bioavailability by delaying its absorption.[50]
   - A case report described increased TSH levels in a patient consuming large amounts of papaya (5-6 servings per day), possibly due to decreased acid secretion, which would reduce LT4 absorption.[51]
   - Among nutritional supplements that could affect LT4 bioavailability is calcium. Regular consumption of 600 to 1000 mg of calcium carbonate near the time of taking LT4 can elevate TSH levels, although this situation diminishes as the time interval between them increases.[34,52]
   - The use of iron supplements also hampers achieving optimal TSH levels, as demonstrated in a study of patients that underwent thyroidectomy, where iron supplement use increased the need for LT4 dose adjustment (OR: 2.4, 95% CI: 1.3-4.13, $P = .004$).[53]
   - Aluminum and chromium may also decrease LT4 bioavailability, although evidence on this is limited.[34]
5. **Interference with other medications**: Some medications can affect LT4 absorption, such as antacids, bile acid sequestrants, and orlistat. Other medications alter transmembrane transport, such as ciprofloxacin and rifampin. Proton pump inhibitors (PPIs) and histamine H2 receptor agonists can modify gastric pH. Estrogens, raloxifene, and carbamazepine can affect LT4 transport in circulation. Additionally, there are medications that alter LT4 catabolism, such as carbamazepine, fluoxetine, sertraline, sorafenib, mifepristone, phenytoin, statins, and protease inhibitors.[38,54]
6. **Pregnancy**: After conception, T4-binding globulin production increases, resulting in an increase in total T4. Additionally, due to stimulation by the beta subunit of human chorionic gonadotropin, TSH concentration normally decreases. In women with hypothyroidism, an up to 50% increase in LT4 dose is required during the first trimester, and this dose is maintained until delivery.[55] A study showed that only 54.1% of pregnant women achieved adequate treatment adherence, possibly due to concurrent use of nutritional supplements.[56]

Table 1
Dietary Interferences of LT4 Absorption

Food or nutritional supplement	Mechanism or effect	Recommendations
High dietary fiber intake	LT4 adsorption to fiber and increased bowel movements	Monitoring of TSH levels
High soy consumption	Slight increase in TSH levels	Avoid high soy consumption
Milk and coffee	Interference with LT4 absorption if consumed together	Exact time interval for adequate absorption remains unknown to make a recommendation
Grapefruit juice 1 h before or after LT4	Absorption delayed	Avoid consuming in this time interval
Large amounts of papaya	Decreased acid secretion and reduced LT4 absorption	Avoid large amounts of papaya
Calcium carbonate near the time of LT4 intake	Decreases LT4 bioavailability	Avoid this time interval, separate it as much as possible
Iron supplements	-	LT4 dose adjustment
Aluminum and chromium	Decrease LT4 availability	Limited evidence to make recommendations

LT4: levothyroxine; TSH: thyroid-stimulating hormone

Pathological Causes

1. **Gastrointestinal disorders**: Lactose intolerance, *Helicobacter pylori* infection, and giardiasis have been observed as the most associated diseases with LT4 malabsorption. Other less frequent conditions such as autoimmune gastritis, gastrectomy, gastroparesis, cirrhosis, and ulcerative colitis can also cause alterations in the bioavailability of LT4.[3]
   - Patients with chronic gastritis and gastric atrophy show a decrease in gastric acid production, which can be blocked by PPIs. In other cases, gastric acid production is partially blocked and countered by ammonia in patients infected with *Helicobacter pylori*, leading to increased LT4 requirements.[3] Even with the eradication of *Helicobacter pylori*, gastric mucosal atrophy may still occur, further increasing LT4 requirements.[3]
   - Lactose intolerance is due to decreased lactase activity, resulting in symptoms such as diarrhea, abdominal distension, and flatulence. The intensity of symptoms is related to the amount of lactose consumed,[57] and gastrointestinal symptoms typically occur when consuming amounts

exceeding 12 g of lactose.[58] It is unlikely that lactose used as an excipient in LT4 tablets would cause significant problems, as studies show that ingestion of up to 400 mg of lactose does not provoke gastrointestinal symptoms.[38,59]

- Giardiasis is a parasitic disease that causes inflammatory damage to the intestinal mucosa and epithelial apoptosis, which complicates the management of patients with hypothyroidism and increases their LT4 requirements.[3,60]
- Cases have been reported in which gastroparesis (diabetic, postsurgical, and idiopathic) has caused LT4 malabsorption, necessitating the use of alternative LT4 formulations.[3,61]
- Gastrectomy for gastric cancer may also be associated with malabsorption.[3]
- Celiac disease is more prevalent in patients with Hashimoto's thyroiditis[62] and causes lymphocytic infiltration and enterocyte atrophy, leading to a progressive reduction in the available intestinal surface area for LT4 absorption, thereby increasing LT4 dosage requirements.[3] It can also present atypically without gastrointestinal symptoms, further complicating its recognition.[63]
- Pancreatic insufficiency, occurring in cystic fibrosis,[53] reduces lipase secretion to approximately 10% of normal, resulting in steatorrhea and an increase in fecal excretion of T4.[3]
- Short bowel syndrome is an evident cause of LT4 malabsorption, occurring as a result of issues requiring surgical resection of a significant portion of the small intestine.[3,64] This reduces the available surface area for absorption and leads to alterations in intestinal motility.[3]
- Ulcerative colitis often increases LT4 requirements, particularly in individuals aged 60 and older, likely due to factors like increased small intestine permeability, electrolyte imbalances, and bacterial overgrowth impacting LT4 absorption, necessitating personalized LT4 treatment.[65] Crohn's disease might potentially elevate LT4 requirements; however, there is limited evidence regarding this.[66]

2. **Impaired conversion of T4 to T3**: Deficiency in the activity of iodothyronine deiodinase type1or D2 can result in altered sensitivity to thyroid hormones.[67] Monotherapy with T4 has been observed to be associated with higher levels of free T4 and below-reference range values of T3 and the fT3:fT4 ratio in 15% to 30% of patients. This suggests that combined treatment with T4 and T3 may be more effective than T4 monotherapy in these patients. These alterations have been observed in patients with polymorphisms in monocarboxylate transporter 10 and D2.[68]
3. **Other causes**: These are much less common and include THR, TSH-secreting pituitary adenomas (TSH-oma), Addison's disease, nephrotic syndrome, and hepatic cirrhosis,[4,69] among others.
   - Type B THR syndrome is characterized by goiter, mental retardation, short stature, and cardiac disorders. This syndrome typically presents with elevated levels of T4 and T3, along with normal or elevated TSH levels. This syndrome usually occurs due to a mutation in the thyroid hormone receptor beta, impairing the negative feedback loop on TSH secretion. Patients with THR typically exhibit normal thyroid function.[70]
   - Patients with TSH-oma present as hyperthyroidism, featuring elevated free thyroid hormone levels and normal TSH levels. Most TSH-omas are macroadenomas causing symptoms of optic chiasm compression and potential impacts on the function of the normal pituitary gland.[71]
   - Consumptive hypothyroidism arises due to an excess of D3 produced by vascular, fibroblastic, and gastrointestinal stromal tumors, leading to an increased elimination of thyroid hormones that exceeds the synthetic capability of the physiologically stimulated thyroid gland.[1,72-74]

Studies indicate that in 10% to 20% of patients with RH, no identifiable cause is found, which is referred to as "idiopathic RH".[4,69]

Diagnosis (Fig. 2)

The diagnostic approach for a patient with RH begins with a comprehensive medical history to assess compliance and the method of LT4 consumption, as treatment errors are the most

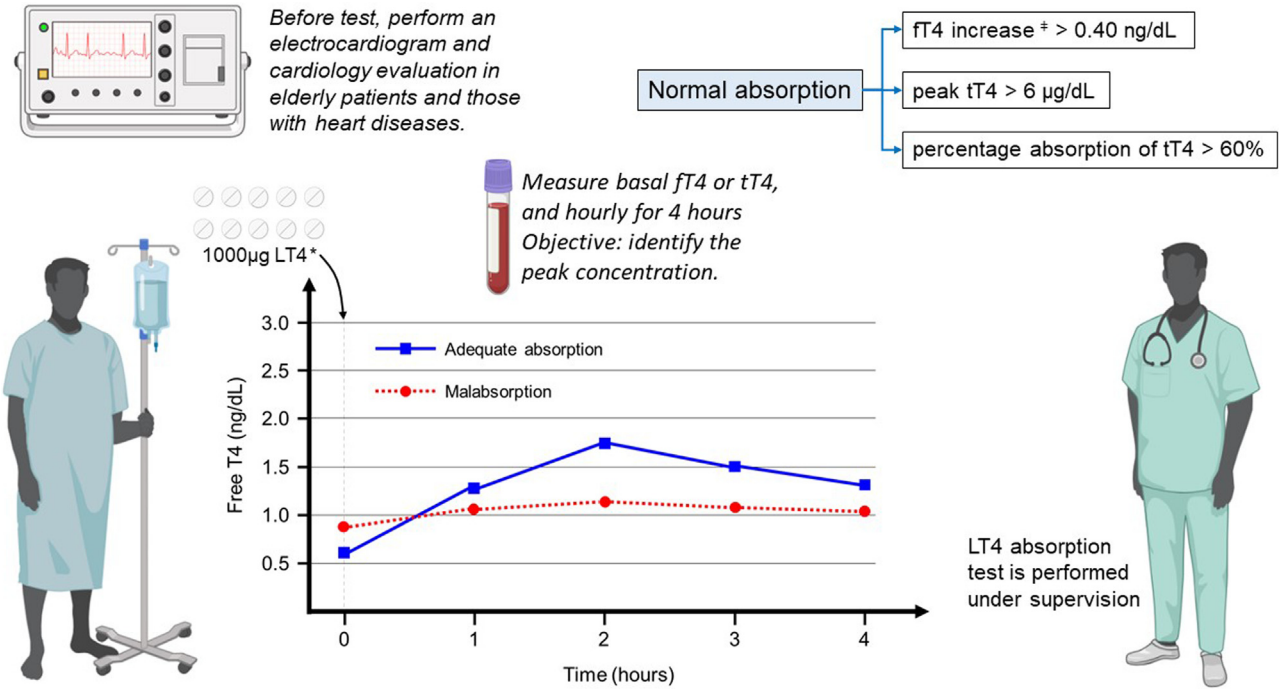

Figure 2. Levothyroxine absorption test. * A fasting dose of 1000 µg of LT4 is administered, according to the patient's formulation. ǂ fT4 increase refers to the difference between the peak and basal values of fT4. LT4: levothyroxine; fT4: free thyroxine; tT4: total thyroxine.

common cause of this issue.[11] Some patients do not wait the minimum 30 min after taking their LT4 dose before having breakfast,[33] or do not take it with water alone, but with another beverage that may decrease its absorption.[34-37] It is important to inquire about the frequency of missed doses, whether there have been prolonged interruptions due to potential adverse effects or lack of medication supply, the storage conditions of the medication,[10] any changes in dosage or brand of the medication,[47] and whether the prescribed dose matches the dose actually taken by the patient.

Another important factor to consider is the concomitant use of medications that can alter the absorption, distribution, and metabolism of LT4. Inquiries should be made about the use of PPIs, antacids, antihistamines, prokinetics, vitamin D, calcium salts, ferrous sulfate, among others,[38] and the timing of their ingestion in relation to LT4.[39] Inquiries should also be made about comorbid conditions and the use of estrogens, tamoxifen, 5-fluorouracil, mitotane,[66] phenytoin, phenobarbital, carbamazepine, and rifampicin.[66] In women of childbearing age, the possibility of pregnancy must be considered and evaluated.[4]

Pseudomalabsorption occurs when there is nonadherence to treatment. In some cases, it refers to a factitious disorder associated with psychiatric issues, in which the patient denies their lack of adherence to LT4 therapy.[40,41]

If there are no observed issues with treatment compliance or interference from food or medications, the possibility of gastrointestinal disorders causing LT4 malabsorption should be evaluated.[3] The LT4 absorption test is used to differentiate between malabsorption and pseudomalabsorption.[75] Protocols for this test differ in terms of dosage and duration of the test, frequency of blood sampling, parameter evaluated (total T4 (tT4) or fT4) and the metric used (absolute or relative peak, increase or area under the curve). The protocol recently published by Caron and Declèves aims to standardize this test.[76] A small proportion of elderly patients and those with heart diseases are at risk of developing angina or cardiac arrhythmia due to a higher-than-usual dose of LT4. As a precautionary measure, it is recommended to perform an electrocardiogram and undergo a cardiology evaluation prior to the LT4 absorption test.[76,77] A fasting dose of 1000 μg of LT4 is administered, according to the patient's formulation, and the test is performed under supervision.[76] In individuals younger than 65 years with a body mass index (BMI) equal to or greater than 40 kg/m^2, a LT4 dose of 1500 μg could be considered, while for individuals aged 65 years and older, a dose of 600 μg might be appropriate.[75] Measurements of fT4 or tT4 are taken at the time of LT4 administration and then hourly for a period of 4 h, aiming to identify the peak concentration in these measurements. LT4 absorption is considered normal in any of these 3 scenarios: if there is an increase greater than 0.40 ng/dL in the peak concentration of fT4, if the peak concentration of tT4 exceeds 6 μg/dL, or if the percentage absorption of tT4 is greater than 60%[76] (Fig. 2). The expected percentage of absorption is calculated using the following formula[75]:

Percentage LT4 absorption (%) = [increase in tT4 (μg/dL) x 10 (dL/L) / total administered dose of LT4 (μg)] x distribution volume (L) x 100. The distribution volume is equal to 0.442 x BMI. The increase in tT4 corresponds to the peak concentration reached minus the basal concentration of tT4.[76]

To facilitate the application of the aforementioned formula, we have included a downloadable spreadsheet (Supplementary File 1) that allows for precise and efficient calculation of the percentage LT4 absorption. This resource serves as a practical tool for clinical evaluation, providing a means to accurately assess LT4 absorption.

If it is determined that there is inadequate intestinal absorption of LT4, referral to a gastroenterologist is needed, and additional tests to investigate the underlying cause must be performed (Fig. 3).

1. **Autoimmune gastritis or Helicobacter pylori-associated gastritis**: *Helicobacter pylori* antigens should be sought in stool samples, serum antibodies against parietal cells and intrinsic factor should be measured, gastrin levels (elevated) and pepsinogen I levels (decreased) should be evaluated, upper

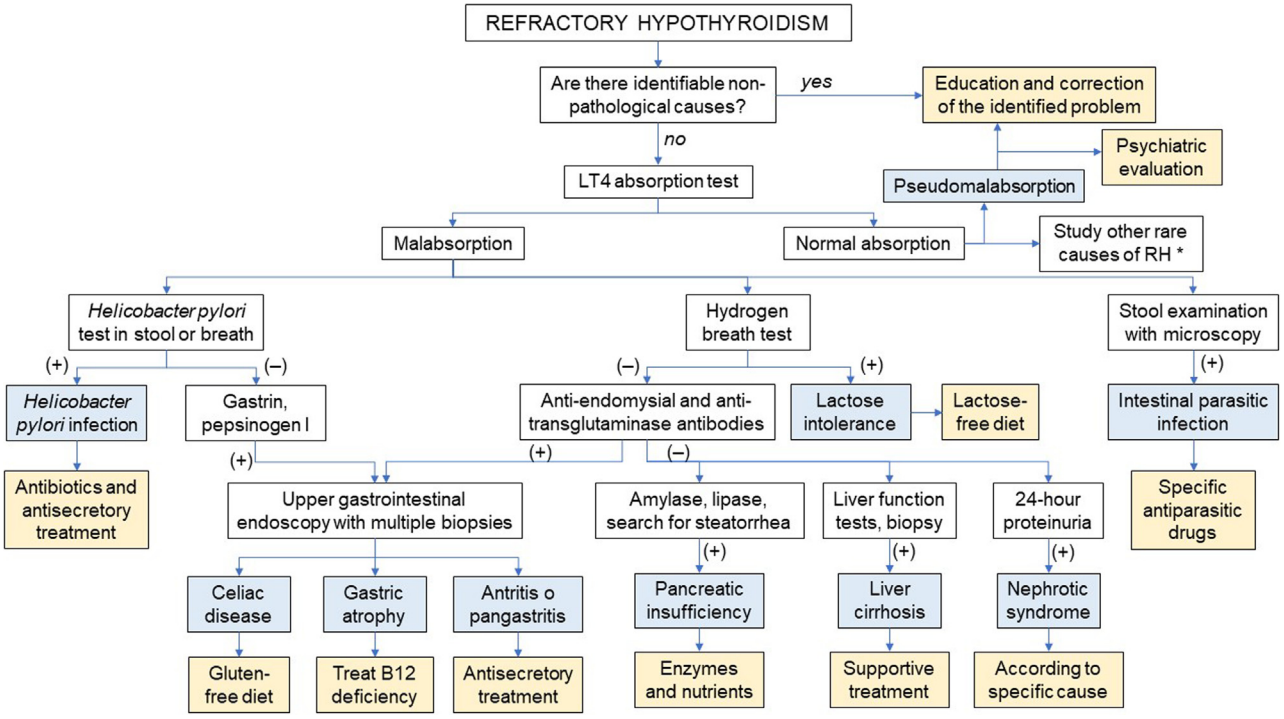

Figure 3. Diagnostic-therapeutic algorithm for refractory hypothyroidism. * Thyroid hormone resistance syndrome, Addison's disease, TSH-secreting pituitary adenomas, consumptive hypothyroidism. LT4: levothyroxine; RH: refractory hypothyroidism; (+): positive; (–): negative.

gastrointestinal endoscopy with mucosal biopsy should be performed to search for *Helicobacter pylori*, or urea breath test can be conducted.[3,69,78]

2. **Lactose intolerance**: Hydrogen breath test should be performed.[3,69,79]
3. **Intestinal parasitic infections**: Complete blood count should be conducted to search for eosinophilia, microscopic examination of stool samples should be performed to detect trophozoites, cysts, eggs, and larvae of *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum*, *Cryptosporidium homini*, *Ascaris lumbricoides*, *Trichuris trichuris*, *Strongyloides stercoralis*, *Necator americanus*, *Ancylostoma duodenale*, *Taenia saginata*, or *Taenia solium*, or real-time polymerase chain reaction molecular diagnosis may be necessary. In some cases, upper and lower gastrointestinal endoscopy may be required.[3,69,80]
4. **Obstructive liver disease or cirrhosis**: Serum bilirubin and liver enzyme levels should be measured and a liver biopsy should be performed as recommended by the hepatologist.[3,69]
5. **Celiac disease**: Serum anti-tissue transglutaminase and anti-endomysial antibodies should be measured, and a jejunal biopsy should be performed.[3,69]
6. **Pancreatic insufficiency**: Serum amylase and lipase levels should be measured, the presence of steatorrhea should be determined, sweat test (to measure chloride levels) should be conducted to diagnose cystic fibrosis, and abdominal imaging and specific tests should be performed as indicated by the gastroenterologist.[3,69]

If it is found that LT4 absorption is adequate, other diagnostic possibilities should be considered and further studies should be conducted based on suspicion.

1. **Pseudomalabsorption**: Other diagnostic possibilities should be ruled out before considering pseudomalabsorption. Since it is a commonly encountered cause, the LT4 absorption test is recommended as the initial diagnostic test (Fig. 3). Once this diagnosis is established, it's important to exclude possible psychiatric disorders.[40]
2. **Interferences affecting TSH measurements**: Immunoassay platforms can be susceptible to interferences, potentially leading to incorrect clinical decisions. Suspecting macro-TSH interference is advised with isolated TSH elevation (typically higher than 10 mUI/L) and thyroid hormones within the upper normal range, without clinical evidence of thyroid dysfunction. Biotin (in doses higher than 1.5 mg/d) can cause falsely low TSH levels and elevated fT4 and fT3, with its impact depending on the platform used, and being avoided with a washout period. Antistreptavidin antibodies cause similar interference to that of biotin, but washout periods are not useful. Anti-Ru interference has a heterogeneous presentation. Anti-T4 and anti-T3 autoantibodies, found in 40% of autoimmune thyroid disease cases, can lead to false hormone elevations, and interference from heterophilic antibodies can result in both low and high measures, with elevated values being more common. Repeating the analysis with the same methodology serves as the initial approach, and after the elimination of human errors, replication can be conducted using an alternate assay, considering intermethod disparities. Additionally, the incorporation of blocking agents, depletion methodologies, polyethylene glycol precipitation, or other suitable techniques can be pursued.[81,82]
3. **Other causes**:
   - When encountering elevated thyroid hormones along with inappropriately non-suppressed or elevated TSH levels, and after excluding assay interferences, THR and TSH-oma must be considered.[83] It is recommended to measure the serum glycoprotein alpha subunit, elevated in 70% of TSH-oma cases, and the thyrotropin-releasing hormone-stimulated TSH level, indicating a low or absent TSH response in TSHoma. Additionally, performing a T3 suppression test, revealing no TSH suppression in TSH-oma, and conducting DNA sequencing to identify the most prevalent mutations occurring in the thyroid hormone receptor β genes, is advisable.[83,84] In the diagnostic evaluation of TSH-omas, conducting a pituitary magnetic resonance imaging is recommended.[69,71,85,86] The assessment of family members for symptoms associated with type B THR holds significant importance. Identifying similar irregularities in thyroid function tests among siblings and parents provides crucial insights for diagnosing of this entity, particularly due to the fact that a considerable proportion, ranging from 80% to 90%, of type B THR cases exhibit a familial component.[87]
   - The diagnostic process for consumptive hypothyroidism requires evidence of augmented thyroid hormone inactivation, which is indicated by either heightened serum rT3 concentrations or an excess demand for LT4. Elevated serum thyroglobulin levels and augmented thyroid radioactive iodine uptake corroborate the normal thyroid stimulation.[72]

Treatment (Fig. 3)

When problems with treatment adherence or drug interactions are detected, and it is confirmed that LT4 absorption is normal, a detailed and specific educational approach should be implemented. This involves addressing the frequency of omissions or errors,[41] the reasons why they occur (gastric discomfort, difficulty waking up early, etc.), improper medication storage[10] and the concomitant use of foods or medications that interfere with its efficacy.[35,54] The doctor-patient relationship plays a key role in achieving adherence to the medication regimen.[88]

In cases of gastrointestinal problems associated with malabsorption, a team-based, multidisciplinary approach is recommended. Specific treatment should be provided to address the underlying issue. If the presence of *Helicobacter pylori* is identified, it should be eradicated with antibiotics and antisecretory agents, following current recommendations.[3,69,78] In cases of lactose intolerance, lactose should be eliminated from the diet. Although it has traditionally been recommended to avoid LT4 tablets containing lactose as an excipient, this has no clinical relevance.[3,69,79] In cases of intestinal parasitic infections, specific treatment should be initiated to eliminate the identified infection.[3,69,80] For those with obstructive liver disease or cirrhosis, except for cases where liver transplantation is indicated, there is no specific treatment. Management is supportive and focuses on controlling protein and sodium intake.[3,69] In celiac disease, a gluten-free diet should be prescribed.[3,69] Patients with pancreatic insufficiency will require the use of pancreatic enzymes, vitamins, and trace elements.[3,69]

In cases of malabsorption that do not improve after correcting the underlying problem, alternative LT4 formulations such as liquid or soft gel capsules can be considered.[3,21] Co-administration with vitamin C may increase LT4 absorption, particularly, in patients with gastrointestinal issues.[89,90] If a good response is not achieved, parenteral administration of LT4 may be necessary.[21]

In cases where normal LT4 absorption has been confirmed and there are no issues regarding noncompliance, errors in LT4 intake, or interferences, after identifying the underlying cause, appropriate management will be provided based on the clinical context. Treatment for TSH-omas involves neurosurgical intervention, and corticosteroid therapy is used to treat Addison's disease.[69,71,85] In the case of THR, there is no therapy that completely corrects the underlying defect, but treatments with thyroid hormone analogs

have been investigated to improve symptoms without excessive activation of the α thyroid hormone receptor, which would worsen cardiac prognosis.[91] Consumptive hypothyroidism usually requires aggressive thyroid replacement treatment, involving gradual LT4 dose increases until TSH normalizes, which should be measured more frequently than usual. In some cases, combined LT4-liothyronine therapy or parenteral administration might be necessary.[73,92] For a more comprehensive understanding of this topic, the reader is encouraged to refer to complete reviews on the subject.

For patients with pseudomalabsorption, supervised LT4 ingestion for at least 4 h is recommended to avoid subreptitious regurgitation or supervised oral administration on a weekly or twice-weekly basis may be carried out.[40] Weekly oral treatment shows slightly less effective control of hypothyroidism, with higher TSH levels and lower total T3 levels. In the short term, higher total T4 and free T4 levels are observed, as well as echocardiographic changes, tachycardia, and palpitations, but these symptoms do not persist in the long term. This option may be considered for non-adherent patients without pre-existing heart disease.[93-95] Parenteral administration of treatment could also be considered.[40] Additionally, addressing the management of concomitant psychiatric disorders is essential.[40]

The appropriate dosage of LT4 is typically determined based on residual thyroid function, target TSH levels, patient weight, and BMI.[96] Determining the optimal dosage for individuals with obesity is challenging, involving considerations of body weight, ideal weight, and lean body mass.[97] Lean body mass is a key predictor of LT4 requirements due to its role in T4 metabolic processes.[97,98] While there are no specific guidelines for hypothyroidism and obesity, studies suggest lean body mass is a better predictor, with around 2.3 μg/kg per day.[97,99,100] Bariatric surgery can impact LT4 pharmacokinetics, and systematic reviews show that it is correlated with a reduction in TSH levels and daily LT4 requirements,[101,102] possibly due to changes in lean body mass.[103]

Conclusion

Early recognition of RH, along with the identification and correction of any identifiable underlying cause, is crucial. This approach helps prevent the use of supratherapeutic doses of LT4, thereby reducing the risk of cardiovascular and skeletal complications associated with this condition. It is important to note that patients with RH may also experience thyroid emergencies, such as myxedema coma, and may require increased utilization of health care resources. Therefore, implementing an individualized approach for cases presenting with RH is vital.

Disclosure

The authors have no multiplicity of interest to disclose.

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None to declare.

Author contributions

JEQA and MJCZ designed the outline of this article review. JEQA, MJCZ, MCDV, LACU, ERGO, JSR and LPRR were the main writers and performed the literature review. MJCZ, JPI and ARG were reviewers and prepared the manuscript. All authors have read and approved the final manuscript.

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