ISSN 1669-9106 MEDICINA (Buenos Aires) 0000: 00: 00-00

Special article - Review

CHALLENGES IN THE TREATMENT OF HYPOTHYROIDISM: MALABSORPTION AND PSEUDO-MALABSORPTION OF LEVOTHYROXINE

DANIELA L. MANA[1], LEONARDO F. L. RIZZO[1,2]

[1]Dirección Médica, Química Montpellier S.A., [2]División Endocrinología, Hospital de Clínicas José de San Martín, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Postal address: Daniela L. Mana, Química Montpellier, Maza 578, 1220 Buenos Aires, Argentina
E-mail: daniela.mana@gmail.com
Received: 19-III-2025
Accepted: 13-VI-2025

Abstract

Levothyroxine (LT4) is the gold standard for the treatment of hypothyroidism. After ingestion, it undergoes changes in the stomach, a process critically dependent on gastric acidity. Within the following three hours, LT4 is absorbed in the small intestine. Taking LT4 on an empty stomach enhances its absorption, although night-time administration has shown similar results. Several foods, particularly fibers, espresso coffee, and grapefruit juice, interfere with its absorption. Certain medications have similar effects (calcium and iron salts and proton pump inhibitors). In the presence of food or medication that may interfere with LT4 absorption, it is recommended to separate their intake by 3 to 4 hours. Certain gastrointestinal conditions can also affect the absorption of LT4 into the bloodstream. Helicobacter pylori infection and atrophic gastritis increase stomach pH, while celiac disease alters the absorption surface in the small intestine. Bariatric surgery can affect LT4 absorption; however, the associated loss of lean body mass can also lower LT4 requirements. As the net effect may be an increase or decrease in LT4 requirement, close monitoring is advisable. Pseudo-malabsorption is a psychiatric condition that is difficult to diagnose and requires an LT4 absorption test for confirmation. Once diagnosed, management is complex. Weekly dosing appears to be the most recommended approach to improve adherence.

Key words: levothyroxine, absorption, interferences, pseudo-malabsorption

Resumen

Desafíos en el tratamiento del hipotiroidismo: malabsorción y pseudo-malabsorción de levotiroxina

La levotiroxina (LT4) es el *gold standard* del tratamiento del hipotiroidismo. Luego de la toma, sufre cambios en el estómago, para lo cual es fundamental la acidez gástrica. En las 3 horas posteriores, la LT4 se absorbe en el intestino delgado. La toma en ayunas favorece su absorción, aunque la administración nocturna ha mostrados resultados similares. Varios alimentos interfieren con su absorción, espacialmente fibras, café *espresso* y jugo de pomelo. Algunos medicamentos muestran efectos similares (las sales de calcio y de hierro y los inhibidores de la bomba de protones). Ante la presencia de un alimento o un medicamento que pudiera interferir con la absorción de LT4, la recomendación es su separación por 3 a 4 horas. Algunos cuadros gastrointestinales también pueden afectar el pasaje de la LT4 a la sangre. La presencia de *Helicobacter pylori* y de gastritis atrófica aumentan el pH del estómago, y la enfermedad celíaca altera la superficie de absorción en el intestino delgado. La cirugía bariátrica puede afectar la absorción de LT4, pero a su vez hay un menor requerimiento por la pérdida de masa magra. El resultado final puede ser un aumento o una disminución de los requerimientos de LT4, por lo que se recomienda un seguimiento cercano. La pseudo-malabsorción es un cuadro psiquiátrico de difícil diagnóstico y requiere la realización del test de

absorción de LT4. Una vez confirmado el cuadro, su abordaje es complejo. La toma semanal parece ser la más recomendada para lograr adherencia.

Palabras clave: levotiroxina, absorción, interferencias, pseudo-malabsorción

KEY POINTS
Current knowledge

- LT4 is the standard treatment for hypothyroidism. Gastric acidity plays a crucial role in LT4 pharmacokinetics; therefore, food, medications that increase gastric pH, or conditions like hypochlorhydria can impair its absorption. Other medications and gastrointestinal disorders may also affect LT4 absorption

Contribution of the article to current knowledge

- This publication reviews the optimal conditions for administering LT4, as well as the foods, medications, and medical conditions that may interfere with its absorption. In patients presenting with elevated TSH levels, it is essential to ensure both adherence to therapy and proper absorption. If TSH levels remain persistently high despite these measures, pseudo-malabsorption should be suspected, and an LT4 absorption test should be performed.

Hypothyroidism is a common condition characterized by a deficiency of thyroid hormone. If left untreated, it can lead to serious adverse health effects and, ultimately, death[1]. Its prevalence in the general population, both in its subclinical and clinical forms, is estimated to be between 3% and 7%[2].

Since the last decades of the past century, levothyroxine (LT4), the synthetic L-isomer of thyroxine, has become the gold standard for the treatment of hypothyroidism. Its absorption in the gastrointestinal tract is one of the critical steps leading to its pharmacological effect. Orally ingested LT4 is absorbed through the intestinal mucosa, particularly in the jejunum and ileum. Approximately 60% to 82% of the ingested dose is absorbed, mainly within the first three hours after drug administration[3]. Numerous factors can affect its absorption, including foods, medications, and gastrointestinal disorders[4].

An important diagnostic challenge arises when patients present with refractory hypothyroidism despite reporting proper adherence to high doses of LT4 and in the absence of known conditions or medications that may interfere with its absorption. In such cases, the LT4 absorption test should be performed, as it allows differentiation between malabsorption and intentional non-adherence, also known as pseudo-malabsorption[5]. Pseudo-malabsorption is defined as the deliberate non-compliance with oral levothyroxine treatment with the intent to deceive. This condition is classified as a psychiatric disorder within factitious disorders and is characterized by inadequate diagnostic processes, patient denial, and challenges in management[6]. It must also be distinguished from cases of poor adherence due to forgetfulness or difficulty accepting long-term treatment.

The objectives of this publication are to describe the normal characteristics of LT4 absorption, identify foods and medications that may interfere with its passage into systemic circulation, and discuss gastrointestinal disorders that can also affect it. Additionally, it outlines the characteristics, diagnostic methods, and treatment of pseudo-malabsorption, along with the complexities surrounding its diagnosis and management.

Normal absorption of levothyroxine

LT4 is the standard treatment for hypothyroidism, and the tablet formulation is the most commonly used[7]. Tablet formulations contain a stable salt, sodium LT4, and various excipients. The gastric environment has a deep impact on the behaviour and pharmacokinetics of drugs, particularly LT4. Once in the stomach, the drug undergoes disintegration, degradation, and dissolution. Disintegration and degradation release the active ingredient from its solid form. Simultaneously, dissolution occurs, which involves the release of solute molecules from the solid phase into the liquid phase (gastric juice). This process is especially influenced by physicochemical conditions, particularly the pH and viscosity of gastric juice[8]. During this phase, a

gastric pH close to physiological levels is necessary[4]. The ionization state of sodium levothyroxine and its dissolution-related pharmacological properties are particularly affected by variations in intraluminal pH. There is an inverse relationship between pH and the degree of absorption: the higher the gastric pH, the lower the absorption of LT4[9].

Within the first three hours after ingestion, LT4 is absorbed throughout the small intestine, with varying percentages in different segments: 15±5% in the duodenum, 29±14% in the proximal jejunum, and 24±11% in the distal jejunum and ileum[4].

According to the Biopharmaceutical Classification System, which categorizes drugs based on solubility and permeability, LT4 belongs to class III. Drugs in this category have high solubility but low permeability, often requiring transporters for absorption[10].

Different categories of transporters can facilitate the passage of thyroid hormones across the cell membrane. In the small intestine, the most significant transporters belong to the monocarboxylate transporter (MCT) family (especially types 8 and 10), the organic anion-transporting polypeptide (OATP) family, the neutral amino acid transporter family, and the ATP-dependent transporter superfamily. The action of medications and foods on these transporters will influence LT4 absorption[4].

Importance of fasting

Gastric pH, along with body mass index, is the most important physiological variables for determining the minimum effective dose of LT4. A higher LT4 requirement is associated with an increase in pH, reaching the highest doses in cases of gastric atrophy and achlorhydria[11]. When taken on an empty stomach, its maximum concentration in the blood (Cmax) is 60-80%, and the time to reach this concentration (Tmax) is approximately 90 to 120 minutes. In the presence of food, Cmax is lower, and Tmax is delayed, which reduces the drug's bioavailability[4]. The influence of food is related to the physicochemical properties of the drug molecules, the quantity and composition of the meals, the timing and interval between food and drug administration, and the state of the digestive system[3]. Different studies have demonstrated the benefits of administering LT4 at least 1 hour before breakfast, which is associated with more stable and predictable TSH values[12]. However, a recent study evaluated patient preferences regarding LT4 intake on an empty stomach. While the majority (89.5%) reported being instructed to take LT4 on an empty stomach, approximately 1 in 3 patients (30.2%) did not follow this instruction. Nearly half of the patients felt overwhelmed by the waiting time until breakfast, and 60.5% preferred taking LT4 without fasting. It is worth noting that 24.9% skipped breakfast and 13.4% forgot to take their medication, both due to the fasting requirement[13].

Night-time or "bedtime" administration, defined as taking the medication 2-3 hours after the last solid meal, showed TSH values close to those obtained when taken 1 hour before breakfast[14]. During the night, intestinal motility is lower, resulting in prolonged exposure of LT4 to the intestinal wall and consequently, increased bioavailability. Additionally, basal acid secretion is higher at night than in the morning, reflecting a circadian intestinal pattern[15]. Bedtime administration has proven particularly convenient for elderly patients on multiple medications and school-aged children[16,17].

In a study, 84 patients received LT4 half an hour before breakfast, one hour before the main meal of the day, and two hours after dinner. TSH levels showed no statistically significant differences between any of the three time points, nor did free T4, cHDL, cLDL, or triglycerides[18]. Other studies support the similarity of administration before breakfast and after dinner[19].

Moreover, liquid and soft capsule formulations were administered during breakfast, and even during lunch, with no variations in TSH, making them a potential alternative for patients with adherence difficulties[20].

The American Thyroid Association (ATA) recommends that to optimize LT4 absorption, it should be taken 60 minutes before breakfast or, alternatively, before bedtime, which means 2 to 3 hours after dinner[21].

Foods that alter LT4 absorption

It has been described that substances such as fibers (like bran for example), coffee, and other foods can influence LT4 absorption. Fibers non-specifically bind to LT4, hindering its absorption,

while products containing insoluble dietary fibers increase bowel movements[22]. Liel et al.[23] observed that excluding fibers from breakfast resulted in a decrease in TSH levels and LT4 dosage. Other authors found differences in healthy volunteers who took LT4 with or without psyllium and banana seeds (which are high in fiber), but considered the result to be clinically insignificant[24]. On the other hand, at the XVIII Congress of the Argentine Society of Endocrinology and Metabolism, results were presented from a study where the intake of up to 3.5 grams of fibers did not alter the thyroid profile of patients adequately treated for hypothyroidism[25]. Currently, the information regarding the effect of fibers on LT4 absorption is limited and contradictory, so caution is recommended when advising its exclusion from breakfast.

Several articles in the literature describe the influence of Italian espresso coffee on LT4 absorption. *In vitro* studies have shown that espresso coffee acted as a "sequestrant" of LT4 in the intestinal lumen[26]. This effect was prevented when LT4 intake was separated by 60 minutes from the coffee, and when LT4 was administered in soft gel capsules[27].

The irreversible inhibitory effect of grapefruit juice on CYP3A4 is well known, increasing blood concentrations of drugs such as felodipine, cyclosporine, and simvastatin. Regarding LT4, a decrease in Cmax and area under the curve (AUC) has been described following concomitant administration with grapefruit juice, without impacting TSH[28]. This effect is attributed to a grapefruit flavonoid, naringin, which may have an inhibitory effect on OATP family transporters[29].

Other foods associated with altered LT4 absorption include infant formulas containing soy derivatives[3]; cow's milk[30], tea[31], and papaya[22]. These publications are isolated case reports or studies of small populations and should not be taken as recommendations for the general public.

Drugs that alter LT4 absorption

Several drugs interfere with LT4 absorption. In most cases, these drugs bind to levothyroxine, forming insoluble complexes. The best examples of this interaction are divalent and trivalent elements, particularly calcium, iron, and magnesium, which reduce LT4 bioavailability[22]. Studies with calcium carbonate, acetate, and citrate (containing 500 mg of elemental calcium) have shown a 20–25% reduction in LT4 absorption when administered together[3,32]. In relation to iron, *in vitro* studies have shown that ferric ions bind to three molecules of LT4, forming an insoluble complex[33]. The TEARS (Thyroid Epidemiology, Audit and Research Study) demonstrated a significant increase in TSH levels in patients undergoing LT4 treatment who added an iron salt, such as ferrous sulphate or other salts like fumarate. The groups at highest risk for this interaction include elderly patients and menstruating and pregnant women, for whom close monitoring is recommended[34]. While some authors suggest a 2- to 4-hour interval between LT4 intake and medications containing calcium or iron, the optimal separation time has not been definitively studied[3,35]. Antacids with aluminium hydroxide may similarly interact with LT4, forming complexes that impair its absorption[36]. Bile acid sequestrants, such as colesevelam and cholestyramine, have been shown to interfere with LT4 absorption when administered together due to an irreversible chelating effect[37]. Given its potent action, cholestyramine has been used to treat exogenous hyperthyroidism, and some propose its use in combination with methimazole for more rapid control of Graves' disease-related hyperthyroidism[38]. In healthy volunteers, an interval of at least 4 to 5 hours was observed to normalize LT4[39] absorption. Isolated cases of LT4 absorption interference have been reported with other medications, such as orlistat[40], sucralfate[41], lanthanum, and sevelamer[42].

The American Thyroid Association (ATA) recommends that, whenever possible, LT4 should be taken separately from other medications and supplements that may interfere with its absorption (e.g., calcium carbonate and ferrous sulphate). A 4-hour separation is the traditional recommendation, although it has not been sufficiently studied[21].

As previously mentioned, gastric acidity is essential for the dissolution and absorption of LT4. Proton pump inhibitors (PPIs) and LT4 are among the most commonly prescribed drugs, particularly in the elderly population. Since they are often recommended to be taken at the same time of the day (before breakfast), their interac-

tion could be clinically relevant. The available literature presents conflicting results[43]. The effect of omeprazole was documented in 10 patients with goitre, in whom the concomitant use of both drugs for six months led to an increase in TSH levels. This interference was reversed by increasing the LT4 dose by 37% or discontinuing the PPI[44]. The TEARS[34] study showed that patients who used PPIs (for at least six months) concomitantly with LT4 had significantly higher TSH levels compared to baseline, and 5.6% had TSH levels above 5 mIU/L. In contrast to these findings, a crossover study in 20 healthy volunteers showed that pantoprazole, when used for only 14 days (7 days before and 7 days concomitantly with LT4), did not affect LT4 absorption. Several factors could explain the variability among studies, as most are retrospective, involve a small number of patients, and have heterogeneous designs (including patients versus healthy volunteers or different underlying conditions for which PPIs were prescribed). Considering all the available evidence, these studies suggest that although concomitant PPI intake numerically affects TSH levels, the clinical impact is modest, as most results remain within the normal range. However, for a specific subset of individuals –particularly those with impaired absorption due to other conditions– these findings may have a more significant clinical impact[43]. LT4 liquid formulations or soft gelatin capsules, which do not require gastric acidity for dissolution, can prevent this interaction[2,44]. From a practical standpoint, in patients requiring PPI therapy for more than two weeks, clinicians should be aware of the potential need for dose adjustments or drug separation. In such cases, bedtime administration of LT4 could be a feasible option. Additionally, vitamin C has been shown to enhance LT4 absorption by lowering gastric pH. An Argentine study showed that in 28 patients treated with LT4 at a dose of 1.7 mcg/kg and with TSH levels above the normal range, the addition of 1 g of vitamin C in 200 cc of water (pH 3) led to a reduction in TSH levels in all patients, with an average decrease of 69.7%, achieving the target TSH level in 68% of them[45]. A more recent study found similar results when administering 500 mg of vitamin C to patients with underlying gastric conditions[46]. Therefore, vitamin C is the only medication positively associated with LT4 absorption and could be considered as an adjuvant therapy in patients with gastrointestinal disorders and LT4 malabsorption[47].

Gastrointestinal disorders that alter LT4 absorption

Several gastrointestinal conditions can affect LT4 absorption, either by altering gastric pH or by impacting motility and/or LT4 absorption[21] (Table 1).

Increased gastric pH is the main cause of LT4 malabsorption in *Helicobacter pylori* (HP) infection and atrophic gastritis. HP infection affects nearly 50% of the global population[7]. Some studies have reported that HP-infected patients (even those without gastric atrophy) required a 22% higher LT4 dose, while those with concomitant atrophic gastritis needed a 37% higher dose[48]. In the initial phase, the infection affects only superficial layers and may be accompanied by increased gastrin levels and higher gastric acidity. Depending on the cytotoxicity of the bacterial strain and the characteristics of the gastric environment, the degree of gastritis can progress to atrophic pangastritis and intestinal metaplasia, leading to hypo- or achlorhydria[8]. Hypochlorhydria due to atrophic gastritis, along with the ammonium production associated with HP infection, may alter the ionization state and conformational characteristics of LT4, thereby reducing its intestinal absorption[49]. In most cases, HP eradication can lead to a reduction in LT4 dose requirements, except in patients who have developed gastric atrophy[4]. HP infection has also been proposed as a trigger for autoimmune atrophic gastritis through molecular mimicry with epitopes of the H+/K+ ATPase. Indeed, chronic autoimmune gastritis is characterized by a high degree of atrophy in the gastric body and fundus, with positive autoantibodies against parietal cells and/or intrinsic factor. Autoimmune atrophic gastritis is characterized by achlorhydria and, consequently, a high LT4 requirement, which is highest in patients with both gastric atrophy and HP infection[8].

Obesity and hypothyroidism are common medical conditions that are frequently associated. Bariatric surgery (BS) is a widely used approach to achieve substantial weight loss in obese patients. However, evidence on the need for LT4 dose adjustments after surgery in hypo-

Table 1 | Major gastrointestinal conditions that Interfere with LT4 absorption

Gastrointestinal condition	Mechanism
Helicobacter pylori infection	Increased gastric pH
	Ammonia production
Atrophic gastritis	Hypoclorhydria
Bariatric surgery	Increased gastric pH
	Use of medications (Ca++, Fe++, PPIs)
	Loss of lean body mass
Celiac disease	Intestinal villous atrophy
	Increased intestinal permeability
	Increased intestinal transit speed
Lactose intolerance	Accelerated intestinal transit
	Bacterial overgrowth
	Altered enterohepatic recirculation of LT4
Giardia lamblia infection	Inflammatory mucosal damage
Pancreatic insufficiency	Steatorrhoea

PPIs: proton pump inhibitors

thyroid patients remains limited[50]. Anatomical and physiological changes following bariatric surgery –such as gastric volume restriction and shortening of both the small intestine's length and transit time– can lead to significant alterations in drug and nutrient absorption. While malabsorption of food components is desirable for achieving and maintaining weight loss, changes in drug absorption can be troublesome. After bariatric surgery, a reduction in the number of parietal cell leads to decreased gastric acid production, resulting in a significant increase in gastric pH. Additionally, patients are often advised to receive prophylactic PPI treatment, which further contributes to an increase in gastric pH. It has been reported that post-bariatric surgery gastric pH may range from 6.4 to 6.8[51]. These patients are also prescribed vitamin and mineral supplements, such as calcium and iron, which, as previously discussed, can interfere with LT4 absorption. Moreover, LT4 is primarily absorbed in the jejunum and the upper ileum, meaning that the anatomical changes induced by bariatric surgery—particularly those involving the bypass of the primary drug absorption sites-can significantly impact its uptake. All the mechanisms described so far suggest a potential alteration in levothyroxine absorption following bariatric surgery, likely requiring an increase in the postoperative dose[52]. Although some studies have reported that higher doses of many medications may be necessary after bariatric surgery due to the aforementioned factors, other studies on LT4 dosage post-surgery show conflicting results. In these studies, the loss of both fat and lean body mass leads to a decreased levothyroxine requirement postoperatively, as LT4 dosage is also weight-dependent. Supporting this finding, a study of 93 obese hypothyroid patients before and after 28 months of bariatric surgery showed a significant reduction in the average LT4 dose, from 130.6 mcg/day to 116.2 mcg/day. In this and other studies, the decrease in LT4 dosage was proportional to the reduction in lean body mass. They concluded that after reaching a stable postoperative weight, a dose of 1.4 µg/kg was sufficient for most patients[53]. Findings from a meta-analysis showed that bariatric surgery is associated with a decline in TSH levels. The exact mechanism underlying this postoperative change is not fully understood. The primary explanation relates to the fall in leptin levels following weight loss, whether due to dietary changes or bariatric surgery. Leptin, a hormone secreted mainly by adipocytes, is proportional to body fat levels and has been suggested to exert a stimulatory effect on thyroid function, promoting increased TSH secretion. Consequently, the drop in leptin levels after weight loss induced by bariatric surgery reduces this stimulatory effect,

resulting in lower TSH secretion. Regarding this TSH decline, bariatric surgery has also been reported to have a positive effect on patients with subclinical hypothyroidism, with 87% (322 out of 371) experiencing resolution of subclinical hypothyroidism after surgery[52]. Given the lack of conclusive evidence, clinicians should be aware that LT4 dosage may require adjustment –either an increase or decrease– in patients undergoing bariatric procedures, highlighting the need for closer follow-up.

Celiac disease (CD) is an autoimmune disorder with a prevalence of 1% in the general population, increasing to 2-5% among individuals with autoimmune thyroid disease, the leading cause of hypothyroidism. The coexistence of both conditions is one of the most common associations and is included in type 3 autoimmune polyglandular syndrome. Celiac disease primarily affects the jejunum and proximal ileum, both of which are involved in LT4 absorption. It causes a progressive reduction in the intestinal surface area due to villous atrophy and lymphocytic infiltration. This results in the loss of brush border proteins and enzymes. Other observed alterations include increased intestinal permeability, accelerated intestinal transit, changes in luminal pH, abnormal gastric emptying, and bacterial overgrowth. All of these pathological changes contribute to drug and nutrient malabsorption[4]. A gluten-free diet may partially or fully restore LT4 absorption, occasionally requiring a dose reduction[3]. CD may present with subtle or atypical symptoms, leading some authors to recommend antibody screening in hypothyroid patients who require higher-than-expected LT4 doses[54].

Lactose intolerance is a disorder with variable prevalence, occurring in 20 to 70% of the population. Undigested lactose molecules increase the amount of fluid in the intestinal lumen, causing accelerated intestinal transit and reduced exposure time of LT4 to the intestinal mucosa[7]. Additionally, the architecture of the intestinal villi may be altered, and bacterial overgrowth could interfere with the enterohepatic recirculation of LT4. Removing lactose from the diet is usually sufficient to improve the condition[4].

Isolated cases have linked *Giardia lamblia* infection to LT4 malabsorption, which resolved after treatment with metronidazole[55]. Pancreatic insufficiency, which causes steatorrhea and short bowel syndrome, may also impair LT4 uptake[4]. Additionally, the literature includes clinical cases of patients with diabetic gastroparesis and LT4 malabsorption, with one case improving after switching from tablets to soft gel capsules of LT4[56]. Other less common digestive disorders that can be associated with thyroid hormone malabsorption include liver cirrhosis and ulcerative colitis. It is estimated that this patient population may benefit from levothyroxine preparations based on solutions to optimize absorption[57].

As a practical recommendation, if a patient requires more than 2 mcg/kg/day of LT4, it is important to rule out treatment non-adherence, interference with absorption (from food or medications), and gastrointestinal pathology[47].

Pseudo-malabsorption of LT4 – LT4 absorption test

The most common cause of failure in oral LT4 treatment is patient non-adherence[5]. A study conducted on 100 patients with persistently elevated TSH levels showed that non-adherence was present in approximately 82% of cases, with 62% of these cases attributed to forgetfulness or negligence in taking the medication[49]. The most extreme form of non-adherence is referred to as "pseudo-malabsorption syndrome." This term was first introduced by Ain and colleagues after they evaluated four cases of persistent hypothyroidism despite high-dose oral thyroid hormone replacement therapy, ultimately confirming that non-adherence was the underlying cause[58]. Pseudo-malabsorption is a severe psychiatric condition, classified as a factitious disorder, which is extremely difficult to manage. Patients (and often their family members) insist on "strictly adhering" to their medication regimen, yet fail to take it or do so inconsistently. This condition is more frequently observed in women, particularly those with a history of total thyroidectomy or ablative iodine therapy, who are aware that LT4 replacement therapy is essential for their survival[59]. Laboratory findings in these patients typically reveal persistently low free T4 levels with progressively increasing TSH, prompting the treating physician to prescribe higher doses of LT4 or even to administer LT4

via alternative routes, such as intramuscular or intravenous administration[60].

The diagnosis of pseudo-malabsorption should be established only after ruling out all possible causes of malabsorption, including gastrointestinal diseases, drug interactions, or difficulties in tablet ingestion. Once all these causes have been excluded, an LT4 absorption test should be performed to confirm the diagnosis. This is a non-invasive and safe test that allows differentiation between true LT4 malabsorption and pseudo-malabsorption[5]. No standardised protocol exists for this test, with variations in duration, LT4 dosage, and diagnostic criteria[61].

For test preparation, it is advisable for the patient to be hospitalised, remain fasting overnight (with no food or beverages other than water), and avoid medications that could potentially interfere with LT4 absorption (such as proton pump inhibitors, calcium salts, iron supplements, etc.)[61].

The most widely used LT4 dose for this test is 1000 mcg in a single administration. However, doses of 2000 and 2500 mcg have been described in the literature, although some authors warn about the risks associated with such high doses[61]. The Mayo Clinic in Rochester, USA, has established a protocol in which the LT4 dose depends on the patient's age and body mass index (BMI). Their protocol recommends administering 1000 mcg to patients aged 18 to 65 years with a BMI <40 kg/m², 1500 mcg to patients of the same age with a BMI >40, and 600 mcg to patients over 65 years of age. The administration must be supervised by medical personnel to ensure proper ingestion and to prevent surreptitious regurgitation[59].

Normally, 70% to 100% of the administered dose is absorbed in the gastrointestinal tract, reaching peak absorption levels within 2 to 4 hours after ingestion. Consequently, baseline blood samples should be collected before LT4 administration, followed by repeated sampling every 1 to 2 hours over the first 4 to 6 hours[61,62]. Prolonged tests lasting several days have been described in the literature, but these lack standardisation[63].

The serum parameters measured may include TSH, total T4, and/or free T4.TSH measurement has not yielded definitive results across different studies. However, in both the Mayo Clínic[5] group and a series of 10 patients from Portugal[64], the decline in TSH levels over the 6-hour period was found to be unreliable, erratic, and of little use in interpreting the results. Consequently, some authors, aiming to simplify the test and reduce resource use, recommend not measuring TSH levels[65]. Regarding total T4, it is used to calculate the absorption percentage based on the following formula:

$$\%\ \text{LT4 Absorption} = \frac{[(\text{Total T4 increase in mcg/dL}) \times 10] \times \text{VD(L)} \times 100}{\text{Total LT4 administered (mcg)}}$$

- Total T4 increase: Peak T4 – baseline T4
- VD (Volume of distribution): 0.442 × BMI

Absorption value of 60% or higher is considered normal. In an analysis of 16 patients, 9 reached their peak total T4 level between 3 and 4 hours. Three patients continued to show an increase in total T4 at hour 6, although all had already achieved a rise greater than 60% before that time. Patients demonstrated an average absorption range of 67% to 158% during the test.

When using free T4 (FT4) measurement, different criteria have been described to determine normal absorption. Soares et al.[66] analysed 19 patients and, after administering 1000 mcg of LT4, considered that a 2.5-fold increase in FT4 from baseline was indicative of normal absorption and, therefore, diagnostic of pseudo-malabsorption. Santos Monteiro et al.[64] considered that an increase in FT4 greater than 50% from baseline corresponded to normal absorption, with observed absolute increases ranging from 0.94 to 2.92 ng/dL (85% to 668%). Ghosh et al.[67] suggested that, with an LT4 dose of 10 mcg/kg (maximum 600 mcg), an FT4 increase of more than 0.40 ng/dL (5.14 pmol/L) at 3 hours' post-administration would be useful for identifying individuals without malabsorption. As we can see, there is no unified criterion for diagnosing normal LT4 absorption. Each physician or medical centre must decide which protocol to adopt and which cut-off values to use.

Medical supervision throughout the test is essential to rule out vomiting intended to produce a false diagnosis of malabsorption[61]. Some authors have even recommended examining

the oral cavity after dose administration[63]. Others suggest measuring blood pressure and heart rate every hour during the test[64].

The treatment of LT4 pseudo-malabsorption is hindered by poor overall adherence and the patient's lack of recognition of the condition. Psychiatrists recommend that patients with this disorder be managed conservatively[62]. Strategies to improve adherence may include direct observation of LT4 administration, either through family or medical support. Scheduled reminders via mobile phones or a seven-day pill organizer may also be useful[5]. Simply informing the patient about the harmful effects of poor treatment adherence is often helpful[5]. Weekly dose administration under direct supervision has proven to be a useful strategy. It is an effective and well-tolerated measure, although caution is advised in patients with a history of arrhythmias or coronary artery disease[68]. The mechanism by which these patients remain asymptomatic may involve a change in the conversion rate of T4 to T3. While free T4 increases significantly (almost threefold) after weekly dose intake, free T3 rises by only 25%, and reverse T3 by approximately 50%, suggesting a preferential conversion of T4 to reverse T3, which is metabolically inactive[69].

Conclusions

The intestinal absorption of LT4 can be affected by multiple factors, including timing of administration, food intake, medications, and gastrointestinal disorders. While current recommendations suggest separating LT4 intake from these potential interferences, the optimal interval has not been firmly established. Night-time administration has shown TSH levels comparable to those observed with fasting intake, making it a viable alternative for patients who are unable to separate LT4 from food or medications. Additionally, new formulations, such as liquid preparations or soft gel capsules, may play a role in overcoming these absorption challenges.

It is crucial to be aware of all potential interferences in LT4 absorption. In cases of persistently elevated TSH levels, adherence to treatment, possible interferences, and underlying gastrointestinal conditions should be assessed. If all these factors are ruled out, the presence of pseudo-malabsorption should be considered, and an LT4 absorption test should be performed.

Challenges remain in the study of LT4 absorption and malabsorption, including the role of liquid and capsule formulations, alternative administration timings (such as 30-60 minutes before breakfast or bedtime administration), and the standardization of the LT4 absorption test. Ultimately, it is essential for treating physicians to properly educate patients on the benefits of LT4 replacement therapy and to conduct regular monitoring for optimal hypothyroidism management.

Conflict of interest: Leonardo F. L. Rizzo is the Medical Director of Química Montpellier S.A. and Daniela Mana is Medical Consultants for Química Montpellier S.A.

Bibliografía

1. Chaker L, Bianco A, Jonklaas J, Peeters R. Hypothyroidism. *Lancet* 2017; 390: 1550–62.
2. Liu H, Li W, Zhang W, Sun S, Chen C. Levothyroxine: conventional and novel drug delivery formulations. *Endocr Rev* 2023; 44:393-416.
3. Skelin M, Lucijanić T, Amidžić Klarić D, et al. Factors affecting gastrointestinal absorption of levothyroxine: a review. *Clin Ther* 2017; 39:378-403.
4. Virili C, Antonelli A, Santaguida MG, Benvenga S, Centanni M. Gastrointestinal malabsorption of thyroxine. *Endocr Rev* 2019; 40:118-36.
5. Gonzales K, Stan M, Morris J, Bernet V, Castro MR. The levothyroxine absorption test: a four-year experience (2015-2018) at the Mayo Clinic. *Thyroid* 2019; 29:1734-42.
6. Rdzak G, Whitman L, Inzucchi S. Levothyroxine pseudo-malabsorption: testing and treatment in the outpatient setting. *Ther Adv Endocrinol Metab* 2018; 9:217-22.
7. Castellana M, Castellana C, Giovanella L, Trimboli P. Prevalence of gastrointestinal disorders having an impact on tablet levothyroxine absorption: should this formulation still be considered as the first-line therapy? *Endocrine* 2020; 67:281-90.
8. Virili C, Brusca N, Capriello S, Centanni M. Levothyroxine therapy in gastric malabsorpti-

ve disorders. *Front Endocrinol (Lausanne)* 2021; 11:621616.

9. Ianiro G, Mangiola F, Di Rienzo TA, et al. Levothyroxine absorption in health and disease, and new therapeutic perspectives. *Eur Rev Med Pharmacol Sci* 2014; 18: 451–6.
10. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm* 2004; 58: 265-78.
11. Virili C, Bruno J, Santaguida MG, et al. Levothyroxine treatment and gastric juice pH in humans: the proof of concept. *Endocrine* 2022 ;77: 102-11.
12. Biondi B, Bartalena L, Chiovato L, et al. Recommendations for treatment of hypothyroidism with levothyroxine and levotriiodothyronine: a 2016 position statement of the Italian Society of Endocrinology and the Italian Thyroid Association. *J Endocrinol Invest* 2016; 39: 1465-74.
13. Willems T, van Twist D, Luu I, Bianchi R, Peeters R, Tummers-de Lind van Wijngaarden R. Breakfast habits in patients using levothyroxine: patient experiences and preferences. *J Endocr Soc* 2024; 8:bvae180.
14. Bach-Huynh T-G, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. *J Clin Endocrinol Metab* 2009; 94: 3905-12.
15. Geer M, Potter DM, Ulrich H. Alternative schedules of levothyroxine administration. *Am J Health Syst Pharm* 2015; 72: 373-7.
16. Bandeira de Mello R, Giassi K, Stahl G, et al. Evaluation of bedtime vs. morning levothyroxine intake to control hypothyroidism in older patients: a pragmatic crossover randomized clinical trial. *Front Med (Lausanne)* 2022; 9:828762.
17. Navid A, Dayal D, Kaur H, Gupta A, Attri S. Comparative efficacy of early morning versus bedtime administration of levothyroxine in children with hypothyroidism: a prospective, open label, randomized, case-control study. *Pediatr Endocrinol Diabetes Metab* 2021; 27:178-82.
18. Skelin M, Lucijani T, Liberati- izmek A-M, et al. Effect of timing of levothyroxine administration on the treatment of hypothyroidism: a three-period crossover randomized study. *Endocrine* 2018; 62: 432-9.
19. Pang X, Pu T, Xu L, Sun R. Effect of l-thyroxine administration before breakfast vs at bedtime on hypothyroidism: A meta-analysis. *Clin Endocrinol (Oxf)* 2020; 92:475-81.
20. Cappelli C, Pirola I, Castellano M. Liquid levothyroxine formulation taken during lunch in italy: a case report and review of the literature. *Case Rep Endocrinol* 2020:8858887. doi: 10.1155/2020/8858887.
21. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid* 2014; 24: 1670-751.
22. Wiesner A, Gajewska D, Paśko P. Levothyroxine Interactions with food and dietary supplements-A systematic review. *pharmaceuticals (Basel)* 2021; 14:1-20
23. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. *J Clin Endocrinol Metab* 1996; 81:857-9
24. Chiu AC, Sherman SI. Effects of pharmacological fiber supplements on levothyroxine absorption. *Thyroid* 1998; 8:667-71.
25. Abalovich M, Calabrese C, Vázquez A, et al. Malabsorción de levotiroxina por consumo de fibras durante el desayuno ¿Mito o realidad? *Rev Argent Endocrinol Metab* 2013; 50 (Suppl): 65.
26. Benvenga S, Bartolone L, Pappalardo MA, Russo A, Lapa D, Giorgianni G, et al. Altered intestinal absorption of L-thyroxine caused by coffee. *Thyroid* 2008; 18: 293-301.
27. Vita R, Saraceno G, Trimarchi F, Benvenga S. A novel formulation of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. *Endocrine* 2013; 43: 154-60.
28. Lilja JJ, Laitinen K, Neuvonen PJ. Effects of grapefruit juice on the absorption of levothyroxine. *Br J Clin Pharmacol* 2005; 60: 337-41.
29. Yamaguchi A, Isolabella D, Politi P. Interacciones relevantes del jugo de pomelo con fármacos. Revisión bibliográfica y soporte para conductas clínicas. *Actual En Nutr* 2016; 17: 128-33.
30. Chon DA, Reisman T, Weinreb JE, Hershman JM, Leung AM. Concurrent milk ingestion decreases absorption of levothyroxine. *Thyroid* 2018; 28: 454-7.
31. Lai YW, Huang YW. Tea consumption affects the absorption of levothyroxine. *Front Endocrinol (Lausanne)* 2022; 13:943775.
32. Zamfirescu I, Carlson HE. Absorption of levothyroxine when coadministered with various calcium formulations. *Thyroid* 2011; 21: 483-6.
33. Campbell NR, Hasinoff BB, Stalts H, Rao B, Wong NC. Ferrous sulfate reduces thyroxine efficacy in

patients with hypothyroidism. *Ann Intern Med* 1992; 117: 1010-3.

34. Irving SA, Vadiveloo T, Leese GP. Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). *Clin Endocrinol (Oxf)* 2015; 82: 136-41.
35. Shakir KM, Chute JP, Aprill BS, Lazarus AA. Ferrous sulfate-induced increase in requirement for thyroxine in a patient with primary hypothyroidism. *South Med J* 1997; 90: 637-9.
36. Liel Y, Sperber AD, Shany S. Nonspecific intestinal adsorption of levothyroxine by aluminum hydroxide. *Am J Med* 1994; 97: 363-5.
37. Harmon SM, Seifert CF. Levothyroxine-cholestyramine interaction reemphasized. *Ann Intern Med* 1991; 115: 658-9.
38. Alswat K. Role of cholestyramine in refractory hyperthyroidism: a case report and literature review. *Am J Case Rep* 2015; 16: 486-90.
39. Northcutt RC, Stiel JN, Hollifield JW, Stant EG. The influence of cholestyramine on thyroxine absorption. *JAMA* 1969; 208:1857-61
40. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. *Clin Oncol (R Coll Radiol)* 2005; 17: 492.
41. Rizzo L, Mana D, Serra H. Drug-induced hypothyroidism. *Medicina (B Aires)* 2017; 77 :394-404.
42. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol* 2007; 39: 599-602.
43. Guzman-Prado Y, Vita R, Samson O. Concomitant use of levothyroxine and proton pump inhibitors in patients with primary hypothyroidism: a systematic review. *J Gen Intern Med* 2021; 36:1726-33.
44. Oteri V, Volpe S, Lopes M, et al. Therapeutic efficacy and patient compliance of levothyroxine liquid and softgel formulations taken with meals: a systematic review. *Endocrine* 2025; 87:48-58..
45. Antúnez PB, Licht SD. Vitamin C improves the apparent absorption of levothyroxine in a subset of patients receiving this hormone for primary hypothyroidism. *Rev Argent Endocrinol Metab* 2011; 48: 16-24.
46. Jubiz W, Ramirez M. Effect of vitamin C on the absorption of levothyroxine in patients with hypothyroidism and gastritis. *J Clin Endocrinol Metab* 2014; 99: E1031-34.
47. Caron P, Grunenwald S, Persani L, Borson-Chazot F, Leroy R, Duntas L. Factors influencing the levothyroxine dose in the hormone replacement therapy of primary hypothyroidism in adults. *Rev Endocr Metab Disord* 2022; 23:463-83.
48. Centanni M, Gargano L, Canettieri G, et al. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. *N Engl J Med* 2006; 354 :1787-95.
49. Ward L. The difficult patient: drug interaction and the influence of concomitant diseases on the treatment of hypothyroidism. *Arq Bras Endocrinol Metabol* 2010; 54: 435-42.
50. Barzin M, Molavizadeh D, Mahdavi M, et al. Thyroid hormone replacement dosing after bariatric surgery in patients with primary hypothyroidism and severe obesity: Tehran Obesity Treatment Sstudy. *Thyroid* 2024; 34:1105-16.
51. Azran C, Porat D, Fine-Shamir N, Hanhan-Shamshoum N, Dahan A. Oral levothyroxine therapy post-bariatric surgery: Biopharmaceutical aspects and clinical effects. Surg *Obes Relat Dis* 2019; 15:333-41.
52. Azran C, Hanhan-Shamshoum N, Irshied T, et al. Hypothyroidism and levothyroxine therapy following bariatric surgery: a systematic review, meta-analysis, network meta-analysis, and meta-regression. *Surg Obes Relat Dis* 2021;17: 1206-17.
53. Fierabracci P, Martinelli S, Tamberi A, et al. Weight loss and variation of levothyroxine requirements in hypothyroid obese patients after bariatric surgery. *Thyroid* 2016; 26: 499-503.
54. Licht S, Antunez P. Factores que interfieren con la absorción de la levotiroxina. Tratado Argentino de Tiroides 2011; Capítulo 50, pp 3-18.
55. Seppel T, Rose F, Schlaghecke R. Chronic intestinal giardiasis with isolated levothyroxine malabsorption as reason for severe hypothyroidism-implications for localization of thyroid hormone absorption in the gut. *Exp Clin Endocrinol Diabetes* 1996; 104: 180-2.
56. Kim P, Sachmechi I. Levothyroxine malabsorption induced by diabetic gastroparesis exacerbated during pregnancies: effect of intramuscular levothyroxine injections and levothyroxine soft gel capsules. *AACE Clin Case Rep* 2015; 1: e73-8
57. Rizzo L, Mana D. Treatment of hypothyroidism in special situations. *Medicina (B Aires)* 2020; 80 Suppl 6:83-93.
58. Ain K, Refetoff S, Fein HG Weintraub B. Pseudomalabsorption of levothyroxine. *Jama* 1991; 266:2118-20.
59. Rizzo L. Hormonoterapia tiroidea. Tratado Argentino de Tiroides 2011, Capítulo 49, pp 3-18.
60. Van Wilder N, Bravenboer B, Herremans S, Vanderbruggen N, Velkeniers B. Pseudomalabsorption of

levothyroxine: a challenge for the endocrinologist in the treatment of hypothyroidism. *Eur Thyroid J* 2017; 6: 52-6.

61. Caron P, Declèves X. The use of levothyroxine absorption tests in clinical practice. *J Clin Endocrinol Metab* 2023; 108:1875-88.
62. Lips D, van Reisen M, Voigt V, Venekamp W. Diagnosis and treatment of levothyroxine pseudomalabsorption. *Neth J Med* 2004; 62:114-8.
63. Aljenaee K, Cheah S, McDermott J. Thyroxine absorption test. *Biomed J Sci Tech Res* 2018; 3: BJSTR. MS.ID.000881.
64. Santos Monteiro S, Silva Santos T, Martins Lopes A, Oliveira JC, Freitas C, Couto Carvalho C. ¿Levothyroxine malabsorption or pseudomalabsorption? A question in the management of refractory hypothyroidism. *Endocr Connect* 2022; 11:e220355.
65. Sözen M, Canturk Z, Cetinarslan B, Tarkun I, Gezer E, Selek A. Diagnosis of levothyroxine pseudo-malabsorption: the results of standardised testing protocol. *J Coll Physicians Surg Pak* 2021; 31:1099-101.
66. Soares R, de Figueiredo R, Dantas M, et al. Rapid levothyroxine (LT4) absorption test for diagnosis of LT4 pseudomalabsorption: case report and proposal of a cutoff point. *J Endocrinol Diabetes Obes* 2016; 4:1083.
67. Ghosh S, Pramanik S, Biswas K, et al. Levothyroxine absorption test to differentiate pseudomalabsorption from true malabsorption. *Eur Thyroid J* 2020; 9:19-24.
68. Walker JN, Shillo P, Ibbotson V, Vincent A, Karavitaki N, Weetman AP, Wass JA, Allahabadia A. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. *Eur J Endocrinol* 2013; 168:913-17.
69. Grebe S, Cooke R, Ford H, et al. Treatment of hypothyroidism with once weekly thyroxine. *J Clin Endocrinol Metab* 1997; 82: 870-5.