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The use of liquid levothyroxine in the treatment of patients with hypothyroidism and comorbidities- a review of the literature

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ABSTRACT

Objective: The primary drug used to treat hypothyroidism is synthetic levothyroxine. Patients with other diseases besides hypothyroidism often have malabsorption of levothyroxine administered in tablet form. In many cases, resistance to levothyroxine decreases or disappears when the drug is used in liquid form. The purpose of this paper is to systematize current knowledge about the effectiveness of using levothyroxine in liquid form when patients have comorbidities in addition to hypothyroidism. Materials and methods: The literature publicly available in the following databases was reviewed: PubMed and Google Scholar. Articles from january 2015- May 2025 were considered. The following keywords were used: "levothyroxine", "hypothyroidism", "levothyroxine absorption", "levothyroxine pharmacokinetics". Results: Patients are given levothyroxine in various forms. The most popular of these is the tablet, but in many cases, its use does not lead to euthyroidism.The main cause is malabsorption in the gastrointestinal tract associated with Helicobacter pylori infection, celiac disease, autoimmune gastritis, and other conditions. The liquid form has a therapeutic effect due to more favorable pharmacokinetics. Conclusion: The absorption efficiency in the gastrointestinal tract of liquid levothyroxine is higher than that of levothyroxine administered in tablet form. This is especially important in patients with comorbidities, where this absorption is often impaired by pathophysiological mechanisms or medications used. For such patients, the use of liquid levothyroxine appears to be the only option, which should be taken into account when recommending treatment for hypothyroidism.

Keywords: hypothyroidism, absorption, levothyroxine, liquid levothyroxine

1. INTRODUCTION

Hypothyroidism is one of the most common endocrine diseases, affecting millions of people worldwide. It is typically associated with reduced production of

thyroxine (T4) and triiodothyronine (T3), which slows down the metabolic rate and results in various clinical symptoms, including constant tiredness, weight gain, depression, and poor concentration. Supplemental thyroid hormone replacement with thyroxine (T4) has been the cornerstone of treatment for hypothyroidism for many years (Jonklaas et al., 2014).

Despite the availability of levothyroxine in tablet form for many years, optimal doses fail to result in a satisfactory clinical response in a subset of patients. A key factor contributing to treatment failure is the inconsistent bioavailability of the medication, often caused by impaired absorption in the digestive system, among other reasons. The use of other drugs, the presence of an abnormal intestinal mucosa, the comorbidities, and even the ingestion of food have a high impact on the response to therapy. In response to these limitations, there is growing interest in a liquid form of levothyroxine, which can be an effective alternative to traditional tablets due to its faster and more predictable absorption.

Absorption of levothyroxine in the gastrointestinal tract

The tablet remains the primary method for administering levothyroxine (LT4). Levothyroxine administration involves its disintegration and solubilization in the stomach, followed by intestinal absorption predominantly in the small bowel. Effective dissolution of levothyroxine tablets depends on a gastric pH range of approximately 1.0 to 3.0, which promotes the dissociation of sodium ions and converts LT4 into its lipophilic form. The solubility of LT4 tablets at pH 1.2 is close to 100% after 30 min. At pH 4.0, however, this value drastically decreases to less than 60%, which may influence the extent of drug absorption (Kocic et al., 2011).

Absorption of levothyroxine from oral forms of the drug takes place mainly in the small intestine and begins about 60-90 minutes after administration. Little levothyroxine is absorbed in the stomach, while about 21% is absorbed in the duodenum, 45% in the jejunum and 35% in the ileum. The rate of absorption is fast, with peak levels occurring 1.5–2 hours after ingestion if taken on an empty stomach (Hays, 1991). Concurrent ingestion of levothyroxine with meals, such as breakfast or coffee, may decrease and postpone its absorption.

The mechanism of LT4 transport across the intestinal mucosa is still controversial and is the subject of further research. In recent years, clinical studies and experimental evidence have shown that LT4 transporters include a family of organic anion transporting polypeptide (OATP), Na-taurocholate co-transporting polypeptide (NTCP), L1 and L2 type amino acid transporter (LAT1 and LAT2), monocarboxylate transporter type 8 and type 10 (MCT8 and MCT10) (Chung et al., 2021).

A significant role in the absorption and metabolism of LT4 is also played by the enteric-hepatic cycle. When enterocytes in the intestines absorb LT4, most of the LT4 molecules first pass through the liver via the mesenteric and portal veins, where they undergo further metabolism. In the liver, a portion of the LT4 molecules undergo conjugation, increasing their water solubility. The conjugated T4 is excreted into the intestine with the bile. The secreted conjugated T4 is deconjugated by the intestinal flora, and a part of it is reabsorbed (Virili and Centanni, 2017).

Factors limiting the bioavailability of levothyroxine tablets

Numerous pathological conditions may hinder the absorption of levothyroxine when administered in tablet form. Several drugs and nutrition supplements can reduce the bioavailability of oral levothyroxine and make it challenging to attain and maintain a euthyroid state (Ruchała, 2021). The mechanisms are essential to understand for agents yet to be employed, and in consideration of the recognition of the benefits of the liquid levothyroxine. Various drugs and dietary substances can affect levothyroxine absorption, thereby influencing the effectiveness of replacement therapy in hypothyroidism. In practice, a certain number of substances are channel modulators whose blocking or opening action can be modulated in several ways by external factors (Trifiro et al., 2015).

One of the key mechanisms is the direct complexation or chelation of levothyroxine in the gastrointestinal tract, which physically prevents its absorption into the bloodstream. These include antacid preparations containing aluminum, magnesium, or calcium ions that affect gastric acid. Among them, calcium carbonate tightly binds to levothyroxine so that the bioavailability of levothyroxine is reduced and TSH concentration is increased (Morini et al., 2019). Iron preparations, in particular ferrous sulphate, have the same effect and can form non absorbable complexes with LT4 (Maltese et al., 2023). For this reason, it is recommended to maintain an interval of several hours (usually 4-6 hours) between taking levothyroxine and these preparations.

Another potential mechanism is the pH-induced effect on levothyroxine solubility in the stomach. Proton pump inhibitors (PPI), such as omeprazole, pantoprazole, or esomeprazole, are also increasingly used in the management of diseases of the gastrointestinal tract, leading to an increased pH in the gastric juice and, in turn, to a reduced absorption of levothyroxine from the tablet preparation.

PPI-induced elevated gastric pH interferes with the correct dissolving of levothyroxine tablet particles, which are necessary to be absorbed subsequently.

An in vivo study confirmed the role of gastric juice pH in LT4 absorption, showing that LT4 requirement increased with increasing gastric pH. A randomized crossover study demonstrated that intravenous PPI esomeprazole could decrease the maximum serum concentration (Cmax) of levothyroxine in patients using LT4 tablets (Seng et al., 2015).

In clinical practice, the use of PPIs may reduce the bioavailability of levothyroxine by decreasing its absorption from the gastrointestinal tract. As a result, hypothyroidism control in patients using PPIs and levothyroxine may be suboptimal, necessitating increased levothyroxine doses. It should be mentioned here that liquid levothyroxine is likely to be less affected by gastric pH and could overcome malabsorption in PPI users. In these cases, switching to another class of acid-reducing drugs or using levothyroxine in liquid form could optimize hormonal control, as absorption from these forms is less affected by gastric pH.

Furthermore, certain medications may alter levothyroxine absorption by the intestinal mucosa. While precise mechanisms of transport are still poorly understood, complex, and under investigation, it is known that some agents may have an influence on expression or activity of membrane transporters involved in LT4 absorption. This kind of interaction can be observed for some antibiotics like ciprofloxacin and rifampicin (Goldber et al., 2013). Also worth mentioning are bile acid sequestrants, such as cholestyramine and colevelam, which reduce the absorption of levothyroxine in the intestines by binding it (Skelin et al., 2017). Similar effects have been reported with other binding drugs, including lanthanum carbonate for renal failure and sucralfate.

The effect of some dietary supplements and other substances cannot be overlooked. For example, grapefruit juice is known to alter membrane transporters and drug metabolism, which may include levothyroxine. Levothyroxine can be nonspecifically adsorbed by dietary fiber, and bioavailability is reduced. Even coffee taken within minutes of the levothyroxine tablets can affect its absorption (Liu et al., 2023).

In clinical practice, to minimize the adverse effects of drugs and supplements on levothyroxine absorption, the medicine should be taken on an empty stomach, ideally 30-60 minutes, or even 1 hour, before eating. If that's the case, you can try to see if taking levothyroxine at night can lead to better absorption. It is also essential not to take levothyroxine at the same time as other medications and supplements; an interval as long as possible should be maintained.

In patients with difficulty achieving stable TSH levels despite adherence to the recommendations, consideration should be given to changing the form of the drug to a liquid form, which has better bioavailability and less susceptibility to interactions.

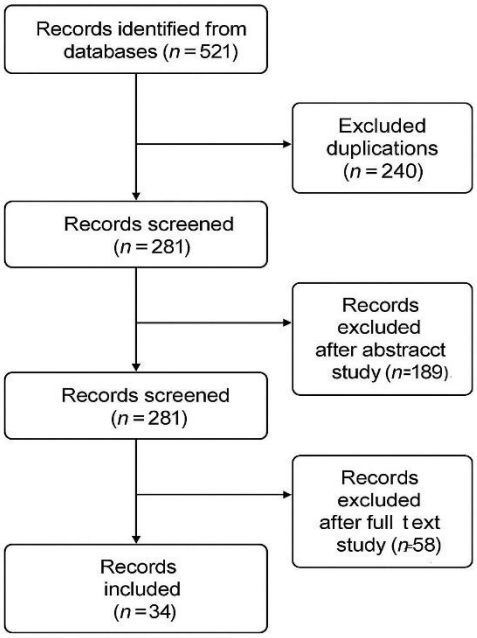

Figure 1: Flow diagram.

2. REVIEW METHODS

An electronic search of PubMed and Google Scholar was performed for articles published up to May 2025. The following keywords and Boolean operators were used: "liquid levothyroxine," "oral solution levothyroxine," "levothyroxine pharmacokinetics, and "levothyroxine absorption." Additional articles were identified through a manual search of the reference lists of key studies and relevant reviews. A total of n=521 records were initially identified. After removing n=240 duplicates, n=281 titles and abstracts were screened. Of these, n=189 were excluded due to lack of relevance, use of non-liquid formulations, or insufficient data presented in the abstract.

The remaining n=92 articles were retrieved for full-text evaluation. Following detailed review, n=58 studies were excluded for reasons including:

- lack of extractable outcome data (e.g., only descriptive findings),
- insufficient study quality (e.g., case reports with <3 patients),
- limited generalizability (e.g., thyroid cancer patients only),
- review-type articles presenting no new results.

Finally, n=34 studies were included in the qualitative synthesis. The selection process is illustrated in Figure 1.

3. RESULTS AND DISCUSSION

Features of liquid levothyroxine

Liquid levothyroxine has several potential advantages over the tablet formulation, particularly in certain patient populations and clinical scenarios. This superiority is explained by the distinct pharmacokinetic and pharmacological properties of liquid levothyroxine. Skipping the disintegration and dissolution process: one of the significant strengths of liquid levothyroxine is the lack of disintegration and dissolution of the drug's solid form and active ingredient, which are required with tablets. Because it's already in the solution, liquid LT4 is immediately available to be absorbed, so it is likely faster to act and less reliant on stomach acid. This is particularly advantageous for patients with increased gastric pH, for example, produced by proton pump inhibitors (PPIs) or atrophic gastritis, leading to compromised LT4 absorption from tablets. The suspension containing LT4 spends less time in the stomach and releases the LT4 earlier, and therefore, in the absorption process of these compounds, it is not as relevant what pH value of the gastric juice prevails (Virili et al., 2016).

Faster and more predictable bioavailability: pharmacokinetic studies consistently show that liquid levothyroxine has a faster rate of absorption. The maximum drug concentration in the blood (Cmax) is reached approximately 30 minutes faster with LT4 tablets compared to LT4 tablets. This faster pharmacokinetics may lead to better and more predictable absorption of LT4. In clinical practice, achieving stable thyroid hormone levels more rapidly may lead to quicker relief of hypothyroid symptoms and improved disease management (Yue et al., 2012).

Less susceptibility to drug and food interactions: as already mentioned, the absorption of levothyroxine tablets can be significantly reduced by various drugs and foods. Due to its reduced dependence on gastric pH and food timing, the liquid formulation of levothyroxine is less vulnerable to absorption-related interactions. Moreover, studies indicate that food and drinking coffee appear to not affect on the bioavailability of LT4 from soft capsules filled with liquid LT4 (Vita et al., 2013).

Use of liquid levothyroxine in patients with comorbidities

The benefits of using liquid levothyroxine become particularly apparent in patients in whom conventional treatment is unsuccessful. In many clinical situations, impaired absorption of levothyroxine in tablet form poses a significant therapeutic challenge. The use of levothyroxine solution can significantly improve treatment efficacy in such cases, enabling stable hormonal control to be achieved. The following are selected clinical conditions in which the liquid form of the drug can be a valuable alternative to traditional tablets.

Problems with the absorption of levothyroxine administered in tablet form have been found in patients infected with Helicobacter pylori. This bacterium, to survive in the acidic environment of the stomach, produces the enzyme urease, which breaks down urea into ammonia and carbon dioxide. The ammonia, in turn, partially neutralizes the hydrochloric acid produced by the lining cells. The pH of the stomach environment then rises, resulting in impaired dissolution of the levothyroxine tablet. Ribichini et al. (2017) reported greater efficacy of liquid levothyroxine compared to the conventional tablet formulation. The study included 28 patients infected with Helicobacter pylori. Some participants were randomly assigned to receive either the liquid or tablet form of levothyroxine. Patients in whom the liquid form was chosen were given a dose of the size they would have received if they had been treated with a tablet. The

study lasted 9 months, with Helicobacter pylori eradicated after 3 months. Patients treated with liquid levothyroxine experienced a greater reduction in TSH levels compared to those receiving tablets, both during Helicobacter pylori infection and following bacterial eradication. The effectiveness of liquid levothyroxine in patients with hypothyroidism and Helicobacter pylori infection is confirmed by other reports. Liquid levothyroxine is more effective than vitamin C administration in lowering gastric pH (Cherchir et al., 2023).

Good results have also been achieved when replacing the tablet with a liquid form when treating hypothyroidism in a patient with autoimmune gastritis. Characteristic of this disease is the presence of autoantibodies against the cells lining the stomach, resulting in impaired secretory function and reduced production of hydrochloric acid. Fallahi et al., (2016) conducted a study on five patients who had high TSH levels as a result of hypothyroidism despite being administered L-thyroxine in tablet form. These patients received the same dose of L-thyroxine in liquid form, which resulted in normalization of TSH levels. Four patients were again given tablets and again had abnormal TSH levels.

In a patient with gastroparesis, satisfactory clinical outcomes were achieved using gelatin capsule administration, whereas nearly double the tablet dose failed to produce similar effects (Reardon and Yoo, 2016). A 51-year-old female patient with Hashimoto's disease, complicated by gastroparesis and small intestinal bacterial overgrowth (SIBO), showed good absorption of liquid levothyroxine. The mechanism of malabsorption associated with gastroparesis involves delayed gastric emptying, which in turn leads to delayed delivery of levothyroxine to the upper ileum, the site of its absorption. In turn, excessive amounts of bacteria associated with SIBO impede absorption within the small intestine. Switching to levothyroxine solution resulted in a stabilization of TSH, but therapy for gastrointestinal complaints was also not insignificant (Bohinic Henderson, 2021).

The presence of parasites negatively affects the absorption of levothyroxine. Tortora described a case of a patient being treated for hypothyroidism who developed nausea, diarrhea, and abdominal cramps. With these symptoms, there was an increase in TSH levels. It was decided to switch to a liquid form of levothyroxine, which brought a reduction in TSH levels despite the persistent gastrointestinal symptoms. The patient was diagnosed with giardiasis caused by the intestinal parasite Giardia lamblia (Tortora et al., 2019).

With bariatric surgery, the area of exposure of gastrointestinal structures to drugs, including levothyroxine, decreases. Fallahi et al., (2017) described the case of 17 patients treated for hypothyroidism who underwent bariatric surgery for RYGB or BPD. Before the surgeries, levothyroxine supplementation was sufficient for them. After the surgeries, they had elevated TSH levels for several months. After switching from tablets to the liquid formulation, TSH levels decreased within 2–3 months.

Abnormalities in the absorption of L-thyroxine often occur in patients with lactose intolerance. This leads to an increase in the drug dosage. It is then necessary to follow a low-lactose diet. The levothyroxine preparation itself must also not contain lactose. Fallahi et al., (2017) presented the case of 8 patients whose TSH levels were stabilized after switching from tablets to a liquid form. Liquid thyroxine was administered at the same dose as before and at the same time, 30 minutes before breakfast. TSH levels decreased significantly within 1-3 months after the switch, dropping from 7.5±3.1 to 3.2±2.4 μIU/ml. After returning to the original pill regimen with unchanged dosage and timing, the patients experienced increased TSH levels. The authors of the study concluded that the oral liquid form of levothyroxine can circumvent the problem of malabsorption in patients with lactose intolerance.

Reduced absorption capacity of levothyroxine also occurs in patients with celiac disease. The key to curbing the effects of this disease is unquestionably maintaining a proper gluten-free diet. Late diagnosis of celiac disease often results in years of problems with stabilizing TSH levels. Asamoah (2021) described the case of a 62-year-old woman who was initially treated for hypothyroidism and then diagnosed with Addison's disease. Treatment with levothyroxine in pill form was undertaken, while autoimmune adrenal insufficiency was treated with prednisone and fludrocortisone acetate. Despite treatment, problems were encountered in stabilizing TSH at normal levels. For 10 years, the patient's levothyroxine dose was adjusted, increasing every 3-6 months. One day, the patient presented with severe gastrointestinal symptoms; she also complained of fatigue, characteristic of hypothyroidism.

On examination, she was diagnosed with celiac disease. The medical team raised the levothyroxine dose to liquid form and suggested adopting a gluten-free diet. After a month, her gastrointestinal symptoms had mostly subsided, but she still complained of malaise and fatigue despite normal TSH levels, which showed significant fluctuations. At that time, the form of levothyroxine administered was changed to liquid. After about 2.5 months, the TSH level stabilized. The patient adhered to her diet, which also promoted the supply of the drug in her body. Undeniably, the inhibition of thyroxine uptake was also influenced by medications taken for Addison's disease, but still excellent results were achieved.

On the other hand, a 51-year-old patient was treated for autoimmune hypothyroidism in the past. She had been taking various levothyroxine preparations for 12 years, and although she had recently taken 200 μg per day, satisfactory results had not been achieved. The patient, when she presented to the endocrinology department, had a TSH of 37.1 μIU/mL. Her history indicated, among

other things, gastrointestinal symptoms due to an unknown food intolerance. Tests revealed that she had celiac disease, which resulted in, among other things, atrophy of the intestinal villi. A gluten-free diet was implemented, but it did not improve the patient's hormone levels. After administering liquid levothyroxine at the same dose of 200 μg per day, the team made the decision. This dose was gradually reduced. The patient achieved a TSH level of 2.24 μIU/mL after 3 months on a daily dose of 112 μg (Ruchała et al., 2022).

A 26-year-old man had endocrine neoplasia (MEN) type 2A, postoperative hypothyroidism, and adrenal insufficiency. This patient underwent prophylactic thyroidectomy as a child, and adrenalectomy was performed due to the development of pheochromocytoma of both adrenal glands. At a dose of 125 μg, his TSH level was between 5.6 and 12 μIU/mL. The patient experienced fatigue, characteristic of hypothyroidism. Attempts to increase the levothyroxine dose to 137 μg caused palpitations, a symptom of clinical thyrotoxicosis. Increased hormone levels caused a faster metabolism of hydrocortisone, leading to a potentially dangerous drop in its blood concentration. In turn, hypothyroidism caused hyponatremia. The decision was made to switch to a liquid form of levothyroxine at a lower dose of 125 μg. Six weeks after the change, the patient's TSH was 2.3 μIU/mL, and after 12 weeks, it was 1.8 μIU/mL (Ruchała et al., 2022).

Increasing the dose from 125 μg to 175 μg and then 200 μg on alternate days in a hypertensive pregnant woman did not improve her condition, and her TSH level remained at 6.6 μIU/mL. For the same dose, in the liquid presentation, TSH was reduced to 2.0 μIU/mL (4 weeks) and 1.4 μIU/mL (8 weeks) (Ruchała et al., 2022).

Diseases that interfere with bile secretion, such as cholelithiasis, cholangitis, pancreatitis, and cirrhosis, can decrease T4 absorption (Benvenga et al., 2018). Unfortunately, the use of liquid levothyroxine for these diseases has not been described in the literature.

The liquid form of levothyroxine is more easily administered in specific patients;

Patients with difficulty swallowing (dysphagia)

People experiencing dysphagia, or trouble swallowing, form a key group that gains considerable advantage from liquid levothyroxine. Dysphagia can occur in the elderly, post-stroke patients, patients with neurological diseases, head and neck tumors, or other conditions that make taking pills difficult. For these patients, swallowing a tablet can not only be difficult but also risky due to the possibility of choking.

Infants and young children with congenital hypothyroidism

For infants and young children with congenital hypothyroidism, precise dosing of levothyroxine is crucial for normal neurological development. Due to LT4's narrow therapeutic index and low body weight in this age group, even minor deviations in dosage can have significant consequences. The liquid form of the drug makes it possible to measure even the smallest doses very accurately, which is much more difficult when splitting tablets, which often do not ensure homogeneous distribution of the active substance. In addition, liquid LT4 can be easily administered to infants by mixing it with a small amount of water or milk, which facilitates acceptance of the drug by the child and parents. It is worth noting that in studies, more reduced TSH levels were observed in infants receiving LT4 solution (Peroni et al., 2014).

Enterally fed patients

In addition, patients who are unable to swallow for any reason and are fed by an enteral probe can be treated with liquid levothyroxine. When administering tablets through a probe, caregivers must crush and dissolve them, but undissolved fragments can block the probe and cause variable absorption. The liquid formulation of LT4 dispensed through the capsule resolves these issues and enables more tractable and efficient absorption of the drug. This form is generally easier to administer and is preferred by nursing staff (Pirola et al., 2014).

Pregnant women

Hypothyroid pregnant women require dose elevation of levothyroxine to satisfy the demands of pregnancy and the developing fetus. Hypothyroidism in pregnancy is related to pregnancy complications and the development of fetal retardation induced by low levels of free thyroxine. Iron supplements, commonly used by pregnant women, may bind with levothyroxine tablets to form non-absorbable complexes, which decrease bioavailability and raise TSH levels. Plus, the nausea and vomiting of pregnancy can make it hard to remember to take the pills regularly. During this specific period, hypothyroidism treatment with liquid form could be better tolerated and with more stable absorption. In a retrospective evaluation of pregnant hypothyroid women treated with liquid LT4 form, fewer

showed need for dose adjustment compared to tablet users. Dose increases were necessary for 41.2% of patients on pills, but only for 7.1% of patients receiving liquid LT4. The rate of up-titration was also lower in the liquid LT4 group (Cappelli et al., 2016). And for nausea and vomiting, two of the most common irritating pregnancy conditions, it seems that the liquid form of the drug might be easier to swallow than pills. The capacity to administer an exact liquid dose might also be helpful if dosing changes are frequently required in small increments during pregnancy.

Critically ill and unconscious patients

Critically ill patients may experience limited absorption of levothyroxine (LT4) from the gastrointestinal tract. In the situation of myxedema coma, which is a rare but life-threatening condition, intravenous levothyroxine is recommended as first-line treatment. When the injectable form of the medication is unavailable, administering liquid levothyroxine through a nasogastric tube provides effective therapy (Elghawy et al., 2021). The use of liquid LT4 circumvents the potential problems associated with improper dissolution of tablets under altered gastrointestinal conditions. Rapid and effective drug administration plays a critical role in saving patients who experience sudden thyroid hormone deficiency, such as metabolic coma.

Patients with hypersensitivity and intolerances

Classical therapy is difficult for hypothyroid patients with associated allergies or intolerances to the many excipients used in levothyroxine tablets. Tablets contain inactive ingredients like dyes, fillers, binders, and preservatives, which can cause reactions in sensitive people.

In such cases, liquid levothyroxine, especially formulations with a simple formulation, can be a beneficial alternative. In these circumstances, liquid levothyroxine, particularly formularies that contain simple ingredients, can be a scientifically valid substitute. Tirosint-SOL, an alcohol-free aqueous solution, contains solely L-thyroxine, glycerin, and water (Gietka-Czernel et al., 2020). By limiting ingredients, this approach greatly lowers the chance of allergic reactions or intolerance to excipients. Hidden allergies or intolerances may be responsible for sub-optimal response to treatment with levothyroxine tablets in many patients. Therefore, taking a thorough medical history to identify potential hypersensitivities is essential before initiating therapy. In case of suspected or demonstrated allergic reaction to components of the tablet, it is possible to substitute the product with a liquid formulation of levothyroxine with a reduced excipient content, like Tirosint-SOL, also avoiding the intake of allergenic substances and then, in theory, providing greater tolerability of the drug and an improvement in hormonal control.

Another critical issue is hypersensitivity to alcohol. Some liquid levothyroxine preparations from the past used alcohol as part of their formulation. Patients with alcohol hypersensitivity, liver disease, epilepsy, or other contraindications to ethanol should avoid products containing alcohol. In this regard, the availability of alcohol-free liquid levothyroxine preparations (Tirosint-SOL) is a significant step forward. This ethanol-free preparation provides a safe treatment choice for patients with alcohol intolerance. In this way, patients with alcohol sensitivity may derive the advantages of liquid levothyroxine in terms of quicker uptake and independent meal relationship of use without being subjected to the adverse effects of alcohol.

Potential to improve adherence

Taking levothyroxine on an empty stomach, at least 30 to 60 minutes before breakfast, is crucial for optimal absorption of the tablet. However, this regimen can be burdensome for some patients and negatively affect the regularity of taking the drug (compliance). Liquid levothyroxine may improve patient compliance because its bioavailability remains consistent, regardless of whether it is taken 15 or 30 minutes before a high-fat meal. The greater convenience of therapy, associated with less restrictive intake times, may lead to improved patient-physician cooperation (Ducharme et al., 2022).

Improved quality of life

Dissatisfaction with bolus LT4 treatment and poor quality of life are frequently reported by hypothyroid patients. Studies evaluating the effect of liquid levothyroxine on patients' quality of life provide objective data on this topic. A survey by Katarzyna Bornikowska et al. directly examined the impact of switching from levothyroxine tablets to the liquid form on patients' quality of life and objectively assessed the outcomes of therapy. This study analyzed changes in the quality of life of hypothyroid patients after switching to liquid levothyroxine. The validated Thyroid-Related Patient-Reported Outcomes (ThyPRO) questionnaire was used as a tool for assessing quality of life. This questionnaire focuses specifically on thyroid disease and evaluates quality of life across several domains. The study

mentioned above showed that patients taking liquid levothyroxine experienced improvements in quality of life in significantly more domains compared to patients continuing therapy with levothyroxine tablets. Specifically, significant improvements were observed in 10 out of 12 quality-of-life domains assessed in the liquid levothyroxine group. These domains included fatigue, weakness, memory and concentration problems, nervousness, anxiety, psychiatric symptoms, social life and sex life, among others. These improvements may be due to better hormonal control, greater convenience of use and a reduction in symptoms associated with drug malabsorption (Bornikowska et al., 2021). Table 1 summarizes clinical scenarios in which liquid levothyroxine may be particularly beneficial.

Table 1: Clinical Scenarios Favoring the Use of Liquid Levothyroxine

Clinical Scenario	**Mechanism of Impaired Absorption**	**Underlying Benefit of Liquid Levothyroxine in Specific Conditions**
Helicobacter pylori infection	Urease-mediated increase in gastric pH impairs tablet dissolution.	Liquid formulation bypasses gastric pH dependency, enabling effective absorption.
Autoimmune gastritis	Achlorhydria due to parietal cell loss diminishes gastric acidity required for tablet solubilization.	Liquid levothyroxine remains bioavailable irrespective of gastric acid levels.
Celiac disease	Villous atrophy reduces mucosal surface area for intestinal absorption.	Liquid LT4 demonstrates improved uptake even in damaged intestinal mucosa.
Lactose intolerance	Excipients such as lactose in tablet formulations may induce gastrointestinal disturbances and compromise levothyroxine absorption.	Lactose-free liquid formulations mitigate intolerance and enhance therapeutic efficacy.
Gastroparesis	Delayed gastric emptying impairs tablet transit and timely disintegration.	Liquid formulation ensures more rapid gastric clearance and absorption.
Small Intestinal Bacterial Overgrowth (SIBO)	Excessive intestinal flora interferes with drug absorption and metabolism.	Earlier absorption of liquid LT4 may circumvent microbial interference.
Bariatric surgery (e.g., RYGB, BPD)	Altered gastrointestinal anatomy limits absorptive capacity.	Liquid LT4 facilitates consistent absorption in surgically modified GI tracts.
Proton Pump Inhibitor (PPI) use	Elevated gastric pH hampers tablet disintegration and solubilization.	Liquid LT4 exhibits pH-independent absorption dynamics.
Iron or calcium supplementation	Chelation with minerals reduces LT4 bioavailability.	Liquid formulation minimizes interaction via accelerated transit and absorption.
Dysphagia or enteral feeding	Physical difficulty swallowing tablets or mechanical limitations with feeding tubes.	Liquid LT4 allows safe and efficient administration via oral or enteral routes.
Infants and children	Challenges in precise dosing and safe administration of tablets.	Liquid form permits accurate dose titration and easier delivery.
Pregnancy	Increased hormonal demands, nausea, and concurrent	Liquid LT4 offers stable pharmacokinetics and improved

	supplement use affect absorption.	tolerability.
Polypharmacy	Drug–drug interactions impede LT4 absorption from tablets.	Liquid LT4 reduces susceptibility to pharmacokinetic interactions.
Allergy or excipient intolerance	Reactions to dyes, binders, or fillers in tablets.	Simplified liquid compositions reduce risk of hypersensitivity.
Refractory hypothyroidism of unknown origin	Unidentified malabsorption or non-compliance with tablet timing.	Liquid LT4 enhances bioavailability and patient adherence.

4. CONCLUSION

As early as 2014, the American Thyroid Association (ATA) indicated that changing the form of administration of levothyroxine may have a beneficial effect on its absorption profile. However, they did not explicitly recommend moving away from tablets and switching to new forms. An insufficiently large number of studies was cited as the main reason, and the need for follow-up was pointed out. Current scientific literature provides enough evidence to recommend liquid forms over tablets.

This is especially true for patients who have other diseases in addition to hypothyroidism. Despite regularly raising the pill dosage, many patients in this group do not achieve a satisfactory reduction in TSH levels. This is because pathological disorders mean that only part of the tablet dose was absorbed. After switching to liquid forms, proper therapeutic effects are achieved after some time. In these patients, there is no alternative to the liquid form because as long as they have other diseases, absorption will be impaired.

An important direction for the future is to develop guidelines for the use of liquid forms in patients with specific disease entities. This list of diseases is still growing and expands as new treatment reports emerge.

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

REFERENCES

1. Asamoah E. Levothyroxine sodium oral solution to control thyroid function in a patient with hypothyroidism and celiac disease. Clin Case Rep 2021;9(5):e04170. doi: 10.1002/ccr3.4170
2. Benvenga S, Capodicasa G, Perelli S, Ferrari SM, Fallahi P, Antonelli A. Increased requirement of replacement doses of levothyroxine caused by liver cirrhosis. Front Endocrinol (Lausanne) 2018;9:150. doi: 10.3389/fendo.2018.00150
3. Bohinc Henderson B. Levothyroxine sodium oral solution normalizes thyroid function in a patient with Hashimoto's disease, gastritis, diabetic gastroparesis, and small intestinal bacterial overgrowth (SIBO). Int Med Case Rep J 2021;14:627–32. doi: 10.2147/IMCRJ.S326481
4. Bornikowska K, Gietka-Czernel M, Raczkiewicz D, Glinicki P, Zgliczyński W. Improvements in quality of life and thyroid parameters in hypothyroid patients on ethanol-free formula of liquid levothyroxine therapy in comparison to tablet LT4 form: An observational study. J Clin Med 2021;10(22):5233. doi: 10.3390/jcm10225233
5. Cappelli C, Negro R, Pirola I, Gandossi E, Agosti B, Castellano M. Levothyroxine liquid solution versus tablet form for replacement treatment in pregnant women. Gynecol Endocrinol 2016;32(4):290–2. doi: 10.3109/09513590.2015.1113518
6. Cherchir F, Oueslati I, Mouelhi Y, Talbi E, Feki M, Yazidi M. Levothyroxine liquid oral substitution as an alternative treatment for refractory hypothyroidism due to gastrointestinal malabsorption: A case report. SAGE Open Med Case Rep 2023;11:2050313X231209229. doi: 10.1177/2050313X231209229
7. Chung CW, Mo EY, Jung GS, Kim YH, Cho SW, Park DJ. Decreased expression of ileal thyroid hormone transporters in a hypothyroid patient: A case report. Front Endocrinol (Lausanne) 2021;12:664839. doi: 10.3389/fendo.2021.664839
8. Ducharme M, Scarsi C, Bettazzi E, Mautone G, Lewis Y, Celi FS. A novel levothyroxine solution results in similar bioavailability whether taken 30 or just 15 minutes before a high-fat high-calorie meal. Thyroid 2022;32(8):897–904. doi: 10.1089/thy.2021.0604
9. Elghawy O, Hafey AC, McCartney CR, Steinman JR. Successful treatment of myxedema coma using levothyroxine and liothyronine in the setting of adrenal crisis and severe cardiogenic shock in a patient with apparent primary empty sella. J Clin Transl Endocrinol Case Rep 2021;22(100095):100095. doi: 10.1016/j.jecr.2021.100095
10. Fallahi P, Ferrari SM, Camastra S, Politti U, Ruffilli I, Vita R. TSH normalization in bariatric surgery patients after the switch from L-thyroxine in tablet to an oral liquid formulation. Obes Surg 2017;27(1):78–82. doi: 10.1007/s11695-016-2247-4
11. Fallahi P, Ferrari SM, Ruffilli I, Antonelli A. Reversible normalisation of serum TSH levels in patients with autoimmune atrophic gastritis who received L-T4 in tablet form after switching to an oral liquid formulation: a case series. BMC Gastroenterol 2016;16(1):22. doi: 10.1186/s12876-016-0439-y
12. Gietka-Czernel M, Hubalewska-Dydejczyk A, Kos-Kudła B, Lewiński A, Ruchała M, Syrenicz A. Expert opinion on liquid L-thyroxine usage in hypothyroid patients and new liquid thyroxine formulation - Tirosint SOL [Opinia ekspertów dotycząca stosowania płynnej postaci lewotyroksyny oraz nowego preparatu Tirosint SOL u chorych na niedoczynność tarczycy]. Endokrynol Pol 2020;71(5):441–65. doi: 10.5603/EP.a2020.0065
13. Goldberg AS, Tirona RG, Asher LJ, Kim RB, Van Uum SHM. Ciprofloxacin and rifampin have opposite effects on levothyroxine absorption. Thyroid 2013;23(11):1374–8. doi: 10.1089/thy.2013.0014
14. Hays MT. Localization of human thyroxine absorption. Thyroid 1991 Summer;1(3):241–8. doi:10.1089/thy.1991.1.241
15. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014;24(12):1670–751. doi: 10.1089/thy.2014.0028
16. Kocic I, Homsek I, Dacevic M, Parojcic J, Miljkovic B. An investigation into the influence of experimental conditions on in vitro drug release from immediate-release tablets of levothyroxine sodium and its relation to oral bioavailability. AAPS PharmSciTech 2011;12(3):938–48. doi: 10.1208/s12249-011-9660-8

17. Liu H, Li W, Zhang W, Sun S, Chen C. Levothyroxine: Conventional and novel drug delivery formulations. Endocr Rev 2023;44(3):393–416. doi: 10.1210/endrev/bnac030
18. Maltese V, Gatta E, Facondo P, Anelli V, Cavadini M, Buoso C. Simultaneous intake of liquid l-t4 formulation and iron salt: Fact or fiction? Acta Endocrinol (Buchar) 2023;19(1):54–8. doi: 10.4183/aeb.2023.54
19. Morini E, Catalano A, Lasco A, Morabito N, Benvenga S. L-thyroxine malabsorption due to calcium carbonate impairs blood pressure, total cholesterolemia, and fasting glycemia. Endocrine 2019;64(2):284–92. doi: 10.1007/s12020-018-1798-7
20. Peroni E, Vigone MC, Mora S, Bassi LA, Pozzi C, Passoni A . Congenital hypothyroidism treatment in infants: a comparative study between liquid and tablet formulations of levothyroxine. Horm Res Paediatr 2014;81(1):50–4. doi: 10.1159/000356047
21. Pirola I, Daffini L, Gandossi E, Lombardi D, Formenti A, Castellano M,C Cappelli. Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube. J Endocrinol Invest 2014;37(6):583–7. doi: 10.1007/s40618-014-0082-9
22. Reardon DP, Yoo PS. Levothyroxine tablet malabsorption associated with gastroparesis corrected with gelatin capsule formulation. Case Rep Endocrinol 2016;2016:1316724. doi: 10.1155/2016/1316724
23. Ribichini D, Fiorini G, Repaci A, Castelli V, Gatta L, Vaira D. Tablet and oral liquid L-thyroxine formulation in the treatment of naïve hypothyroid patients with Helicobacter pylori infection. Endocrine 2017;57(3):394–401. doi: 10.1007/s12020-016-1167-3
24. Ruchała M, Bossowski A, Brzozka MM, Gietka-Czernel M, Hubalewska-Dydejczyk A, Kos-Kudła B. Liquid levothyroxine improves thyroid control in patients with different hypothyroidism aetiology and variable adherence - case series and review. Endokrynol Pol 2022;73(5):893–902. doi: 10.5603/EP.a2022.0078
25. Ruchała M. Increased efficacy of hypothyroidism control with liquid levothyroxine. Endokrynol Pol 2021;72(3):271–5. doi: 10.5603/EP.a2021.0049
26. Seng Yue C, Benvenga S, Scarsi C, Loprete L, Ducharme MP. When bioequivalence in healthy volunteers may not translate to bioequivalence in patients: Differential effects of increased gastric pH on the pharmacokinetics of levothyroxine capsules and tablets. J Pharm Pharm Sci 2015;18(5):844–55. doi: 10.18433/j36p5m
27. Skelin M, Lucijanić T, Amidžić Klarić D, Rešić A, Bakula M, Liberati-Čizmek A-M. Factors affecting gastrointestinal absorption of levothyroxine: A review. Clin Ther 2017;39(2):378–403. doi: 10.1016/j.clinthera.2017.01.005
28. Tortora A, La Sala D, Vitale M. Switch from tablet levothyroxine to oral solution resolved reduced absorption by intestinal parasitosis. Endocrinol Diabetes Metab Case Rep 2019;2019. doi: 10.1530/EDM-19-0026
29. Trifirò G, Parrino F, Sultana J, Giorgianni F, Ferrajolo C, Bianchini E. Drug interactions with levothyroxine therapy in patients with hypothyroidism: observational study in general practice. Clin Drug Investig 2015;35(3):187–95. doi: 10.1007/s40261-015-0271-0
30. Virili C, Centanni M. "With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling. Mol Cell Endocrinol 2017;458:39–43. doi: 10.1016/j.mce.2017.01.053
31. Virili C, Trimboli P, Romanelli F, Centanni M. Liquid and softgel levothyroxine use in clinical practice: state of the art. Endocrine 2016;54(1):3–14. doi: 10.1007/s12020-016-1035-1
32. 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(1):154–60. doi: 10.1007/s12020-012-9772-2
33. Yue CS, Scarsi C, Ducharme MP. Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms. Arzneimittelforschung 2012;62(12):631–6. doi: 10.1055/s-0032-1329951