Medical Science

To Cite:
Szczerkowska K, Chwiejczak J, Górny A, Seroka A, Rybicka M, Kościan J, Młynarska J, Wójcik A, Langa J, Obrębski M, Mitkowska M, Górecki B. Using the liquid form of levothyroxine in patients after bariatric surgery: An overview of the latest knowledge. *Medical Science* 2024; 28: e89ms3402 doi: https://doi.org/10.54905/disssi.v28i150.e89ms3402

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Peer-Review History
Received: 12 May 2024
Reviewed & Revised: 16/May/2024 to 29/July/2024
Accepted: 01 August 2024
Published: 07 August 2024

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Using the liquid form of levothyroxine in patients after bariatric surgery: An overview of the latest knowledge

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ABSTRACT

Hypothyroidism is a common condition affecting approximately 5% of the global population, with an estimated 5% remaining undiagnosed. This disease does not exclude the group of patients after bariatric surgery, the number of whom is constantly growing, posing new challenges to practitioners providing medical care to them. Bariatric patients previously treated for hypothyroidism should theoretically have their drug dosage reduced due to postoperative weight loss. In practice, it is often the opposite, and the doses are increased. In recent years, levothyroxine in the liquid form (LT4) was introduced for the treatment of hypothyroidism. Liquid levothyroxine, such as Tirosint SOL and Althyxin, has shown promising results, especially by improving absorption in bariatric patients. The present work contains the latest reports on the treatment of bariatric patients with liquid levothyroxine, focusing on such factors as the microbiome, polypharmacy, and the administration of proton pump inhibitors (PPI). It explains the mechanisms influencing the outcome of the above-mentioned medication.

Keywords: Liquid levothyroxine, bariatric surgery, hypothyroidism, novel levothyroxine

1. INTRODUCTION

Hypothyroidism is a widely prevalent endocrine condition, the frequency of which increases with age and is approximately ten times more common in women. We can distinguish between primary and secondary hypothyroidism. Primary hypothyroidism is most often caused by chronic autoimmune thyroiditis. It may also follow thyroid surgery, I-131 treatment, or the intake of

certain medications (e.g. lithium compounds, amiodarone). Secondary hypothyroidism is the consequence of the hypothalamic-pituitary area damaged by cancer, trauma, surgery, or radiotherapy of the central nervous system. Primary hypothyroidism results from reduced synthesis and secretion of hormones by the thyroid gland. This causes a decrease in the level of FT3 and FT4 hormones and an increase in thyrotropin (TSH) in the peripheral blood (Devdhar et al., 2007). Primary hypothyroidism may be subclinical or overt. In the first form, increased TSH occurs with average FT4 and FT3 hormones, while in the overt form, increased TSH is accompanied by decreased FT4 and, or FT3 (Chaker et al., 2017).

The most common symptoms of hypothyroidism include chronic fatigue, weight gain, increased sensitivity to cold, constipation, and dry skin. Hypothyroidism also affects obese patients qualified for bariatric surgery. The qualification criteria for bariatric surgery mainly include the patients' age and body mass index (BMI). Currently, metabolic surgery is recommended for patients with a BMI ≥ 40 kg/m², regardless of their level of glycemic control, and for people with a BMI ≥ 35 kg/m² whose diabetes does not respond adequately to pharmacological treatment. Additionally, clinicians should evaluate the suitability of bariatric surgery for patients with a BMI in the range of 30–35 kg/m² who exhibit insufficient glycemic control. Bariatric procedures are categorized into three main groups: restrictive procedures, malabsorptive procedures, and a combination of both.

Restrictive surgeries, which aim to limit the volume of food intake, include sleeve gastrectomy (SG), the most performed procedure for the surgical treatment of obesity. Malabsorptive treatments include turning off the biliopancreatic tract (BPD). Restriction-malabsorption surgery includes procedures that combine elements that limit the volume of food and exclude certain parts of the digestive tract. Examples of such procedures include Roux-Y-gastric bypass (RYGB), mini-gastric bypass (MGB), biliopancreatic diversion with duodenal switch (BPD-DS), as well as new methods of metabolic surgery such as single anastomotic duodenal-ileal bypass (SADI) (Tarnowski and Jaworski, 2018).

2. METHODS

The search used freely accessible medical databases such as PubMed or Sciencedirect.com. The following keywords were used to find relevant articles: "liquid levothyroxine", "bariatric surgery and hypothyroidism", "bariatric surgery and levothyroxine", "novel levothyroxine". Articles were chosen based on their titles and abstracts, covering the period from 2012 to 2024. The research aimed to investigate the effects of liquid l-thyroxine usage in patients after bariatric surgery and focus on potential benefits of the new liquid formula of the levothyroxine, as well as compare the impact of the latest and classic levothyroxine formulas.

3. RESULTS & DISCUSSION

General principles of treatment of hypothyroidism

The aim of hypothyroidism therapy is the clinical improvement and normalization of laboratory test results, i.e., achieving normal TSH and FT4 levels. The treatment involves levothyroxine (LT4) administered daily on an empty stomach. The doses of the drug depend on the cause of hypothyroidism, the patients' age, and coexisting diseases (Jonklaas et al., 2014). Typically, in mild to moderate cases of hypothyroidism, the initial dose of levothyroxine is 50-75 μg/day. The clinical benefits of the therapy become noticeable after 3-5 days, reaching full effect after 4-6 weeks. Any correction of the LT4 dose should take place every 4-6 weeks, under the control of TSH and FT4. One of the challenges of treatment challenges is the limited therapeutic range of LT4, defined as the slight difference between the minimum effective and minimum toxic concentrations in the blood. Therefore, even minor modifications of the LT4 dose may lead to significant clinical consequences (Orlander and Griffing, 2022).

Liquid levothyroxine

Liquid levothyroxine was introduced into clinical practice over a decade ago and is available in the United States and several European countries. Initially, LT4 preparations were solutions in 85% glycerol and 96% ethanol, dosed in the form of drops or single-dose vials. Relatively recently, a new preparation, Tirosint SOL, has become available on the market in the form of an oral solution consisting of a solution of the sodium salt of LT4 dissolved in a mixture of water and glycerol. In 2017, Tirosint SOL (produced by IBSA, Institut Biochimique SA) received FDA approval for replacement therapy in patients with hypothyroidism and as an adjunct to TSH inhibition in patients with well-differentiated thyroid cancer (Gietka-Czernel et al., 2020).

Since 2023, another preparation of liquid levothyroxine under the name Althyxin has been registered in some European Union countries, including Poland. The data show that using the liquid LT4 preparation compared to tablets resulted in significantly more patients maintaining TSH values within the target range recommended by the American Thyroid Association (Bornikowska et al., 2021). Liquid LT4 also seems to be a promising solution for elderly patients, patients with absorption disorders, children, and potentially pregnant women.

Enhanced absorption of the drug

The central aspect that improves the results of the treatment of hypothyroidism in patients after bariatric surgery is the better absorption of the liquid form of levothyroxine in comparison with the tablets (Fallahi et al., 2017a). In the study by Fallahi et al., (2017a) patients were eligible for bariatric surgery; thirteen underwent Roux-en-Y gastric bypass (RYGB), while four received biliopancreatic diversion (BPD). All the patients suffered from hypothyroidism but had been euthyroid for over one year before the surgery (Fallahi et al., 2017a). In these patients, despite regular intake of LT4 in the tablet form, increased TSH levels occurred 3 to 8 months after surgery.

Therefore, the patients were switched from the oral preparation LT4 to the liquid form at the same dose. 2-3 months after the drug change, the TSH values were significantly reduced in both the RYGB and BPD groups, while the FT4 and FT3 concentrations did not show significant changes (RYGB group, TSH μIU/ml: 7.58 ± 3.07 vs 3.808 ± 1.83, $P < 0.001$; BPD group, TSH μIU/ml: 8.82 ± 2.76 vs 3.12 ± 1.33, $p < 0.01$). The study confirmed the effectiveness of liquid LT4 in patients after RYGB and BPD. However, the final dose of the drug, regardless of whether it was an oral or liquid preparation, increased after the surgery. The study did not include patients who had undergone sleeve gastrectomy; therefore, future research should investigate the changes in TSH values based on the type of levothyroxine administered to this patient group. There are, however, single reports confirming that liquid levothyroxine is absorbed better after sleeve gastrectomy (Schiavo et al., 2021).

Microbiome after bariatric surgery

The rich intestinal microbiota also influences the absorption of the drug (Adlercreutz et al., 1984). Changes in bile salt metabolism at the bacterial and systemic levels may modulate the absorption of orally administered drugs. After bariatric surgery, modifications in the composition of the intestinal microflora affected the absorption processes of oral drugs, with variations depending on the type of bariatric surgery. Still, they varied according to the type of bariatric surgery. The intestinal microflora plays a crucial role in the metabolism of certain medicinal substances, and research has confirmed the relationship between intestinal microflora and the bioavailability, activity, and effectiveness of drugs (Mercado et al., 2023). It is worth noting that studies have shown that the RYGB procedure induces more significant changes in the intestinal microbiome compared to sleeve gastrectomy (Shao et al., 2017). Therefore, it is important to evaluate how drug absorption varies with different types of bariatric procedures.

Multimorbidity in patients after bariatric surgery

There is no doubt that obesity (BMI>30 kg/m2) is correlated with an increased risk of multimorbidity (Apovian, 2016). Excessive body weight markedly elevates the risk of various comorbid conditions, such as hypertension, dyslipidemia, type 2 diabetes, ischemic heart disease, cerebrovascular disorders, sleep apnea, and certain cancers (De-Lorenzo et al., 2019). Reducing body weight is associated with a reduced risk of multimorbidity (Agborsangaya et al., 2015). Due to the higher prevalence of diseases in obese patients undergoing bariatric surgeries—many of which do not achieve therapeutic success—these patients often experience polypharmacy. They frequently need to take various groups of drugs interacting with levothyroxine such as proton pump inhibitors (PPIs), calcium, iron, sevelamer, aluminum hydroxide, magnesium, and sodium alginate preparations, which may cause difficulties in the control of TSH and FT3, FT4 (Liwanpo and Hershman, 2009).

Impaired absorption is well-documented for tablet formulations, which need to dissolve in the acidic environment of the stomach before the active substance can be absorbed in the duodenum and small intestine. The mechanism that disrupts intestinal LT4 absorption in patients with altered gastric pH remains unclear. It is possible that the hydrophilic sodium salt (pharmaceutical form LT4) remains in its non-ionized form in lower gastric acid concentrations, and its absorption may thus be reduced (Gatta et al., 2022). LT4 has a limited therapeutic range, and cross-sectional studies show that 30% to 50% of people using LT4 have abnormal plasma TSH concentrations, particularly among those taking multiple medications (Okosieme, 2011; Canaris et al., 2000; Parle et al., 1993).

Therefore, the use of liquid levothyroxine seems to be an excellent option to correct hypothyroidism in bariatric patients taking multiple medications (Fallahi et al., 2017a).

Bariatric patients and the use of PPIs

A particularly important group of drugs used with greater frequency in patients after bariatric surgery are proton pump inhibitors. As a result of bariatric surgery, particularly sleeve gastrectomy, the risk of gastroesophageal reflux disease increases significantly (Roth et al., 2020). Due to the influence of PPIs on gastric pH, the simultaneous use of PPIs and L-thyroxine substantially affects the absorption of levothyroxine in the tablet form, giving a significant advantage to the liquid form. In a systematic review conducted by Yuli Guzman-Prado et al., each of the included studies showed an increase in TSH levels after consuming LT4 and PPIs, and in most of them, this increase was statistically significant (Guzman-Prado et al., 2021). Therefore, converting the treatment of hypothyroidism from tablets to liquid levothyroxine in patients using PPIs will possibly facilitate the control of TSH levels.

The time interval for using liquid thyroxine

Another advantage of administering LT4 in liquid form is that it does not require adherence to the 30–60-minute fasting interval before food intake. The need to take a standard LT4 tablet precisely 60-30 minutes before a meal result from a significantly lower bioavailability of the drug in the presence of food. Administering LT4 tablets with a high-fat, high-calorie meal decreases the maximum concentration (Cmax) of T4 by 40–49% and reduces the area under the curve (AUC0–48) by 38–40%, relative to administration under fasting conditions (Wenzel and Kirschsieper, 1977). Therefore, administering LT4 tablets on an empty stomach, ideally 60 minutes prior to breakfast, is advisable.

Pharmacokinetic parameters such as the maximum concentration, time to reach the maximum concentration, and area under the concentration-time curve were analyzed for various forms of levothyroxine. They demonstrated the benefits resulting from minimizing the interactions of the solution with food and a faster onset of its absorption (Yue et al., 2012). In a randomized study, Ducharme et al., (2022) evaluated the bioavailability of a levothyroxine solution administered to 36 healthy volunteers 15 minutes before a high-fat, high-calorie meal, compared with the recommended 30-minute interval. There was no significant difference in the pharmacokinetic properties of the new LT4 solution administered 15 or 30 minutes before the meal. Still, the specificity of the study group (healthy volunteers) should be considered.

Patient compliance after bariatric surgery

A systematic review of patients after bariatric surgery suggests a lasting improvement in the Quality-of-Life parameter (Sierżantowicz et al., 2022). Moreover, studies on a group of patients with primary and central hypothyroidism using a liquid form of levothyroxine also included an increase in QoL compared to patients treated with oral tablets (Bornikowska et al., 2021). The greater ease of dividing the dose of the liquid form than dividing the tablet can be considered another reason for increasing the chance of high patient compliance. Moreover, studies have shown that it does not matter whether the patient takes liquid thyroxine with water - the bioavailability is the same both with and without drinking water (Tanguay et al., 2019). It will probably allow for more effective therapy due to the convenience of using the liquid form of LT4.

A summary Table 1 contains the reports on the effects of the liquid form of levothyroxine. The use of liquid levothyroxine in hypothyroid patients after bariatric surgery offers advantages over traditional tablets, particularly in terms of improved drug absorption and more stable TSH outcomes. Changes in gastrointestinal function following bariatric surgery can significantly hinder the effective absorption of oral medications, making the liquid form of levothyroxine more effective. Studies indicate that liquid levothyroxine better controls thyroid-stimulating hormone (TSH) levels in patients who have undergone biliopancreatic diversion (BPD) and Roux-en-Y gastric bypass (RYGB).

Liquid levothyroxine offers the significant advantage of not requiring a fasting period prior to administration. In contrast to traditional tablet formulations, which necessitate a 30–60-minute fasting interval to optimize absorption, liquid levothyroxine can be administered without such constraints, thereby improving patient adherence. This advantage is particularly relevant for bariatric patients undergoing polytherapy, as it helps mitigate the risk of potential drug interactions.

Table 1 Recent findings regarding the potential benefits of liquid levothyroxine for bariatric patients

Authors, year	Main findings	Limitations	Type of the study
Bornikowska et al., 2021	• Liquid LT4 displays higher efficacy in patients with hypothyroidism ▪ Liquid LT4 provides a better improvement in patients' QoL than tablets.	• Short observation period: The study duration was only eight weeks • Small sample size: the group with central hypothyroidism included only 30 patients. • Lack of control group	Observational study
Fallahi et al., 2017a	▪ Liquid LT4 could prevent drug malabsorption after BPD. ▪ The study confirms that Liquid LT4 is better absorbed in patients after RYGB than tablets.	▪ Small sample size: the study included only 17 patients ▪ Lack of control group. ▪ patients underwent only two types of bariatric procedures: RYGB or BPD	Original research study
Fallahi et al., 2017b	▪ Better absorption of the liquid formula in all patients.	▪ Short observation period: the study duration was only eight weeks.	Review article
Schiavo et al., 2021	▪ Alteration of TSH following SG (sleeve gastrectomy) was treated by switching a patient from tablet L-T4 to liquid formulation before hypothyroidism could occur.	▪ Case report nature: the study presents only a single case. ▪ Lack of control group	Case report
Shao et al., 2017	▪ RYGB, but not SG, alters the gut microbiota ▪ RYGB reduces the diversity of gut microbiota	▪ Use of Non-Obese Rats: The study employed rats fed a standard diet instead of high-fat diet-induced obese rats.	Comparative study
Gatta et al., 2022	▪ Liquid LT4 can be co-administered with drugs interfering with L-T4 absorption.	-	Review study

Ducharme et al., 2022	▪ No significant difference in the pharmacokinetic properties of a novel LT4 solution administered either 15 or 30 minutes before a high-fat, high-calorie meal	▪ Healthy patients: The study involved on healthy volunteers under controlled conditions. ▪ High single dose administration: a high single dose of 600 mcg was used in healthy volunteers to ensure robust detection of the orally administered LT4.	Randomized controlled trial
Bornikowska et al., 2021	▪ Liquid LT4 demonstrates superior efficacy, resulting in an improved thyroid hormone profile and a more significant enhancement in patients' quality of life compared to the tablet form of LT4	▪ The small number of participants-70 patients. ▪ Lack of control group	Observational study

Despite promising results, current research on liquid levothyroxine has significant limitations. Many studies involve small sample sizes, limiting the generalizability of the findings. For example, the survey by Fallahi et al., (2027a) included only 17 patients and lacked a control group, making it difficult to definitively assess the effectiveness of liquid levothyroxine compared to tablets. Similarly, the study by Bornikowska et al., (2021) on quality of life and thyroid parameters included 70 patients. The limited duration of many studies restricts the assessment of the long-term efficacy and safety of liquid levothyroxine. For instance, the survey by Ducharme et al., (2022) on the bioavailability of a new levothyroxine solution lasted only a few weeks and involved healthy volunteers, making it challenging to extrapolate the results to the bariatric patient population.

Variations in the techniques of bariatric surgeries performed (e.g., RYGB vs. BPD) can also impact drug absorption outcomes, highlighting the need for further research comparing effects in different patient groups. Additionally, changes in gut microbiota following bariatric surgery can influence the metabolism and absorption of levothyroxine, which warrants further investigation. The cost and availability of liquid levothyroxine compared to tablet formulations may present significant barriers to its widespread adoption. Although the liquid form provides distinct clinical advantages, its higher cost and restricted availability in certain regions could constrain its utilization. Consequently, future studies should evaluate patient compliance, considering the limited availability of this relatively new formulation.

4. CONCLUSION

The latest research collectively aligns with the findings of previous reviews. The administration of liquid levothyroxine in hypothyroid patients after bariatric surgery demonstrates significant therapeutic benefits. Although the appropriateness of treating patients after RYGB or BPD with liquid levothyroxine is well-documented, there remains a lack of literature concerning its use in patients who have undergone other bariatric procedures, particularly the widely performed SG. Further research should involve randomized controlled trials with larger patient cohorts to compare therapeutic outcomes across different bariatric procedures.

Author's Contributions

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Informed Consent
No applicable.

Funding
This study has not received any external funding.

Ethical approval
Not applicable.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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