SAGE Open Medical Case Reports
Volume 11: 1–4

DOI: 10.1177/2050313X231209229
journals.sagepub.com/home/sco
Sage

Levothyroxine liquid oral substitution as an alternative treatment for refractory hypothyroidism due to gastrointestinal malabsorption: A case report

Faten Cherchir[1], Ibtissem Oueslati[1], Yasmine Mouelhi[1], Emna Talbi[2], Moncef Feki[2], Meriem Yazidi[1] and Melika Chihaoui[1]

Abstract

Tablets of levothyroxine (LT4) are the most used form for the treatment of hypothyroidism. Some patients may present with refractory hypothyroidism despite a high daily LT4 dose. We report the case of a 49-year-old woman who was admitted to our department for refractory hypothyroidism. She was treated with 300 μg oral LT4 tablets daily (3.9 μg/kg/day). Despite good compliance and regular intake of high doses of LT4, she had persistent symptoms of hypothyroidism and a thyroid-stimulating hormone level of 92.4 mIU/L. LT4 absorption test was consistent with the diagnosis of malabsorption. Etiological investigations revealed Helicobacter pylori gastritis. Helicobacter infection was adequately treated, but symptoms of hypothyroidism and elevated thyroid-stimulating hormone persisted. Increased LT4 doses (400 μg) failed to normalize thyroid-stimulating hormone levels. Thus, she was put on LT4 liquid form at a dose of 80 drops/day per day (400 μg). Two weeks later, she presented with clinical and biological improvement with a normal free thyroxine level of 1.14 ng/dL. Patients with gastrointestinal disorders may present with refractory hypothyroidism despite increasing doses of LT4. Switching to liquid formulation may resolve this problem.

Keywords

Refractory hypothyroidism, malabsorption, levothyroxine, levothyroxine absorption test

Date received: 23 June 2023; accepted: 2 October 2023

Introduction

Primary hypothyroidism is a common thyroid disease. It is caused by autoimmune thyroiditis, thyroid surgery, radioactive iodine (RAI) therapy, and drugs such as amiodarone, interferon, and lithium.[1] Biochemically, the diagnosis of overt primary hypothyroidism is established in the presence of an elevated thyroid-stimulating hormone (TSH) concentration and a low free thyroxine (FT4) level.[2] Oral levothyroxine (LT4) in solid tablet form represents the conventional treatment for hypothyroidism. Most patients require approximately 1.6–1.8 μg/kg/day.[3] The treatment target is to reverse the clinical signs of hypothyroidism and to normalize TSH levels. In most cases, appropriate doses of LT4 restore euthyroidism.[1] However, some patients may present with refractory hypothyroidism, which is defined as a persistent elevated TSH level despite a regular daily LT4 dose higher than 1.9 μg/kg.[3,4] Therapeutic failure can be due to poor adherence to treatment or impaired LT4 absorption because of drug interactions or gastrointestinal diseases such as atrophic gastritis, Helicobacter pylori gastritis, celiac disease, inflammatory diseases, and lactose intolerance.[3–6] In such conditions, the management of hypothyroidism is challenging.

Herein, we report the case of a patient with refractory hypothyroidism due to gastrointestinal malabsorption that was improved after switching to LT4 oral liquid form.

[1]Faculty of Medicine of Tunis, Department of Endocrinology, La Rabta University Hospital, University of Tunis El Manar, Tunis, Tunisia
[2]Faculty of Medicine of Tunis, Laboratory of Biochemistry, La Rabta University Hospital, University of Tunis El Manar, Tunis, Tunisia

Corresponding Author:
Ibtissem Oueslati, Faculty of Medicine of Tunis, Department of Endocrinology, La Rabta University Hospital, University of Tunis El Manar, Rue Jbel Lakhdar, La Rabta Jebbari, Tunis 1007, Tunisia.
Email: ouesibtissem@gmail.com

Table 1. Serum biological and hormonal parameters.

Biological and hormonal parameters	Values	Normal ranges
Fasting blood glucose level (mmol/L)	4.84	3.88–5.55
Total cholesterol (mmol/L)	9.6	3.2–5.5
Triglycerides (mmol/L)	1.2	0.56–1.92
Natremia (mmol/L)	142	135–145
Kalemia (mmol/L)	4	3.5–5.1
Creatinine level (μmol/L)	109.01	53–97
CPK (IU/L)	2747	30–200
LDH (IU/L)	797	125–245
Calcium (mmol/L)	2.48	2.2–2.6
Phosphorus (mmol/L)	1.22	0.8–1.4
White blood cells (elements/mm3)	4340	4000–10,000
Hemoglobin (g/dL)	12.9	12–16
TSH (mIU/L)	92.4	0.35–4.94
FT4 (ng/dL)	<0.42	0.7–1.5

CPK: creatine phosphokinase; LDH: lactate dehydrogenase; TSH: thyroid-stimulating hormone; FT4: free thyroxine.

Case presentation

A 49-year-old woman was admitted to our department for refractory hypothyroidism. Her past medical history included left adrenalectomy for ganglioneuroma, asthma treated with salbutamol, vitamin D deficiency, and Graves' disease treated with RAI therapy. The patient was treated with daily 300 μg oral LT4 tablets (3.9 μg/kg/day). Despite regular intake of this high dose of LT4, she had persistent symptoms of hypothyroidism. She presented with general weakness, weight gain, depressive mood, and persistent constipation.

On physical examination, she had myxedema, a body weight of 76 kg, a height of 156 cm, a body mass index of 31.2 kg/m^2, a blood pressure of 110/80 mmHg, and a heart rate of 68 beats/min. Electrocardiogram showed a normal sinus rhythm of 65 beats/min without obvious repolarization abnormalities.

Biological investigations revealed hypercholesterolemia, elevated muscle enzymes, elevated TSH level, and decreased FT4 level (Table 1). Two LT4 absorption tests were successively performed. On the first day, 300 μg of LT4 was orally administered. On the second day, a concomitant oral administration of 300 μg of LT4 and 1 g of vitamin C was performed. FT4 levels were measured before drug intake (T0), 2 (T2H), 4 (T4H) and 8 (T8H) hours after. The absorption rate was calculated using the following formula: %LT4 absorption = ((peak ΔT4 × volume distribution (dL))/administered dose of LT4(μg)) × 100 (Volume distribution = 4.42 × body mass index (kg/m^2)). It was equal to 0% after the two tests. The diagnosis of LT4 malabsorption was established. Etiological workup showed negative anti-transglutaminase and anti-endomysium antibodies and the presence of antral gastritis on endoscopy. Histopathological examination showed non-atrophic pan-gastritis with no signs of intestinal metaplasia. *Helicobacter pylo*ri (*H. pylori*) infection was positive and adequately treated. However, symptoms of hypothyroidism and elevated TSH persisted. The LT4 dose was progressively adjusted from 300 μg to 400 μg per day. Two months later, biological tests showed a TSH level of 92.4 mIU/L and a FT4 level lower than 0.42 ng/dL (normal range: 0.7–1.5). The patient was treated with LT4 liquid form at a dose of 80 drops/day (400 μg). Two weeks later, she presented with a significant clinical improvement of hypothyroidism symptoms with a normal FT4 level of 1.14 ng/dL.

Discussion

Conventional treatment of primary hypothyroidism consists of oral LT4 substitution in solid tablet form. Compared to other drugs, oral LT4 substitution requires fasting and abstinence from eating for at least 30 min after its ingestion.[7]

Orally administrated LT4 is absorbed through the small intestine mucosa with an absorption rate ranging from 60% to 82% during the first 3 h after ingestion.[3,8] However, oral substitution fails to achieve euthyroidism in some patients despite escalating dosages of LT4 beyond 1.9 μg/kg/day. This situation is not uncommon in clinical practice.[4,9] Data regarding treatment-refractory hypothyroidism are increasingly published. However, its prevalence has not been fully determined.[4]

Establishing the cause of refractory hypothyroidism can be particularly difficult. Assessing compliance with treatment and adequate drug intake should be the first step. Poor adherence to treatment is the most common cause of increased LT4 doses.[10] Then, other causes should be rigorously screened using appropriate diagnostic tools. Questioning should screen the concomitant use of other drugs that affect LT4 absorption and bioavailability, particularly proton-pump inhibitors, calcium carbonate, iron salts, and laxatives.[3,11]

LT4 absorption can also be compromised by several gastrointestinal diseases, including celiac disease, atrophic gastritis, *H. pylori* infection, gastroparesis, inflammatory bowel disease, short bowel syndrome, and lactose intolerance.[3,4] Identification and adequate treatment of these conditions generally lead to TSH level normalization. However, in our case, TSH levels did not normalize even after appropriate treatment of *H. pylori* infection. In such cases, LT4 absorption test is needed to distinguish malabsorption syndrome from pseudomalabsorption (noncompliance to treatment).[12]

The protocol and interpretation of LT4 absorption test results are not standardized.[9,13,14] The protocol involves oral administration of a single dose of LT4, typically ranging from 600 to 1000 μg, followed by hourly FT4 monitoring during 2–5 h.[14,15] This test requires careful hemodynamic monitoring since hypothyroidism decreases cardiac output and increases the risk of coronary artery disease.[16] Gonzales et al.[17] established that an LT4 absorption rate higher than 60% should be considered as normal. Our patient had an absorption rate of 0% that did not improve by concomitant

administration of vitamin C. Several studies have shown improvement in hypothyroidism control by adding vitamin C alongside with LT4 dose.[18,19] Patients with gastrointestinal diseases could have an elevated gastric pH, which may decrease LT4 dissolution and thus absorption. Adding vitamin C temporarily decreases gastric pH, which improves the dissolution of LT4 tablets.[18]

Some authors suggested that alternative formulations of LT4, including soft gel, liquid, intravenous, subcutaneous and intrarectal formulations are more effective than LT4 solid tablets in controlling refractory hypothyroidism.[20–25] Naman et al.[25] demonstrated the efficacy of subcutaneous injection of LT4 three times weekly in restoring euthyroidism in a patient with refractory hypothyroidism due to malabsorption. Santaguida et al.[21] showed that switching from LT4 tablets to soft gel capsules led to the reduction of the required dose of LT4 and improved hypothyroidism symptoms in most patients with impaired gastric acid secretion. In fact, many authors showed that changes in gastric pH have a negligible effect on liquid and soft gel capsule LT4 absorption compared to LT4 tablets.[23–25] As in previously reported cases, our patient's FT4 level normalized 2 weeks after switching to a liquid formulation.[5]

Conclusion

LT4 oral substitution may fail to restore euthyroidism in patients with gastrointestinal disorders. The present case serves as a reminder that refractory hypothyroidism warrants rigorous investigations to identify the underlying cause of malabsorption. In case of gastrointestinal malabsorption, switching to a liquid formulation may resolve this issue.

Acknowledgements

The abstract is published online in Endocrine Abstracts.

Author contributions

I.O.: conception and design, acquisition, analysis, and interpretation of data, article creation, and drafting; F.C.: acquisition, analysis, and interpretation of data, article creation, and drafting; Y.M., E.T., M.Y., and M.C.: acquisition, analysis, and interpretation of data; M.C.: revising the article critically for important intellectual content. All authors were involved in the management of the patient and the revision of the article and approved the final version.

Data sharing is not applicable

No new data were generated.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics statement

Ethical approval for this case report was not required.

Consent statement

A written informed consent was obtained from the patient for the publication of this report.

ORCID iD

Ibtissem Oueslati https://orcid.org/0000-0002-4278-9447

References

1. Chakera AJ, Pearce SHS and Vaidya B. Treatment for primary hypothyroidism: current approaches and future possibilities. *Drug Des Devel Ther* 2012; 6: 1–11.
2. Ashraff S and Razvi S. Diagnosis and treatment of hypothyroidism. In: Vitti P and Hegedüs L (eds.) *Thyroid diseases. Endocrinology*. Cham: Springer International Publishing, 2018. pp. 391–426.
3. Santos Monteiro S, Santos TS, Lopes AM, et al. Levothyroxine malabsorption or pseudomalabsorption? A question in the management of refractory hypothyroidism. *Endocr Connect* 2022; 11: e220355.
4. Centanni M, Benvenga S and Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. *J Endocrinol Invest* 2017; 40: 1289–1301.
5. Stupperich S, Kotliarevskaia J, Nies R, et al. Primary hypothyroidism resolves after switching from L-thyroxine solid tablets to liquid oral substitution. A rare case without evidence of an underlying gastrointestinal malabsorption syndrome. *Clin Case Rep* 2022; 10: e6223.
6. Ramadhan A and Tamilia M. Treatment-refractory hypothyroidism. *CMAJ* 2012; 184: 205–209.
7. Nagy EV, Perros P, Papini E, et al. New formulations of levothyroxine in the treatment of hypothyroidism: trick or treat? *Thyroid* 2021; 31: 193–201.
8. Skelin M, Lucijanić T, Amidžić Klarić D, et al. Factors affecting gastrointestinal absorption of levothyroxine: a review. *Clin Ther* 2017; 39: 378–403.
9. Younes N, Pinto S and Valensi P. Severe refractory hypothyroidism in a 48-year-old female: role of low-dose thyroxine absorption test in establishing diagnosis of noncompliance. *Acta Endocrinol Buchar* 2022; 18: 375–378.
10. Lips DJ, van Reisen MT, Voigt V, et al. Diagnosis and treatment of levothyroxine pseudomalabsorption. *Neth J Med* 2004; 62: 114–118.
11. Singh N, Weisler SL and Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. *Thyroid* 2001; 11: 967–971.
12. Caron P and Declèves X. The use of levothyroxine absorption tests in clinical practice. *J Clin Endocrinol Metab* 2023; 108: 1875–1888.
13. Walker JN, Shillo P, Ibbotson V, et al. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess nonadherence to treatment. *Eur J Endocrinol* 2013; 168: 913–917.
14. Ghosh S, Pramanik S, Biswas K, et al. Levothyroxine absorption test to differentiate pseudomalabsorption from true malabsorption. *Eur Thyroid J* 2020; 9: 19–24.

15. Balla M, Jhingan RM and Rubin DJ. Rapid levothyroxine absorption testing: a case series of nonadherent patients. *Int J Endocrinol Metab* 2015; 13: e31051.
16. Udovcic M, Pena RH, Patham B, et al. Hypothyroidism and the heart. *Methodist Debakey Cardiovasc J* 2017; 13: 55–59.
17. Gonzales KM, Stan MN, Morris JC, et al. The levothyroxine absorption test: a four-year experience (2015–2018) at the mayo clinic. *Thyroid* 2019; 29: 1734–1742.
18. Antúnez PB and 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.
19. Jubiz W and Ramirez M. Effect of vitamin C on the absorption of levothyroxine in patients with hypothyroidism and gastritis. *J Clin Endocrinol Metab* 2014; 99: E1031–1034.
20. Virili C, Trimboli P, Romanelli F, et al. Liquid and softgel levothyroxine use in clinical practice: state of the art. *Endocrine* 2016; 54: 3–14.
21. Santaguida MG, Virili C, Del Duca SC, et al. Thyroxine softgel capsule in patients with gastric-related T4 malabsorption. *Endocrine* 2015; 49: 51–57.
22. Fallahi P, Ferrari SM and Antonelli A. Oral L-thyroxine liquid versus tablet in patients with hypothyroidism without malabsorption: a prospective study. *Endocrine* 2016; 52: 597–601.
23. Vita R and Benvenga S. Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. *Endocr Pract* 2014; 20: e38–e41.
24. Ritter MJ, Gupta S and Hennessey JV. Alternative routes of levothyroxine administration for hypothyroidism. *Curr Opin Endocrinol Diabetes Obes* 2020; 27: 318–322.
25. Naman A, Delemer B, Marot D, et al. Efficacy of subcutaneous levothyroxine in a case of refractory hypothyroidism: a case report. *Medicine (Baltimore)* 2022; 101: e29690.