JCEM Case Reports, 2025, **3**, luaf085
https://doi.org/10.1210/jcemcr/luaf085
Advance access publication 23 April 2025
Case Report

Pseudo-Malabsorption in High Dose Levothyroxine–Resistant Hypothyroidism

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Abstract

A 38-year-old woman was diagnosed with hypothyroidism during pregnancy at age 35 years and started on levothyroxine (LT4). Despite increasing the dose to 400 μg/day and adding liothyronine, her thyroid function did not improve, leading to hospitalization. Upon admission, her thyroid-stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4) levels were 255 μIU/mL (255 mIU/L) (reference range [RR]: 0.35–4.94 μIU/mL; 0.35–4.94 mIU/L), 3.42 pg/mL (5.27 pmol/L) (RR: 1.71-3.71 pg/mL; 2.63-5.70 pmol/L), and 0.153 ng/dL (1.97 pmol/L) (RR: 0.70-1.48 ng/dL; 9.01-19.05 pmol/L), respectively. She reported good adherence to medication and not consuming interfering food or medication. Endoscopic examination revealed no malabsorption. A 1000-μg oral LT4 loading test showed an increase in free T4 level from 0.787 (10.1 pmol/L) to 2.40 ng/dL (30.9 pmol/L), indicating pseudo-malabsorption. After presenting the loading test results, she admitted to nonadherence. A multidisciplinary team intervened, conducting individual counseling and simplifying treatment. Post-discharge, with LT4 200 μg/day, her TSH, free T3, and free T4 levels improved to 0.496 μIU/mL (0.496 mIU/L), 5.23 pg/mL (8.05 pmol/L), and 2.19 ng/dL (28.2 pmol/L), respectively. When addressing treatment-resistant hypothyroidism, it is crucial to evaluate patient history and medication schedule and to check for malabsorption. Comprehensive interventions are recommended if nonadherence is suspected.

Key Words: hypothyroidism, thyroid-stimulating hormone, levothyroxine

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LT3, liothyronine; LT4, levothyroxine; RR, reference range; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin (thyroid-stimulating hormone).

Introduction

Hypothyroidism is typically managed effectively with levothyroxine (LT4) replacement therapy at a dose of 1.6 to 1.8 μg/kg/day [1]. However, a subset of patients fails to achieve adequate thyroid function despite receiving high-dose LT4 therapy. Treatment resistance in hypothyroidism stems from both pathological and nonpathological factors. Nonpathological causes include medication adherence issues and intake of interfering foods or drugs [2-6]. Pathological causes include decreased LT4 absorption due to various gastrointestinal conditions such as post-gastrectomy status, *Helicobacter pylori* infection, and inflammatory bowel diseases such as celiac disease and Crohn disease [7-9]. The etiology of treatment-resistant hypothyroidism is complex, and standardized treatment protocols are not yet established.

Oral LT4 loading test is a crucial diagnostic tool for distinguishing between pseudo-malabsorption and true malabsorption in treatment-resistant hypothyroidism. A significant increase in free thyroxine (T4) levels following the test suggests pseudo-malabsorption [1, 10, 11]. When pseudo-malabsorption is suspected, measures should be taken to improve medication adherence.

In this report, we present a case of severe hypothyroidism that persisted for over 2 years despite escalating doses of LT4 and the addition of liothyronine (LT3), and we propose diagnostic and intervention methods for treatment-resistant hypothyroidism.

Case Presentation

A 38-year-old woman was initially diagnosed with marked hypothyroidism during the eighth week of her pregnancy at age 35 years and referred for LT4 treatment. Her initial thyroid function tests revealed thyroid-stimulating hormone (TSH) level of 142 μIU/mL (142 mIU/L) (reference ranges [RR]: 0.35-4.94 μIU/mL; 0.35-4.94 mIU/L), free triiodothyronine (T3) level of 1.87 pg/mL (2.88 pmol/L) (RR: 1.71-3.71 pg/mL; 2.63-5.70 pmol/L), and free thyroxine (T4) level of 0.331 ng/dL (4.26 pmol/L) (RR: 0.70-1.48 ng/dL; 9.01-19.05 pmol/L). During pregnancy, the LT4 dose was increased to 300 μg/day, but normal TSH levels were not achieved. Postpartum, reducing LT4 to 150 μg/day temporarily improved the TSH level to 0.341 μIU/mL (0.341 mIU/L) and free T4 level to 2.48 ng/dL (31.92 pmol/L), but these subsequently worsened. Over 3 months, LT4 was increased to 400 μg/day. The combination of LT3 for 15 months did not improve thyroid function, nor did switching to LT4 suppositories for 3 months (Fig. 1). During multiple outpatient visits, she consistently reported good medication adherence and denied intake of seaweed, soy, coffee, grapefruit, or supplements known to affect thyroid function,

Received: 11 February 2025. **Editorial Decision:** 3 April 2025. **Corrected and Typeset:** 23 April 2025

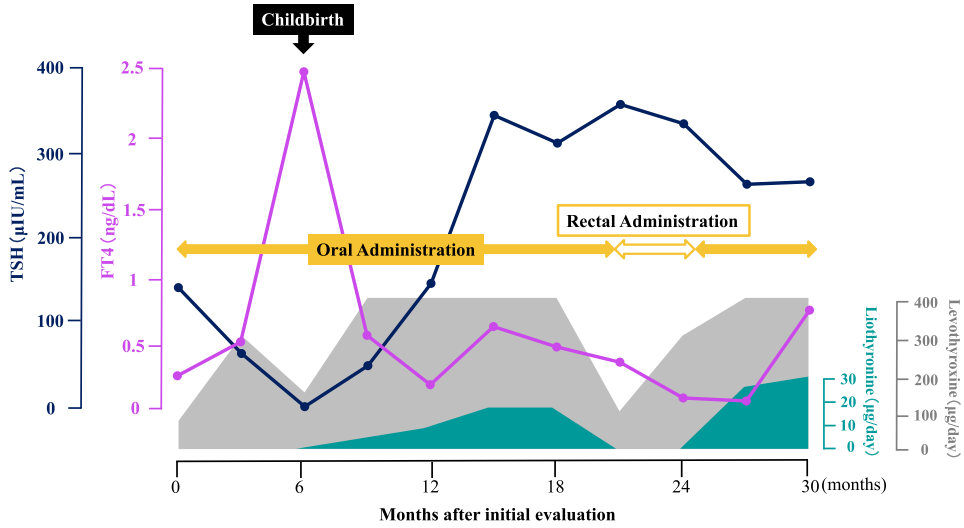

Figure 1. Clinical course showing changes in thyroid function and treatment adjustments from initial evaluation to hospitalization. The lines represent free T4 levels, and changes in TSH levels over time. The shaded areas indicate levothyroxine and liothyronine dosage adjustments. Treatment administration routes are denoted by arrows: solid arrows indicate periods of oral administration and outlined arrows represent periods of rectal administration. TSH and free T4 measurements demonstrate persistent thyroid dysfunction despite progressive medication adjustments, ultimately leading to diagnostic admission.

Abbreviations: FT4, free thyroxine; TSH, thyroid-stimulating hormone.

including iron, zinc, and calcium. She took LT4 on an empty stomach and had no gastrointestinal symptoms suggestive of malabsorption, such as diarrhea or bloating. Following 3 years of unresponsive replacement therapy, she was admitted for further evaluation.

The patient's medical history included dyslipidemia, managed with pemafibrate 0.2 mg/day and rosuvastatin calcium 2.5 mg/day. She had no significant family history of thyroid disorders.

Diagnostic Assessment

Physical examination revealed patient height of 150 cm, weight of 92.3 kg, body mass index of 41 kg/m², blood pressure of 129/88 mmHg, and pulse rate of 73 beats/min. Palpation of the thyroid revealed elastic firmness without obvious masses. Initial blood tests revealed marked hypothyroidism despite the concurrent administration of LT4 400 μg/day and LT3 35 μg/day (Table 1). Both anti-thyroglobulin and anti-thyroid peroxidase antibodies were positive, accompanied by dyslipidemia and elevated liver enzyme levels.

Thyroid ultrasonography revealed dimensions of 9.3 × 9.2 mm² for the right lobe and 14.1 × 11.1 mm² for the left lobe, characterized by irregular surfaces, heterogeneous internal structure, and mildly increased blood flow, consistent with Hashimoto thyroiditis. Cardiac evaluation revealed normal function with good left ventricular wall motion and no significant valvular disease.

Gastrointestinal evaluation included upper and lower endoscopies, which revealed no significant mucosal atrophy or abnormalities in the stomach, duodenum, small intestine, or colon. Multiple-site biopsy results were normal, and *Helicobacter pylori* immunoglobulin G level was <3 U/mL. To evaluate potential malabsorption, a 1000-μg oral LT4 loading test was conducted, which showed an increase in free T4 level from a baseline of 0.787 ng/dL (10.1 pmol/L) to a peak of 2.40 ng/dL (30.9 pmol/L) at 3 hours post-load, indicating pseudo-malabsorption (Fig. 2).

Treatment

On reviewing the test results with the patient, she disclosed that childcare demands interfered with her ability to maintain consistent medication adherence. Following this discovery, we implemented a comprehensive treatment strategy. First, the physician provided a detailed explanation of the patient's condition and emphasized the importance of consistent thyroid hormone replacement therapy. We then simplified her medication regimen by discontinuing LT3 and adjusting LT4 dosage to 200 μg/day, with all medications being taken in the morning. To accommodate her schedule, we advised that if she missed a dose, she could take it as soon as she remembered.

Our intervention involved a coordinated multidisciplinary approach during hospitalization. A dedicated nurse monitored the patient's emotional and physical states, providing regular assessments and support. Additionally, a clinical pharmacist conducted detailed counseling sessions to explain the properties of LT4 and potential drug interactions that could affect its efficacy.

Outcome and Follow-Up

Two weeks after discharge, follow-up laboratory tests demonstrated significant improvement in thyroid function: TSH level decreased to 0.496 μIU/mL (0.496 mIU/L), free T3 level rose to 5.23 pg/mL (8.05 pmol/L), and free T4 level improved to 2.19 ng/dL (28.2 pmol/L). In addition, the patient's lipid profile showed improvement, with changes in level of triglycerides from 455 mg/dL (5.14 mmol/L) (RR: 30-149 mg/dL; 0.34-1.68 mmol/L) to 231 mg/dL (2.61 mmol/L); high-density lipoprotein cholesterol (HDL-C) from 47 mg/dL (1.22 mmol/L) (RR: 40-103 mg/dL; 1.04-2.67 mmol/L) to 33 mg/dL (0.85 mmol/L); and low-density lipoprotein cholesterol (LDL-C) from 150 mg/dL (3.88 mmol/L) (RR: 65-139 mg/dL; 1.68-3.60 mmol/L) to 60 mg/dL (1.55 mmol/L), respectively.

Table 1. Results of blood tests conducted on admission

Laboratory data					Reference range			
	Conventional units		SI units		Conventional units		SI units	
TSH	255	μIU/mL	255	mIU/L	0.35–4.94	μIU/mL	0.35-4.94	mIU/L
FT3	3.42	pg/mL	5.27	pmol/L	1.71-3.71	pg/mL	2.63-5.70	pmol/L
FT4	0.153	ng/dL	1.97	pmol/L	0.70-1.48	ng/dL	9.01-19.05	pmol/L
TgAb	237	IU/mL	237	kIU/L	0-28.0	IU/mL	0-28.0	kIU/L
TPOAb	31.4	IU/mL	31.4	kIU/L	0-16.0	IU/mL	0-16.0	kIU/L
TRAb	1.18	IU/L			0-2.00	mg/dL		
Tg	<0.04	ng/mL	<0.04	μg/L	0-33.7	mg/dL	0-33.7	μg/L
TG	455	mg/dL	5.14	mmol/L	30-149	mg/dL	0.34-1.68	mmol/L
HDL-Chol	47	mg/dL	1.22	mmol/L	40-103	mg/dL	1.04-2.67	mmol/L
LDL-Chol	150	mg/dL	3.88	mmol/L	65-139	mg/dL	1.68-3.60	mmol/L
γ-GT	40	U/L	0.67	μkat/L	9-32	U/L	0.15-0.53	μkat/L
AST	60	U/L	1.00	μkat/L	13-30	U/L	0.22-0.50	μkat/L
ALT	58	U/L	0.97	μkat/L	7-30	U/L	0.12-0.50	μkat/L
ACTH	26.2	pg/mL	5.76	pmol/L	7.2-63.3	pg/mL	1.58-13.9	pmol/L
Cortisol	6.00	μg/dL	165.53	nmol/L	3.7-19.4	μg/dL	102.08-535.21	nmol/L
PRA	0.2	ng/min/h	0.2	μg/L/h	0.2-3.9	ng/min/h	0.2-3.9	μg/L/h
PAC	12.7	pg/mL	35.23	pmol/L	4.0-82.1	pg/mL	11.1-227.75	pmol/L
Ad	<0.01	ng/mL	<54.6	pmol/L	<0.17	ng/mL	<928	pmol/L
NAd	0.25	ng/mL	1477.75	pmol/L	0.15-0.57	ng/mL	886.65-3369.27	pmol/L
DA	<0.02	ng/mL	<130.56	pmol/L	<0.03	ng/mL	<195.84	pmol/L

Abbreviations: ACTH, adrenocorticotropic hormone; Ad, epinephrine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DA, dopamine; FT3, free triiodothyronine; FT4, free thyroxine; γ-GT, γ-glutamyltransferase; HDL-Chol, high-density lipoprotein cholesterol; LDL-Chol, low-density lipoprotein cholesterol; NAd, norepinephrine; PAC, aldosterone; PRA, plasma renin activity; Tg, thyroglobulin; TG, triglycerides; TgAb, thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TRAb, TSH receptor antibody; TSH, thyroid-stimulating hormone.

Discussion

This case demonstrates severe hypothyroidism persisting for over 2 years despite increased LT4 dosage and LT3 supplementation. Through LT4 loading test results and subsequent interventions, we identified pseudo-malabsorption as the underlying cause of persistent hypothyroidism and were able to provide successful treatment and improve outcomes. This case highlights the importance of considering pseudo-malabsorption in diagnosing treatment-resistant hypothyroidism. It spares patients from unnecessary diagnostic procedures, medication escalation, and associated healthcare costs.

The standard approach to primary hypothyroidism typically involves increasing LT4 doses until target TSH levels are achieved. However, prolonged high-dose LT4 therapy carries potential risks, including bone loss and cardiovascular complications [10]. In addition, this approach requires frequent monitoring and testing, resulting in increased healthcare costs and reduced patient satisfaction [10].

When facing or managing treatment-resistant hypothyroidism, a systematic diagnostic approach is essential rather than simply escalating LT4 doses. Nonpathological factors include medication nonadherence and dietary interactions. Specific foods such as high-fiber products, soy, coffee, and grapefruit can inhibit thyroid hormone absorption, whereas iodine, chromium, and zinc may enhance thyroid hormone metabolism [2-6]. Certain medications, including proton pump inhibitors, anion exchange resins, iron supplements, calcium supplements, and aluminum-containing medications, can inhibit absorption, whereas antiepileptic and antituberculosis drugs may enhance metabolism [2-6]. Pathological causes of malabsorption include post-gastrectomy status, *Helicobacter pylori* infection, and inflammatory bowel diseases such as celiac disease and Crohn disease [7-9].

The diagnostic process for treatment-resistant hypothyroidism should begin with a thorough review of the LT4 dosing schedules. Although patient self-reporting and use of pharmacy claims data are common evaluation methods, self-reporting may overestimate adherence [12]. Environmental factors and medication history should be assessed, with particular attention paid to the timing of medications that may interact with LT4 absorption. For optimal absorption, LT4 should be taken on an empty stomach, avoiding other medications and food for 30 to 60 minutes, preferably 60 minutes [10]. If these measures prove insufficient, gastrointestinal endoscopy [13, 14] and LT4 loading tests should be considered [1, 10, 11]. LT4 loading tests are performed to evaluate the absorption capacity of oral LT4 and to differentiate between pseudo-malabsorption and malabsorption. In pseudo-malabsorption, free T4 levels increase when LT4 is taken during the test, whereas in malabsorption, free T4 levels do not increase. A loading test showing a free T4 level increase of 0.4 ng/dL (5.15 pmol/L) or more within 2 to 3 hours effectively rules out malabsorption with 97% sensitivity and 80% specificity and enables diagnosis of pseudo-malabsorption [11].

When pseudo-malabsorption is identified, comprehensive approaches for improving medication adherence become crucial. Randomized clinical trials have shown the effectiveness of several interventions, including patient education, regimen

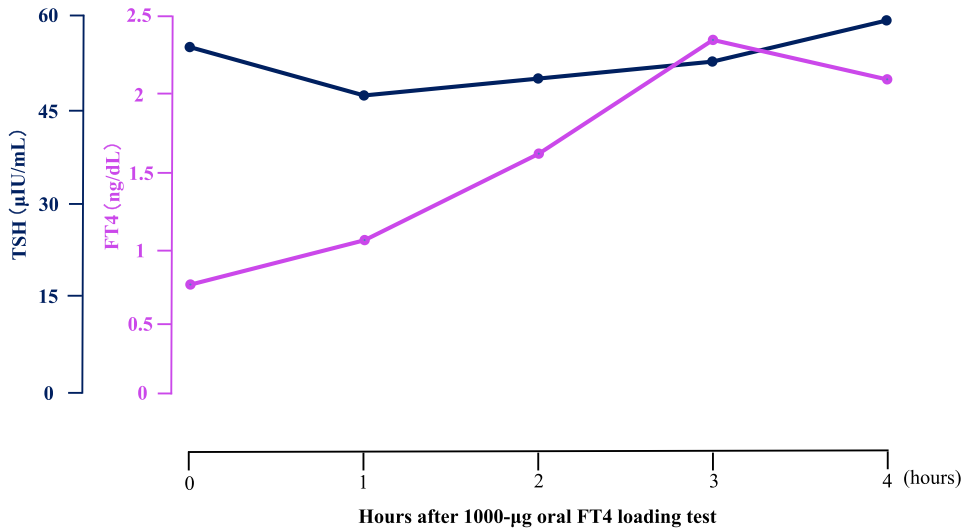

Figure 2. Results of the 1000-μg oral LT4 loading test. The lines represent free T4 levels, and changes in TSH levels. After the loading, free T4 levels appropriately increased, suggesting pseudo-malabsorption.

simplification, clinical pharmacist consultations, medication reminders, and various incentives [12]. Caron et al [15] emphasize the importance of physicians highlighting treatment benefits and potential adverse outcomes of hypothyroidism in a nonconfrontational manner, with collaboration with nurses and pharmacists proving essential [16, 17].

In cases where oral LT4 therapy is ineffective, alternative administration routes (intravenous, intramuscular, subcutaneous, and rectal) or supervised oral dosing should be considered [15, 18]. Intramuscular administration has shown particular promise, with studies supporting its safety and flexibility in dosing frequency [19-21]. Recent advances in regenerative technology, including the development of human thyroid organoids, offer promising therapeutic options [22].

The role of combination therapy with LT4 and LT3 remains controversial [23]. While some patients receive combination therapy when LT4 alone proves insufficient, challenges include complex dosing requirements [23, 24]; short half-life of LT3 [23, 24]; and potential side effects, including hyperthyroid symptoms, atrial fibrillation [25], heart failure [26], decreased bone density [23], and increased stroke risk [26]. Therefore, new sustained-release LT3 formulations are being developed to address these limitations [22]. For a physiological approximation, current evidence suggests an ideal hormone replacement ratio of 13:1 to 20:1 for LT4:LT3 [22-25].

Thyroid hormones significantly influence lipid metabolism, with hypothyroidism leading to reduced activity of cholesterol 7-alpha-hydroxylase and ATP-binding cassette subfamily G member 5/8, resulting in decreased LDL clearance [27]. Additionally, hypothyroidism affects HDL-C particle functionality [27] and increases triglyceride levels via TSH receptor-mediated pathways [27, 28]. LT4 therapy typically improves these lipid abnormalities through metabolic correction [29], as demonstrated in our case.

This case report has several limitations. The short follow-up period limited the evaluation of long-term intervention effects. Objective medication adherence monitoring tools were not used, preventing accurate adherence data collection. The patient's psychological status and social support system were not evaluated. Additionally, significant obesity might have influenced LT4 pharmacokinetics, although this impact was not evaluated. These limitations suggest the need for more comprehensive protocols in future cases of treatment-resistant hypothyroidism.

This case reveals the importance of systematic evaluation of treatment-resistant hypothyroidism. Through careful exclusion of causative factors and identification of nonadherence, followed by comprehensive intervention, we achieved successful normalization of thyroid function. This approach provides a valuable framework for the management of similar cases in clinical practice.

Learning Points

- Managing treatment-resistant hypothyroidism requires a systematic diagnostic approach: evaluating the patient's medication history, assessing malabsorption factors through endoscopy, and confirming diagnosis with a levothyroxine (LT4) loading test.
- Effective management of pseudo-malabsorption necessitates a multidisciplinary team approach involving patient education, simplification of treatment regimens, and medication adherence support. Alternative routes of LT4 administration should be considered when oral therapy is ineffective.
- Treatment success depends on identifying and addressing the root cause rather than simply escalating doses. Regular monitoring of thyroid function and targeted interventions for medication adherence can prevent prolonged exposure to suboptimal thyroid hormone levels and associated complications.

Acknowledgments

The authors would like to thank Editage for English language review.

Contributors

All authors contributed individually to authorship. R.S. and N.H. wrote and completed the paper; M.Y. and T.H. were

involved in the diagnosis and management of the patient and in drafting the manuscript; and K.T. corrected and advised on the content of the paper. All authors reviewed and approved the final draft of the manuscript.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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