ORAL L-LEVOTHYROXINE (L-T4) is used to treat hypothyroidism and is absorbed through the intestinal mucosa at the level of the duodenum, jejunum, and ileum [1]. Various conditions may interfere with the intestinal absorption of T4, including drugs and gastric and intestinal resection or diseases [2]. The need to use high doses of L-T4 in replacement treatment for hypothyroidism is often the first sign of a pathological condition associated with malabsorption syndrome [3].

Lactose intolerance (LI) should be considered in the differential diagnosis of gastrointestinal diseases that may be causing malabsorption of L-T4 [4, 5]. LI may interfere with the absorption of L-T4 tablet because the tablet contains lactose, so patients with LI may need a higher dose of L-T4 [6], and severe resistance to oral L-T4 treatment has been described in a patient with LI [4]. A previous study demonstrated that switching patients with LI from the tablet to the oral liquid formulation of L-T4 improved levels of thyroid-stimulating hormone (TSH) [7].

Here, we describe a patient with LI who, after thyroideotomy and radiiodine therapy for Graves’ disease, presented with severe hypothyroidism despite replacement therapy with high-dose LT4 tablets, and in whom euthyroidism was restored by switching from the tablet to the powder formulation of L-T4.

Case Report

A 38-year-old woman was diagnosed with Graves’ disease and underwent subtotal thyroidectomy at the age of 25. However, she subsequently presented with persistent hyperthyroidism and was referred to our outpatient clinic at age 27.

Radioactive iodine (RI) therapy was performed. One year later, the patient developed overt hypothyroidism

Abstract. We describe a case of a 38-year-old woman who, after radioactive iodine therapy for Graves’ disease, developed severe hypothyroidism despite receiving a high dose of levothyroxine (L-T4) tablet as replacement therapy. Her thyroid stimulating hormone (TSH) remained to be high despite the dose of L-T4 tablets to 400 μg/day after treatment for hypothyroidism, and the patient complained of general malaise and edema of the legs. Reduced intestinal absorption of L-T4 is the most common cause of failure to achieve the therapeutic target in hypothyroid patients receiving replacement therapy. She was admitted to our hospital for severe hypothyroidism due to resistance to treatment with L-T4 tablet. Our patient was found to have lactose intolerance (LI) by a detailed examination during hospitalization. Therefore, we assumed that LI was impairing intestinal absorption of L-T4 tablet in our patient, leading to severe hypothyroidism. The patient was switched to the powder formulation of L-T4 at the same daily dose, and serum levels of thyroid-stimulating hormone and thyroid hormones normalized. This is the case in which hypothyroidism due to reduced absorption of L-T4 tablet in a patient with LI was resolved by switching to L-T4 powder formulation.

Key words: Levothyroxine, Tablet, Powder formulation, Lactose intolerance, Hypothyroidism
(0.3 ng/dL of free thyroxine [FT4]; 1.2 pg/mL of free triiodothyronine [FT3]; and 80.9 μU/mL of TSH). Replacement therapy for hypothyroidism was started with L-T4 tablets (50 μg/day). Because serum TSH remained high, the dosage was gradually increased to 200 μg/day. However, TSH was still high with this dose, so we added 30 mg/day of dried thyroid extract (Teikoku Hormone, Tokyo, Japan), which resulted in a euthyroid state (1.3 ng/dL of F-T4, 3.4 pg/mL of F-T3, 0.06 μU/mL of TSH).

With the combination therapy of dried thyroid extract and L-T4 tablet, the patient maintained a euthyroid state up to age 36 years. However, when she was aged 37 years the pharmaceutical company stopped producing dried thyroid extract, so we had to treat her with L-T4 tablet in monotherapy. Four months later, she showed hypothyroidism (0.54 ng/dL of F-T4, 0.94 pg/mL of F-T3, 91.17 μU/mL of TSH) despite replacement therapy with 200 μg/day L-T4 tablet. Although the dose of L-T4 tablet was increased gradually to 400 μg/day, the patient complained of general fatigue and edema in her legs. At age 38 years, she was admitted to our hospital for severe hypothyroidism due to resistance to treatment with L-T4 tablet.

On physical examination, the patient was 164.8 cm tall, weighed 75.2 kg and had a body mass index of 27.9 kg/m². Her temperature (37.0°C) and blood pressure (126/68 mmHg) were normal, but she had bradycardia (47 beats per minute). Non-pitting edema was found in both pretibial regions.

The patient had childhood-onset epilepsy and continued to take antiepileptic drugs (carbamazepine 600 mg/day, levetiracetam 2,750 mg/day, and lamotrigine 400 mg/day). She had noticed sporadic watery diarrhea since childhood, especially after drinking milk. She had no history of gastrointestinal diseases.

Laboratory tests revealed severe hypothyroidism, with a serum TSH level of more than 100 μU/mL and FT4 level of 0.44 ng/dL (Table 1). Biochemical tests showed an increase of creatinine phosphokinase and elevated levels of transaminase and lactate dehydrogenase (Table 1). Serum total and low-density lipoprotein cholesterol were elevated at 322 mg/dL and 197 mg/dL, respectively. The test for antibody against Helicobacter pylori was negative.

We suspected intestinal malabsorption of L-T4 tablet in our case. Based on the history of sporadic watery diarrhea, we considered that lactose intolerance may contribute to the malabsorption of L-T4 tablet in the intestine. We therefore performed a 50 g lactose tolerance test to make a diagnosis of LI (The lactose tolerance test showed sensitivity of 0.94 (0.9–0.97) and specificity of 0.90 (0.84–0.95)) [8]. We made the diagnosis of lactose intolerance in our case, because the glucose level was less than 20 mg/dL above the baseline at 60 and 120 min after the lactose tolerance test (LLT) (Table 2). After the LLT, she complained of lower abdominal pain and diarrhea.

We switched L-T4 tablet to the powder formulation (Thyradin®-S powder, ASKA Pharmaceutical Holdings Co., Tokyo, Japan) of L-T4 at the same dose. After 1 week, serum TSH was markedly decreased and FT4 was increased to the normal range (Fig. 1). We decreased the dose to 125 μg of powdered L-T4, and the patient continued to maintain a euthyroid state (Fig. 1).

**Discussion**

We experienced a case of severe hypothyroidism that was restored by switching from the tablet to the powder formulation of L-T4 at the dose of 150 μg/day in a patient with LI and hypothyroidism whose serum TSH was markedly high despite a large dose of L-T4 tablet (>5.3 μg/kg). Failure to adequately control hypothyroidism with oral L-T4 is a common clinical problem. Although non-adherence to the prescription, called pseudo-malabsorption, is reported as the most common cause [9], a variety of conditions can interfere with the intestinal absorption of L-T4 tablets [2, 3]. In particular, to avoid the risk of iatrogenic hyperthyroidism, drugs and conditions (gastric and bowel diseases) that may cause malabsorption should be investigated before increasing the LT4 dosage [9]. An abnormality in the absorption of L-T4 should be considered in patients who require large doses of L-T4 (>2 μg/kg/day) to achieve euthyroidism [3]. In our patient, severe hypothyroidism was not successfully treated by replacement therapy, even at a dose of 400 μg/day (5.3 μg/kg/day) of L-T4 tablet.

LI should be considered in the differential diagnosis of gastrointestinal diseases that may cause malabsorption of L-T4 [4, 5]. LI occurs when a considerable amount of lactose is not absorbed in the intestines because of a lactase deficiency in the small intestinal brush border [10]. Undigested lactose draws water into the intestinal lumen by osmosis and accelerates small intestinal transit, which reduces the contact time between lactose and residual enzymes and further decreases the hydrolysis of lactose [11]. This process increases the degree of maldigestion, which may lead to insufficient absorption of LT4 in the intestine.

However, there was little lactose in the L-T4 tablets which our used. It is unlikely that a very small amount of lactose in the L-T4 tablet might be responsible for its malabsorption, because a previous study demonstrated that ingestion of up to 400 mg of lactose does not trigger
gastrointestinal symptoms in LI [12]. Moreover, considering that the patient required a high-dose of antiepileptic drugs (carbamazepine 600 mg/day, levetiracetam 2,750 mg/day, and lamotrigine 400 mg/day) for the treatment of epilepsy, she was most likely to have an intestinal malabsorption due to LI. Taken together, we think the essential point for this case is malabsorption possibly due to LI, but not lactose as an ingredient in the LT4 tablet itself. We concluded that the powder formulation of L-T4 can circumvent malabsorption in patients with LI.

Mechanisms responsible for severe hypothyroidism that was resistant to a high dose of L-T4 tablet in our patient remained to be determined. Lactose accumulation leads to bacterial overgrowth and gas formation and alters the intestinal environment, which may induce inflammation and cause intestinal villus injury [13]. Thus, LI can impair intestinal absorption and disrupt the entero-hepatic circulation of L-T4. One possible explanation is that the different microbiota of patient with LI alters the intestinal environment, which may induce inflammation and cause intestinal villus injury, leading to intestinal malabsorption of L-T4 tablets.

Recently, new L-T4 formulations, i.e., a soft gel capsule and an oral solution (liquid), have become available in some countries [14]. A previous case series in five patients with LI showed that switching patients with LI and Hashimoto thyroiditis from the L-T4 tablet to the same dose of the liquid (or soft gel) formulation of L-T4, which did not contain lactose, normalized TSH levels themselves.
In 3 of the patients, TSH levels increased again after the patients were switched back to the tablets [7].

L-T4 liquid and soft gel capsules may be indicated for the treatment of athyreotic patients in whom TSH target levels cannot be achieved with conventional L-T4 tablets [15]. Unfortunately, the liquid and soft gel capsule formulations of L-T4 are not available in Japan. Therefore, we tried switching our patient to the powder formulation of L-T4, which also does not contain lactose. After 8 days treatment with the powder formulation of L-T4 at the same dose, the patient’s TSH level was within the normal range and FT4 also had increased. Even after the dose of L-T4 was decreased to 125 μg of powdered L-T4, the patient remained in a euthyroid state, suggesting that the powder formulation of L-T4 was absorbed better than the tablet formulation. To confirm that the powder formulation itself worked for our patient because it may be better to be absorbed than the L-T4 tablet, we administered the L-T4 tablet after being pulverized at the same dose of powder formulation. Her FT4 and FT3 levels were maintained in the normal range, although her TSH level was slightly increased.

A previous case series of 3 patients with hypothyroidism who were being treated with a large dose of L-T4 tablet also showed that serum TSH normalized when L-T4 tablets were pulverized before administration [15]. In the past, our patient achieved a euthyroid state when taking dried thyroid extract, which is a similar dosage form to the powder.

In conclusion, we experienced a patient with LI who presented with severe hypothyroidism that was resistant to a high dose of L-T4 tablet. We were able to restore a euthyroid state by switching the patient from the tablet to the powder formulation of L-T4. This case suggests that the powder formulation of L-T4 could be an option to circumvent the malabsorption of L-T4 in hypothyroid patients with LI.

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References

1. Hays MT (1991) Localization of human thyroxine absorption. Thyroid 1: 241–248.
2. Virili C, Antonelli A, Santaguida MG, Benveniga S, Centanni M (2019) Gastrointestinal malabsorption of thyroxine. Endocr Rev 40: 118–136.
3. de Carvalho GA, Paz-Filho G, Mesa Junior C, Graf H (2018) Management of endocrine disease: pitfalls on the replacement therapy for primary and central hypothyroidism in adults. Eur J Endocrinol 178: R231–R244.
4. Muñoz-Torres M, Varsavsky M, Alonso G (2006) Lactose intolerance revealed by severe resistance to treatment with levothyroxine. Thyroid 16: 1171–1173.
5. Ruchala M, Szczepanek-Parul ska E, Zybek A (2012) The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption. Endokrynol Pol 63: 318–323.
6. Cellini M, Santaguida MG, Gatto I, Virili C, Del Duca SC, et al. (2014) Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. J Clin Endocrinol Metab 99: E1454–E1458.

7. Fallahi P, Ferrari SM, Marchi S, De Bortoli N, Ruffilli I, et al. (2017) Patients with lactose intolerance absorb liquid levothyroxine better than tablet levothyroxine. Endocrine 57: 175–178.

8. A. Marton, X. Xue A. Szilagyi. (2012) Meta-analysis: the diagnostic accuracy of lactose breath hydrogen or lactose tolerance tests for predicting the North European lactase polymorphism C/T-13910. Aliment Pharmacol Ther 35: 429–440.

9. Benvenga S (2013) When thyroid hormone replacement is ineffective? Curr Opin Endocrinol Diabetes Obes 20: 467–477.

10. Lomer MC, Parkes GC, Sanderson JD (2008) Review article: lactose intolerance in clinical practice—myths and realities. Aliment Pharmacol Ther 27: 93–103.

11. Ladas S, Papanikos J, Arapakis G (1982) Lactose malabsorption in Greek adults: correlation of small bowel transit time with the severity of lactose intolerance. Gut 23: 968–973.

12. M Montalto 1, A Gallo, L Santoro, F D’Onofrio, V Curigliano, et al. (2008) Low-dose lactose in drugs neither increases breath hydrogen excretion nor causes gastrointestinal symptoms. Aliment Pharmacol Ther 28: 1003–1012.

13. Asik M, Gunes F, Binnetoglu E, Eroglu M, Bozkurt N, et al. (2014) Decrease in TSH levels after lactose restriction in Hashimoto’s thyroiditis patients with lactose intolerance. Endocrine 46: 279–284.

14. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, et al. (2021) L-T4 therapy in enteric malabsorptive disorders. Front Endocrinol (Lausanne) 12: 626371.

15. Yamamoto T (2003) Tablet formulation of levothyroxine is absorbed less well than powdered levothyroxine. Thyroid 13: 1177–1181.