Switching from the tablet to the powder formulation of levothyroxine corrects severe hypothyroidism in a patient with lactose intolerance

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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
levels of transaminase and lactate dehydrogenase (Table 1). She had no history of gastrointestinal diseases.

Both pretibial regions were evident. 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 we 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
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...
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


