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RESEARCH LETTER

Patients with lactose intolerance absorb liquid levothyroxine better than tablet levothyroxine

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Introduction

The need to use high L-thyroxine (L-T4) doses in the replacement treatment of hypothyroidism is often the very first sign of one of the pathologies that are connected with malabsorption syndrome [1–6]. Also lactose intolerance (LI) should be considered in the differential diagnosis of gastrointestinal diseases that can cause malabsorption of L-T4 [3]. The prevalence of LI in Caucasian adult patients ranges 7–20 %, but its occurrence may be frequently ignored [3]. In the case of a diagnosis of LI, both a low lactose diet, and a lactose-free L-T4 preparation, should be administered to restore euthyroidism or make it possible to decrease the dose of the L-T4 [7].

Here we report our experience, in 5 patients with LI with an increase in serum thyrotropin [thyroid stimulating hormone (TSH)] levels, while receiving 'L-T4 in tablet form containing lactose' (L-T4-Tab+Lactose), that was reversibly resolved by switching to the same dose in a 'liquid (Tirosint® vial, IBSA Farmaceutici Italia) oral formulation (lactose-free)' (L-T4-Liq).

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Methods and patients

Informed consent was obtained from each patient included in the study. The study was approved by the local Ethical Committee.

All patients (women) taking part in the study were screened for other gastrointestinal diseases to avoid bias in the assessment of T4 malabsorption: a) clinically by excluding anemia caused by cobalamin deficiency or iron deficiency; b) gastrin, antiparietal cell antibodies, anti-tissue transglutaminase IgG and IgA antibodies, antiendomysial IgG and IgA antibodies, *Helicobacter pylori* (HP) antigen in the stool were measured [8]; only patients with negative results were included in the study. All patients were not affected by other conditions associated with L-T4 malabsorption as: a-concomitant therapy with proton-pump inhibitors (PPIs), or amiodarone, beta-blockers, lithium, orlistat, raloxifen, cholestyramine, interferons, antiacids; b-previous bariatric surgery, or gastric or intestinal surgery. Furthermore, pseudo-malabsorption because of poor compliance was excluded after an accurate examination for each patient.

All patients were switched from a L-T4-Tab+Lactose to receive L-T4-Liq maintaining the same dosage (both ingested 30 min before breakfast). They did not receive any other therapy.

Results

Patient 1

For the presence of LI symptoms and a positive lactose breath test (LBT) a low lactose diet was started in 2010. In January 2011 a replacement therapy for hypothyroidism due

Table 1 Thyroid parameters measured while patients were receiving oral L-T4 in tablet, after 1–2 months of L-T4 in the liquid formulation, and then after 1 month switching back to tablets

	L-T4 µg tablet	TSH µIU/mL	FT4 ng/dL	FT3 pg/mL	L-T4 µg liquid	TSH µIU/mL	FT4 ng/dL	FT3 pg/mL	L-T4 µg tablet	TSH µIU/mL	FT4 ng/dL	FT3 pg/mL
1	125	7.87	1.15	2.78	125	2.42	1.40	3.19	125	5.44	1.24	2.98
2	150	10.1	0.89	2.84	150	3.25	1.32	2.78	150	6.87	1.18	3.07
3	100	8.86	1.27	3.01	100	1.89	1.21	3.29	100	7.27	1.07	2.83
4	200	26.7	0.56	2.25	200							
					1 month	1.89	1.27	3.06	–	–	–	–
					2 months	0.01	1.31	3.24	–	–	–	–
5	125	5.8	1.09	2.96	125	3.44	1.15	3.01	–	–	–	–
					2 months	–	–	–	–	–	–	–

TSH, normal range 0.3–3.5 µIU/mL; FT4, normal range 0.8–1.7 ng/dL; FT3, normal range 2.3–4.2 pg/mL

to Hashimoto's thyroiditis (HT) was started with L-T4-Tab +Lactose, but TSH remained high and L-T4 dosage was gradually increased, till November 2012. Than we changed the formulation from L-T4-Tab+Lactose to L-T4-Liq. After 1 month, her TSH levels were in the normal range. To confirm the presumed relationship between oral formulation and TSH normalization, L-T4-Tab+Lactose was re-administered at the same dosage for 4 weeks. Once again, serum TSH increased (Table 1).

Patient 2

In 2010 a replacement therapy for hypothyroidism due to HT was started with L-T4-Tab+Lactose. TSH remained high and L-T4 dosage was gradually increased, without a significant correction of hypothyroidism. For the presence of LI symptoms and a positive LBT, in 2012 she started a low lactose diet. In February 2013, TSH was high with L-T4-Tab+Lactose 150 µg daily. We changed the formulation from L-T4-Tab+Lactose to L-T4-Liq. After 1 month, her TSH levels were in the normal range. To confirm the presumed relationship between oral formulation and TSH normalization, L-T4-Tab+Lactose was re-administered at the same dosage for 4 weeks. Once again, serum TSH increased (Table 1).

Patient 3

In this patient in July 2009, a replacement therapy for hypothyroidism due to HT was started with L-T4-Tab +Lactose with a good control of TSH. For the presence of LI symptoms and positive LBT, in March 2012, the patient started a low lactose diet. In October 2012 with the same dosage of L-T4-Tab+Lactose TSH was high, and the dose was gradually increased, without a significant correction of hypothyroidism. In April 2013 we changed the formulation from L-T4-Tab+Lactose to L-T4-Liq, maintaining the same dosage. After 1 month, her TSH levels were in the normal range. To confirm the presumed relationship between L-T4-Liq and TSH normalization, L-T4-Tab+Lactose was re-administered for 4 weeks. Once again, serum TSH increased (Table 1).

Patient 4

This patient was operated in 2007 with total thyroidectomy for papillary thyroid cancer (PTC) (pT2, N0, M0), and subsequently treated with radioiodine and L-T4-Tab+Lactose. A recombinant human thyroid-stimulating hormone (rhTSH) test in 2009 was negative for recurrence of PTC. In 2010 and 2011, with a stable dosage of L-T4-Tab+Lactose (125 µg/day), TSH was suppressed (<0.001 µIU/mL), with normal FT4 and FT3. For the presence of LI symptoms, and positive LBT, in February 2012 she started a low lactose diet. In December 2012, TSH was high and LBT dosage was gradually increased, without a significant correction of hypothyroidism. In April 2013 we changed the formulation from LBT to the liquid L-T4. After 1 month, her TSH levels were in the normal range and she felt better; after 2 months TSH was suppressed, and it remained stably suppressed in the subsequents controls.

Patient 5

This patient was diagnosed with autoimmune thyroiditis and hypothyroidism in 2013, and treated with L-T4-Tab +Lactose, with a good control of TSH levels. For the presence of LI symptoms and a positive LTB, in May 2014 she started a low lactose diet. TSH levels resulted high while in therapy with L-T4-Tab+Lactose 125 µg/day in August 2014. We changed the formulation from L-T4-Tab+Lactose to the liquid form; after 2 months, her TSH levels were normal.

Since the liquid L-T4 formulation resulted in a better control of TSH levels, all 5 patients were finally treated with the liquid L-T4, and TSH, FT3, FT4 were evaluated again after 6 months, resulting in the normal range in all subjects (range TSH 0.7–2.9 μIU/mL).

Discussion

An abnormality in the absorption of L-T4 should be considered in patients requiring large doses of L-T4 (>1.7–2 μg/kg per day) to achieve euthyroidism [9, 10]. First of all, pseudo-malabsorption owing to poor compliance should be excluded, then other conditions that could be associated with L-T4 malabsorption, as gastric and bowel diseases, or medications must be evaluated [3]. Also LI should be considered in the differential diagnosis of gastrointestinal diseases that can cause malabsorption of L-T4, because cases of severe hypothyroidism have been described in LI patients, resolved with lactose-free L-T4 [11]. It has been also shown that [8] the replacement L-T4 dose in hypothyroid patients with HT and LI, non-compliant with a lactose-free diet, was 1.72 μg/kg/d (vs. 1.31 μg/kg/d, in controls); suggesting that LI is associated with a significant increased need of oral T4 [8]. Furthermore it has been shown that lactose restriction leads to decreased levels of TSH, in hypothyroid patients who require L-T4 substitutive therapy [8, 11, 12].

The most recent advance concerning L-T4 therapy is the development of a novel oral liquid preparation [13], that has been shown to overcome different malabsorption conditions [14–20].

Here, we report 5 patients with LI and hypothyroidism while on therapy with L-T4 in tablets containing lactose, in whom the switch to an oral liquid L-T4 formulation (lactose free) maintaining exactly the same dosage induced the normalization of thyrotropin circulating levels. Interestingly, in 3 of these patients switching back from the liquid formulation to the tablets (containing lactose) caused thyrotropin levels to worsen again. Moreover, in the patient 4, the switching from the tablet to the liquid formulation (maintaning the same dosage of L-T4, 200 μg/day) caused a decrease of TSH from 26.7 to 0.01 μIU/mL. Other studies in larger number of patients are needed to confirm our observations. However, these results suggest that the L-T4 oral liquid formulation could circumvent malabsorption in patients with lactose intolerance.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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