Systematic Appraisal of Lactose Intolerance as Cause of Increased Need for Oral Thyroxine

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Context: An increased need for T_4 has been described in patients with different gastrointestinal disorders. However, there is a lack of systematic studies assessing the need for T_4 in hypothyroid patients with lactose intolerance, a widespread and often occult disorder.

Objective: The objective of the study was to assess the replacement T_4 dose required in hypothyroid patients with lactose intolerance.

Design: This was a cohort study.

Setting: The study was conducted at an outpatient endocrinology unit in a University Hospital.

Patients: The replacement T_4 dose has been analyzed, from 2009 to 2012, in 34 hypothyroid patients due to Hashimoto's thyroiditis and lactose intolerance and being noncompliant with a lactose-free diet.

Main Outcome Measure: An individually tailored T_4 dose was measured.

Results: In all patients with isolated Hashimoto's thyroiditis, target TSH (median TSH 1.02 mU/L) was obtained at a median T_4 dose of 1.31 μg/kg/d. In patients with lactose intolerance, only five of 34 patients reached the desired TSH (median TSH 0.83 mU/L) with a similar T_4 dose (1.29 μg/kg/d). In the remaining 29 patients, the T_4 dose was progressively increased and the target TSH (median TSH 1.21 mU/L) was attained at a median T_4 dose of 1.81 μg/kg/d (+38%, $P < .0001$). In six of these patients, other gastrointestinal disorders were diagnosed, and their median T_4 requirement was higher (2.04 μg/kg/d; +55%; $P = .0032$). In the remaining 23 patients with isolated lactose intolerance, a median T_4 dose of 1.72 μg/kg/d (+31% $P < .0001$) has been required to attain pharmacological thyroid homeostasis.

Conclusions: These findings show that lactose intolerance significantly increased the need for oral T_4 in hypothyroid patients. **(*J Clin Endocrinol Metab* 99: E1454–E1458, 2014)**

Levothyroxine (T_4) is one of the most prescribed drugs worldwide, and a narrow serum TSH concentration represents the best marker to assess a successful treatment (1). The absorption of oral T_4 is incomplete and occurs in the small intestine (2, 3); an efficient absorption of oral T_4 represents a critical step to attain the pharmacologic thyroid homeostasis (4). Different conditions may interfere with intestinal hormone absorption of T_4, and these include drugs and gastric and intestinal resection or diseases (5). Indeed, it is known that increased need for T_4 is required in patients with *Helicobacter pylori* infection and atrophic gastritis in which gastric acid secretion is impaired (6, 7). An increased

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Abbreviations: GI, gastrointestinal; HT, Hashimoto's thyroiditis; IQR, interquartile range; LBT, lactose hydrogen breath test; LI, lactose intolerance; TPOAb, thyroperoxidase antibody.

need for T_4 has been also described in patients with celiac disease, even in its atypical form (8).

Lactose intolerance (LI) represents a further widespread intestinal disorder due to reduced lactase enzymatic activity that breaks down lactose into glucose and galactose (9, 10). Very active in humans at birth, lactase function physiologically declines after weaning and persists only in about 30% throughout adulthood (lactase persistence) (10). Indeed, adult hypolactasia (lactase nonpersistence) is quite common and is often undiagnosed because its clinical presentation is variable and depends on several factors (eg, the amount of lactose ingested and the ability to digest it, even in relation with the individual intestinal microflora) (10–12). LI may interfere with the absorption of some drugs (13), and severe resistance to oral T_4 treatment has been described in a patient with LI (14). The improving effects of a lactose-free diet on TSH levels of T_4-treated patients with LI have also been reported (15), but systematic studies evaluating the need for T_4 in this condition are lacking.

So far, this study was aimed at investigating the therapeutic replacement dose of T_4 required in hypothyroid patients with Hashimoto's thyroiditis (HT) and confirmed diagnosis of lactose intolerance, alone or associated with further gastrointestinal (GI) disorders.

Materials and Methods

Patients and study design

This study has been conducted in a tertiary outpatient endocrinology unit in a cohort of patients sequentially examined and referred for thyroid diseases from 2009 to 2012. All patients enrolled in this study were treated with one brand of levothyroxine tablets (Eutirox; Bracco). They all agreed to take T_4 under fasting conditions, waiting at least 1 hour before eating or drinking (3, 7, 16).

Inclusion criteria were to be as follows: 1) adults patients aged from 18 to 60 years in replacement treatment with levothyroxine for HT; 2) patients with LI confirmed by a positive lactose hydrogen breath test; and 3) patients noncompliant with a lactose-free diet based on a specific questionnaire.

Exclusion criteria were to be as follows: 1) pregnant or lactating; 2) patients using iodine-containing substances and/or diet creams or pills; 3) patients treated with drugs interfering with levothyroxine absorption and action, including estrogens (5); and 4) patients on a lactose-restricted diet and/or using exogenous lactase. These criteria were ascertained before and during the period of study.

A questionnaire was administered to all patients to assess their nutritional habits and voluntary and occult lactose consumption as well as symptoms related to lactose ingestion. A total of 49 T_4-treated patients (48 females and one male, median age 42 y) with lactose intolerance were initially enrolled. Based on exclusion criteria, 15 patients were subsequently excluded. The remaining 34 patients [33 females and one male, median age 41 y; interquartile range (IQR)-1-IQR3 36–48 y] represented the study group. An age- and sex-comparable reference group, with no evidence of LI and/or other GI disorders, was represented by 68 patients (61 females and seven males; median age 41 y) with HT. All patients were initially treated with a similar T_4 dose to obtain the same target TSH (target TSH 0.5–2.5 mU/L) as reported elsewhere (1). The dose was progressively increased until the therapeutic goal had been achieved in at least two consecutive measurements in those patients who did not reach the expected TSH.

The study has been conducted upon written informed consent and as part of the diagnostic workup of the patients involved, according to the local ethical rules and the guidelines in the Declaration of Helsinki.

The diagnosis of HT

The diagnosis of HT was based on the presence of at least two of these three criteria: characteristic ultrasonographic pattern, hypothyroidism, and high titers of antithyroperoxidase antibodies (TPOAbs).

Diagnosis of LI

Diagnosis of LI, suspected on the basis of clinical symptoms, was confirmed by a lactose hydrogen breath test (LBT) (10). An LBT is considered the test of choice for the diagnosis of LI (10) and gave unequivocal abnormal results in all patients with LI. A targeted questionnaire was administered to all patients in the study group to ascertain that they were noncompliant with a lactose-free diet. Data on the frequency and amount of the consumption of lactose-containing foods (milk, yogurt, cheeses, ice cream, cookies and cakes, cold cuts, preservatives, etc) were scored as 0, 1, or 2 corresponding to no, occasionally, or daily use.

Diagnosis of additional GI disorders

Patients were screened for other GI diseases to avoid bias in the assessment of T_4 malabsorption. The screening was performed by measuring gastrin, antiparietal cell antibodies, antitissue transglutaminase IgG and IgA antibodies, antiendomysial IgG and IgA antibodies, anti-*H pylori* antibodies, and the execution of a urea breath test. Patients with positive antibodies and/or hypergastrinemia underwent esophagogastroduodenoscopy with multiple mucosal biopsies to obtain a histological diagnosis (7, 8, 17), assessed by the Sydney system score (18) or according with the American Gastroenterological Association (17).

Methods

Serum free T_4, TSH, and anti-TPOAbs were measured by an immunoradiometric assay (Thermo Scientific).

The LBT is based on measurements of breath hydrogen by gas chromatography at baseline and every 30 minutes over the following 3–4 hours after oral ingestion of 25 g of lactose. The test result, expressed as parts per million of hydrogen, was considered abnormal when its concentration overcame 20 parts per million above baseline. The LBT has a sensitivity of 77.5% and a specificity of 97.6% (19).

The urea breath test was performed with the use of an acid meal containing 75 mg of ^{13}C-labeled urea. Breath samples were analyzed by infrared spectroscopy (Iris; Wagner-Analysen-Technik). Anti-*H pylori* antibodies were detected by an ELISA com-

Table 1. Anthropometric and Functional Characteristics of Patients at Baseline

	Patients With Isolated HT	Patients With HT and LI	*P* Value
n	68	34	
Sex (female/male)	61/7	33/1	.2633[a]
Age, y	41 (33–51)	41 (36–48)	.9871
Weight, kg	66.0 (60–77)	58.0 (52–66)	**<.0018**
Height, cm	166 (157–170)	161 (157–164)	.0976
Body mass index, kg/m^2	24.2 (21.3–26.4)	21.3 (19.4–24.2)	.1583
TSH, mU/L	5.7 (4.1–7.6)	4.6 (4.1–6.7)	.3900
FT_4, ng/dL	1.04 (0.83–1.22)	1.00 (0.94–1.06)	.8361
TPOAbs, U/mL	554 (207–1247)	740 (351–1428)	.3475
Perimenopausal status	18/61 (29%)	9/33 (27%)	1.000

Results are expressed as median values and IQR (IQR1-IQR3). Statistical analysis was performed using a Mann-Whitney *U* test or Fisher's exact test. Significant *P* values are in bold.

[a] Fisher's exact test.

mercial kit (G.A.P. test; Bio-Rad Laboratories), antitissue transglutaminase IgG and IgA antibodies using an ELISA in which the microtiter plate wells were coated with recombinant human tissue transglutaminase (Eu-tTG kit; Eurospital). Antiendomysial IgG and IgA antibodies were screened by the direct immunofluorescent method on cryostat sections of monkey esophagus (antiendomysium kit; Eurospital). Plasma gastrin levels were measured by a RIA using antibody 4562 (courtesy of Professor J. F. Rehfeld, Department of Clinical Biochemistry, University of Copenhagen, Denmark) (7).

Statistical analysis

INSTAT GraphPad software version 3.06 (GraphPad Inc) statistical software for Windows was used for statistical analysis. Data are expressed as a median value (IQR). A Mann-Whitney *U* test (with or without the Welch's correction where appropriate) has been used to compare the nonparametric data. Subgroup percentages were compared using a Fisher's exact test.

Results

Baseline characteristics of the patients enrolled in the study and the reference group are summarized in Table 1. In addition to an expected weight difference, the two groups appeared to be similar.

The results of the questionnaire revealed that all patients in the study group have an ascertained consumption of lactose. Indeed, 65% of these have a significant daily intake of lactose, whereas the remaining 35% reported an occasional consumption.

In the reference group, target TSH (median TSH 1.02 mU/L) was obtained in all patients after 5 ± 2 months of treatment, with a median T_4 dose of 1.31 μg/kg·d (IQR1-IQR3 1.22–1.42 μg/kg/d). In patients with LI similarly treated (T_4 1.29 μg/kg/d), only 5 of 34 patients (Fisher's exact test, $P < .0001$) reached the expected TSH (median TSH 0.83 mU/L, P = NS) in a similar period of time (4 ± 2 mo). Conversely, the remaining 29 patients failed to achieve the target TSH (median TSH 3.02 mU/L; IQR1-IQR3 2.58–3.8 mU/L) despite a higher T_4 dose (1.44 μg/kg/d; $P = .0046$). So far, in these latter patients, the T_4 dose was progressively increased until the target TSH had been reached in at least two consecutive measurements. Finally, a serum TSH comparable with the one observed in the reference group (median TSH 1.21 mU/L; IQR1-IQR3 0.86–1.62 mU/L; P = NS) was attained at a median T_4 dose of 1.81 μg/kg/d (IQR1-IQR3 1.61–1.94 μg/kg/d; +38%, $P < .0001$) as shown in Figure 1A.

All 29 patients with an increased need for T_4 were afterward screened for other GI disorders to restrict the cause of T_4 malabsorption to iso-

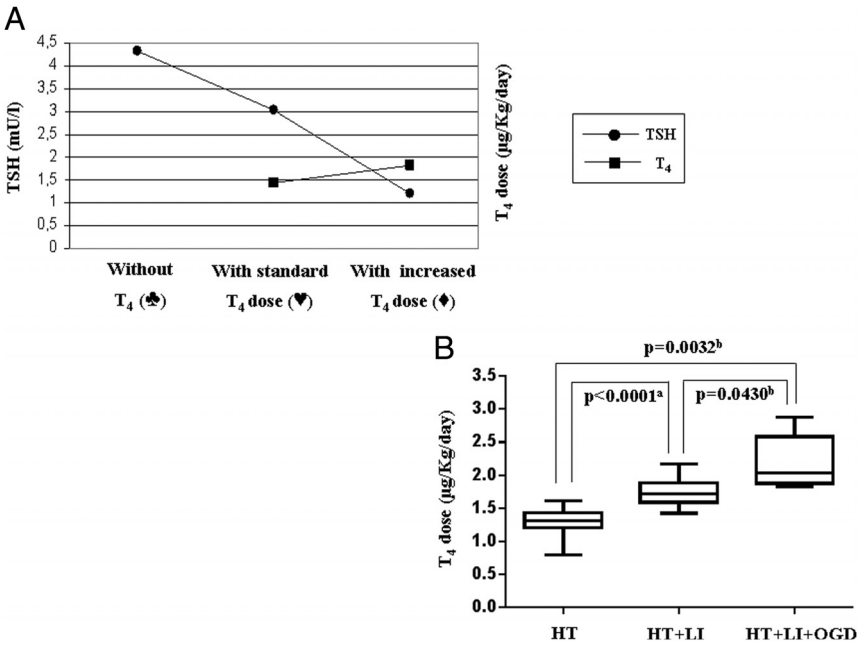

Figure 1. A, Median TSH values (*) and median T_4 dose (**) in patients with HT and LI without T_4 therapy and with different T_4 doses. The same numeric scale has been used. *, Serum TSH IQR values were the following: clover, IQ1-IQ3 4.1–6.7 mU/L; heart, IQR1-IQR3 2.58–3.8 mU/L; filled diamond, IQR1-IQR3 0.86–1.62 mU/L; **, T_4 dose IQR values were the following: heart, IQR1-IQR3 1.30–1.59 μg/kg/d; filled diamond, IQR1-IQR3 1.61–1.94 μg/kg/d. B, Median T_4 dose in patients with isolated HT in patients with HT and isolated LI (HT+LI) and in patients with HT, LI, and other GI diseases (HT+LI+OGD). Data are expressed as micrograms of T_4 per kilogram body weight per day. Mann-Whitney *U* test without (a) or with Welch's correction (b) have been used for statistical analysis.

lated lactose intolerance. In 6 of 29 patients, other GI disorders were diagnosed (three patients with atypical celiac disease, one patient with autoimmune atrophic gastritis, and two patients with *H pylori* related gastritis); in these patients, the target TSH (median TSH 1.10 mU/L, IQR1-IQR3 0.89–1.26 mU/L) was obtained with a median T_4 dose of 2.04 μg/kg/d (IQR1-IQR3 1.92–2.37 μg/kg/d; +55%; $P = .0032$) (Figure 1B).

In the remaining 23 patients with isolated LI, a median T_4 dose of 1.72 μg/kg/d (IQR1-IQR3 1.60–1.87 μg/kg/d; +31%, $P < .0001$) has been required to attain pharmacological thyroid homeostasis (median TSH 1.28 mU/L; IQR1-IQR3 0.86–1.70 mU/L). Such a dose is significantly higher when compared with that observed in the reference group and also different with the one measured in those patients with LI and other GI disorders ($P = .0430$) (Figure 1B).

Discussion

The dose of T_4 required to reach target TSH was higher in hypothyroid patients with HT and LI than in patients with isolated HT. In hypothyroid patients with LI, the T_4 dose had to be increased by almost one third to obtain the therapeutic goal, and the concurrent presence of further GI disorders almost doubled the increased T_4 need.

The pathogenic mechanism leading to T_4 increased need in patients with LI is still unclear. However, the presence of undigested lactose increases the amount of fluid in the bowel lumen (12), and this osmotic alteration accelerates intestinal transit time and decreases the binding between lactose and residual enzyme (15). So far, in subjects with LI, the absorption of oral T_4 may be affected in at least three ways. First, oral T_4 may be adsorbed and trapped by the modified intestinal content, similarly to what is described for several drugs (5) and for celiac disease (8). Second, a faster intestinal transit may reduce the exposure time for T_4 interaction with intestinal mucosa, therefore reducing the bioavailability of T_4 (20). Lastly, the different microbiota of patients with LI may impair the villous architecture, essential for proper absorption of drugs and nutrients (11, 12, 21).

The presence, in our study, of five patients (15%) not showing T_4 malabsorption has no obvious explanation. However, an individual level of LI has been described (10, 12), depending on the amount of lactose ingested, the coingestion of others foods, the residual lactase activity, and the gut microbiota composition in each patient (10, 11). These hypotheses are supported by a recent study that provided evidence for a reduction of serum TSH levels after lactose restriction in hypothyroid patients with LI, without the need to increase T_4 dose (15). However, a lactose-free diet is a difficult task to evaluate due to the sneaky ingestion of this disaccharide contained as a preservative in many foods and excipient in drug preparations, including levothyroxine (10, 12, 22). Recently, in fact, it has been proven that lactose-containing medications may contribute to intestinal symptoms in patients with LI (22). However, Montalto et al (23) have clearly shown that lactose concentrations lower than 400 mg neither increase breath hydrogen excretion nor cause GI symptoms. On the other hand, the exact content of lactose in each drug is not always listed in the information leaflets (22).

In conclusion, these findings show that LI is a not negligible cause of an increased need for T_4 due to its widespread diffusion. Furthermore, the increased T_4 requirement may help to suspect unrecognized LI in hypothyroid patients.

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