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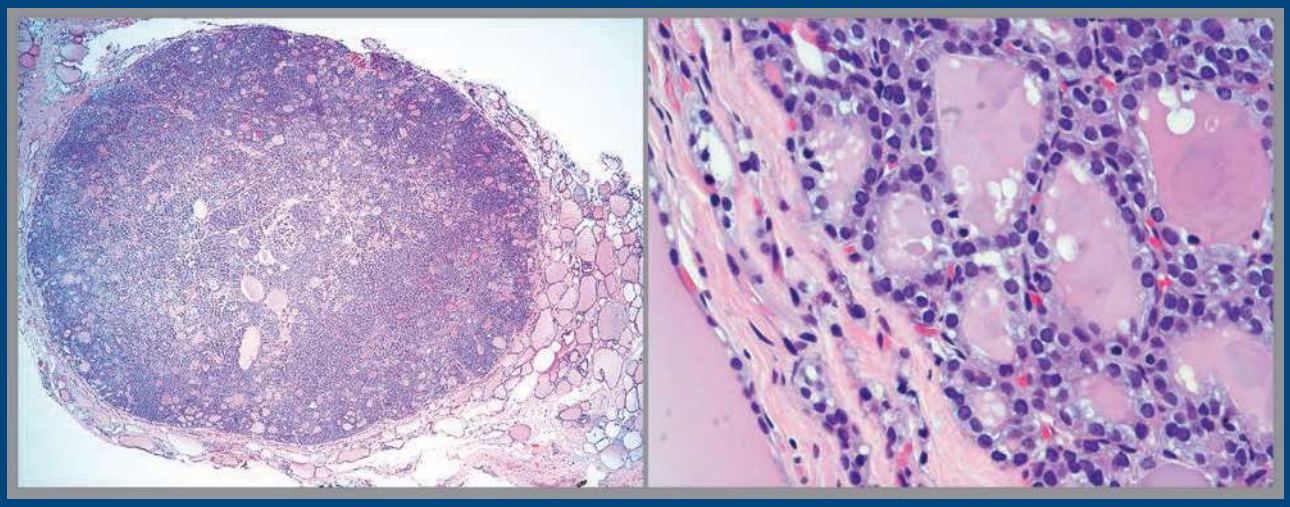

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A Double-Blind Placebo-Controlled Trial of Liquid Thyroxine Ingested at Breakfast: Results of the TICO Study

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Background: Levothyroxine (LT4) is the recommended treatment for millions of hypothyroid patients. Current guidelines recommend that LT4 tablets be taken in a fasting state, but inability to adhere to this often leads to poor therapy compliance.
Methods: A randomized, double-blind, placebo-controlled, crossover trial was conducted in previously untreated hypothyroid patients randomly assigned to receive an oral solution of LT4 either at least 30 minutes before breakfast or directly at breakfast time. Each patient completed two six-week treatment periods, with different timing of active LT4 administration: placebo before breakfast and active LT4 at breakfast, or *vice versa*. At the end of each period, thyrotropin (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) were measured. The primary endpoint was to verify any difference in serum TSH levels whether consuming liquid LT4 at breakfast or 30 minutes prior to breakfast.
Results: A total of 77 patients (64 females; median age 45.4 ± 3.7 years) completed the study. No statistically significant differences in serum TSH, fT4, or fT3 levels were observed whether LT4 was taken at breakfast or 30 minutes before, in a fasting state. No significant effect from the sequence of regimens, breakfast composition, and/or concomitantly administered drugs was observed on the dose of LT4 administered, or on the post-treatment serum TSH values.
Conclusions: The TICO study suggests that a liquid LT4 formulation can be ingested directly at breakfast, thus potentially improving therapeutic compliance. This observation is of considerable clinical relevance, since non-adherence to LT4 therapy requirements is more likely to cause variability in serum TSH concentrations.

Introduction

Hypothyroidism is one of the most common chronic disorders worldwide, with prevalence rates ranging from 0.1% to 2% of the population (1–3). Levothyroxine (LT4) is the treatment of choice, and a serum thyrotropin (TSH) concentration maintained within a narrow range represents the best marker of successful treatment (4,5). The management of hypothyroidism is generally considered straightforward, even though cross-sectional surveys of patients taking LT4 demonstrate that between 40% and 48% are either over- or undertreated (2,6).

Different factors may interfere with intestinal absorption of LT4, including food ingestion, dietary fiber, coffee, drugs, gastric or intestinal resection, and diseases, and current guidelines recommend that LT4 should be taken in a fasting state (4,7).

On the other hand, adherence to medical recommendations has been recognized as challenging, especially with regard to drug therapy (8), and a significant number of patients have difficulty complying with LT4 therapy, as they have to postpone their breakfast by 30–60 minutes (9). Over the last few years, new non-tablet LT4 formulations, such as liquid and soft gel capsules, have been introduced in some countries. Recently, hypothyroid patients were serendipitously identified who maintained euthyroidism despite taking liquid LT4 contrary to guidelines at breakfast, with their coffee. When the same patients started to ingest the same dose of liquid LT4 as recommended at least 30 minutes before breakfast, no changes in TSH, free thyroxine (fT4), and free triiodothyronine (T3) values were observed (10). To evaluate the efficacy of oral liquid LT4 administration at breakfast further prospectively, the TICO study (*TIroxina a COlazione*, translated as "Thyroxine at Breakfast") was conducted: a double-blind,

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placebo-controlled trial, involving naïve hypothyroid patients starting replacement therapy.

Materials and Methods

Study design and conduct

The TICO study (EUDRACT registration number: 2013-001696-21) is a randomized, double-blind, placebo-controlled, crossover trial in which previously untreated hypothyroid patients were randomly assigned to receive an oral solution of LT4 (Tirosint® fiala monouso, IBSA Farmaceutici Italia) in the morning. The drug was administered either before breakfast ("before"), after an overnight fast and at least 30 minutes prior to food ingestion, or in a fed state directly at breakfast time ("at"). The study was approved by an independent Institutiona Review Board and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All the participants provided prior written informed consent.

The study was designed by the investigators and supported by IBSA Farmaceutici Italia. The pharmaceutical company prepared two identical and indistinguishable vials (labeled A and B) containing either a specified dose of LT4 (25, 50, 75, or 100 μg) dissolved in a 1 mL solution of 85% glycerol and 96% ethanol (243 mg) or a placebo vehicle control (1 mL of glycerol/ethanol solution).

In the morning, all patients were given two vials, labeled A and B. The first vial was to be ingested after an overnight fast half an hour before breakfast diluted in a glass of water. Data indicate that gastric emptying after drinking plain water is almost complete within 30 minutes (11), so it can be assumed that absorption of liquid LT4 is not influenced by food ingested 30 minutes thereafter. The second vial was ingested during each patient's usual breakfast, mixed with tea, coffee, milk, cappuccino, orange juice, and so on. Each patient completed two six-week regimens, corresponding to the sequence vial A–vial B, or *vice versa*, with regimens defined by the timing of active LT4 administration: the placebo vial before breakfast and the active LT4 vial at breakfast (regimen "at" → "before"), or *vice versa* (regimen "before" → "at"). Regimen sequence order was randomized according to a permuted blocks allocation scheme (1:1 ratio, with random block size of two, four, and six). The placebo or active drug content of vials A and B was determined by the manufacturers at IBSA Farmaceutici and disclosed to the investigators only after study completion and blinded data analysis by the investigators.

The intake of drugs potentially interfering with LT4 absorption (in particular, iron or calcium supplements and proton pump inhibitors) was monitored and recorded. In addition, a detailed description of each subject's breakfast composition was obtained, particularly of insoluble fibers and/or soymilk. The study design is shown in Figure 1.

The authors assume responsibility for the accuracy of the data and full observance of the study protocol.

Study participants

Patients, aged 18–75 years old, were eligible if they presented symptoms of hypothyroidism and/or TSH values >10 mIU/L, due to Hashimoto's thyroiditis or thyroidectomy for proven benign goiter. None of the patients had received previous treatment.

Subjects with congestive heart failure (NYHA III–IV), coronary heart disease, severe hypertension, uncontrolled diabetes mellitus (HbA1c >64 mmol/mol or 8%), or untreated dyslipidemia were excluded. In order to avoid any possible persistence of TSH elevation in the early phase of pregnancy, women who were pregnant or lactating and women who could possibly become pregnant at any time during the entire study were also excluded. All participants were required to maintain the same breakfast habits and any ongoing therapy for the full duration of the study. The introduction of any additional drugs had to be reported to the researchers.

Patient enrollment took place from October 2013 through November 2014. The starting dose of LT4 was determined through clinical judgment, taking into account TSH levels, estimate of residual thyroid function, age, body weight, and comorbidities (4).

After the first six-week, regimen all patients were submitted to TSH, fT4, and fT3 evaluation to verify achievement of euthyroidism ($0.2 \leq$ TSH ≤ 4.2 mIU/L). If this was not achieved, an appropriately adjusted LT4 dose was administered for six more weeks, and thyroid function parameters rechecked afterwards.

When a euthyroid state was reached, the patients had to switch the order in which the vials were ingested, and they underwent treatment for a second six-week period. Individual LT4 doses titrated during the first sequence period did not change during the second sequence. At the end of the second sequence, measurements of TSH, fT4, and fT3 values were repeated, and the study was completed. Adherence to protocol requirements (regularity and timing of taking the drugs, unchanged eating habits at breakfast) was assessed by a physician via personal interviews at the end of each regimen period. At the end of the study, all patients were formally asked whether they would prefer their daily LT4 treatment directly at breakfast or 30–60 minutes before.

Study endpoints

The primary endpoint was to verify any difference in serum TSH levels (and secondarily in fT4 and fT3) when *ingesting* liquid LT4 at breakfast compared with 30 minutes earlier.

Statistical analysis, based on pilot data from patients taking LT4 for thyroiditis, indicated that 80 subjects would provide 80% power to detect a 20% difference between TSH levels of the two regimen sequences, using a critical significance level of $p = 0.05$. In the pilot data, a 20% difference corresponded to 0.6 mIU/L.

Hormone assays

Serum concentrations of fT4 (normal range 8.0–19.0 pg/mL, analytical sensitivity 1 pg/mL), fT3 (normal range 2.4–4.7 pg/mL; analytical sensitivity 0.35 pg/mL), and TSH (normal range 0.4–4.5 mIU/L, analytical sensitivity 0.004 mIU/L) were measured using a fully automated Architect i2000 analyzer (Abbott Diagnostics, Abbott Park, IL) using chemiluminescent magnetic immunoassays.

Statistical analysis

Data are presented as means ± standard deviations for parameters with normal distribution (age, body mass index).

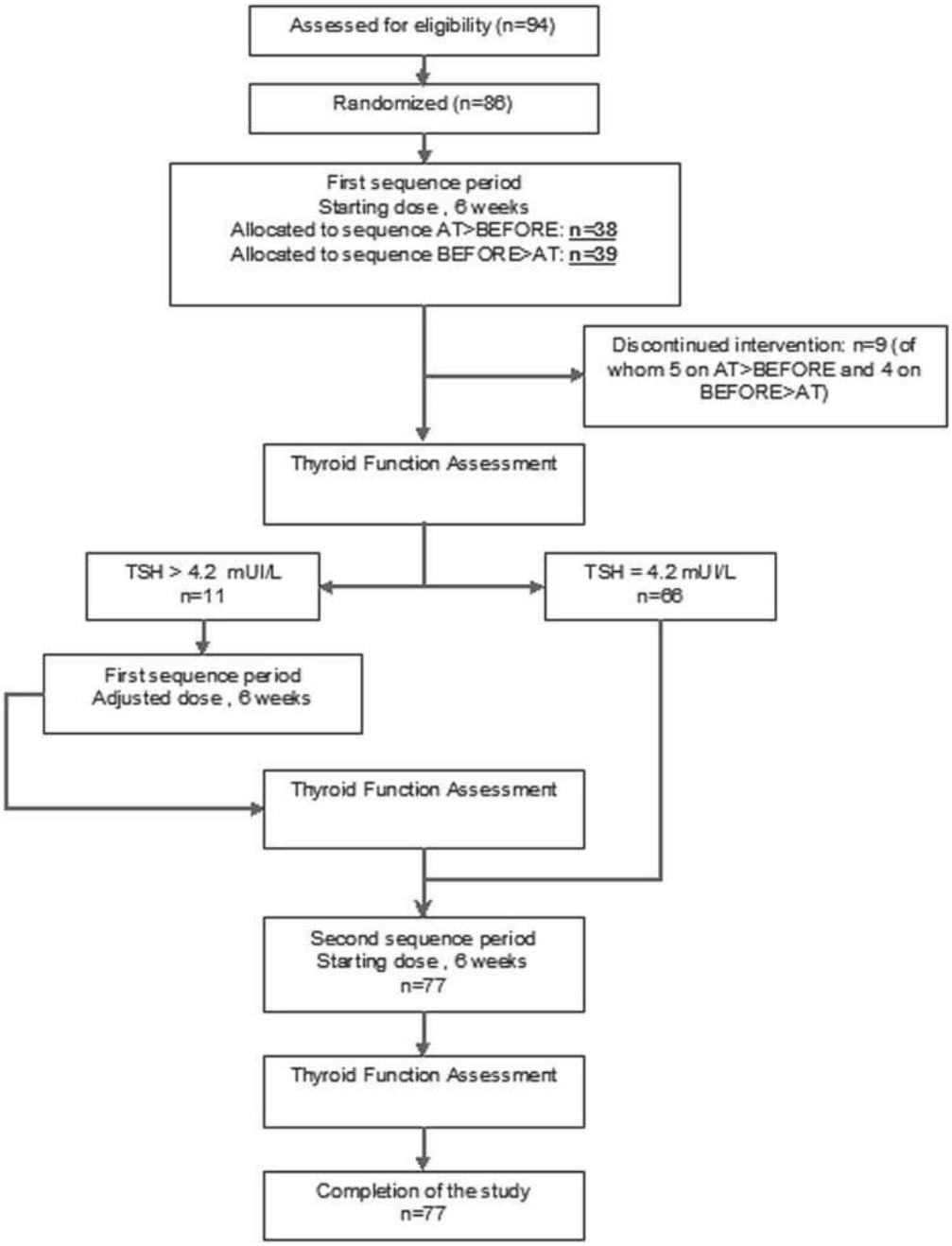

FIG. 1. Flowchart of the TICO study.

Normal distribution was checked by the Shapiro–Wilk test. TSH, fT4, and fT3 levels resulted in non-normally distributed data and were not normalized by the usual procedures of data transformation. In these cases, results are presented as medians plus ranges. Comparisons between continuous variables were performed by paired samples *t*-test or related samples by the Wilcoxon signed rank test, as appropriate. Categorical variables were compared by the chi-square test. A generalized linear model analysis was performed to examine the influence of potential confounders (e.g., different types of breakfast, dietary supplements, or concomitantly administered drugs) on serum TSH levels.

Two-tailed *p*-values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows v17.0 software (SPSS, Inc., Chicago, IL).

Results

Ninety-four patients were assessed for eligibility, and 86 patients (71 females, median age 46.0 ± 13.8 years) were eligible and enrolled in the study. Of these 86 patients, nine withdrew from the trial during the first sequence period, in six cases due to non-adherence to protocol requirements and in the remaining three cases for unspecified personal reasons. No patient abandoned the study over the second period of treatment, so that 77 patients (64 females, median age 45.4 ± 13.7 years) completed the study. Sixty-six patients started replacement therapy for Hashimoto's thyroiditis. Eleven patients started replacement therapy after thyroidectomy for the removal of histologically proven benign goiter (details are provided in Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/thy).

Table 1. Baseline Demographic and Clinical Characteristics According to Regimen Sequence of LT4 Administration

	All patients	*Sequence "at" → "before"*	*Sequence "before" → "at"*	p-*Value*
Number of patients	77	38	39	
Sex (female/male)	64/13	32/6	32/7	NS
Age (years)	45.4 ± 13.7	46.2 ± 14.1	44.8 ± 13.4	NS
BMI	24.2 ± 4.7	24.1 ± 4.1	24.3 ± 4.6	NS
Hashimoto thyroiditis (*n*)	66	33	33	NS
Total thyroidectomy (*n*)	11	5	6	
TSH (mIU/L)	15.3 (8.13–87.1)	15.1 (8.13–33.2)	16.2 (10.1–87.1)	NS
fT4 (pg/mL)	10.8 (5.3–17.5)	10.3 (5.7–17.5)	11.1 (5.3–16.1)	NS
fT3 (pg/mL)	3.0 (2.1–4.4)	3.0 (2.1–4.4)	3.0 (2.1–4.2)	NS

Values are reported as mean ± standard deviation or as median (min–max) values for variables with normal or non-normal distribution, respectively.

LT4, levothyroxine; NS, not significant; BMI, body mass index; TSH, thyrotropin; fT4, free thyroxine; fT3, free triiodothyronine.

After data analysis and blinding disclosure, 38 patients were found to have started the regimen sequence with active LT4 at breakfast (sequence "at" → "before"), while the remaining 39 patients followed the opposite sequence ("before" → "at"). Baseline demographic and clinical characteristics according to regimen sequence are shown in Table 1. No difference in age, sex, cause of hypothyroidism, and baseline thyroid hormonal profile was observed between the two regimen sequences.

After six weeks of the first period of treatment, a similar number of patients (32/38, 84%, sequence "at" → "before"; 34/39, 87%, sequence "before" → "at") achieved euthyroidism. In the subjects with TSH values still >4.2 mIU/L, the LT4 dose was adjusted, and treatment continued for six more weeks. All these patients ultimately became euthyroid.

The median dose of LT4 *ingested* by the 77 patients at the end of the first regimen sequence was 75 μg daily; individual LT4 doses titrated during the first sequence period were not changed during the second treatment period.

No difference in serum TSH, fT4, and fT3 levels was observed irrespective of whether LT4 was ingested at breakfast or 30 minutes prior in a fasting state. The sequence of regimen ("at" → "before" vs "before" → "at") influenced neither the dose of LT4 administered nor the post-treatment TSH values (Table 2). Similarly, no influence of breakfast composition on TSH and thyroid hormone levels was observed in subgroup analyses, comparing subjects taking a beverage-only breakfast ($n=33$) with subjects taking solid foods in addition to beverages ($n=44$).

Table 2. Thyroid Hormonal Profile of All Patients According to Regimen Sequence of LT4 Administration (All Patients and "At" → "Before" vs. "Before" → "At")

	LT4 at breakfast	*LT4 before breakfast*	p-*Value*
All patients (n = *77*)			
TSH	2.58 (0.03–10.04)	2.69 (0.03–8.02)	0.81
fT4	10.4 (8.1–15.0)	10.2 (8.1–13.7)	0.09
fT3	2.7 (2.05–3.5)	2.8 (1.9–3.8)	0.62
Patients on sequence "at" → "before" (n = *38*)			
TSH	2.42 (0.03–5.32)	2.26 (0.03–8.02)	0.85
fT4	10.7 (8.1–14.3)	10.2 (8.6–12.3)	0.03
fT3	2.8 (2.05–3.5)	2.8 (1.9–3.8)	0.45
Patients on sequence "before" → "at" (n = *39*)			
TSH	2.59 (0.09–10.04)	3.0 (0.19–5.37)	0.97
fT4	10.3 (8.2–15.0)	10.2 (8.1–13.7)	0.80
fT3	2.7 (2.2–3.4)	2.7 (2.2–3.8)	0.87

Data shown as median (min–max).

Any patient on concomitant drug treatment (including proton pump inhibitors, calcium or iron supplements) or patients taking fiber and soymilk products at breakfast were purposely not excluded from the study (Supplementary Table S1). Generalized linear model analysis shows that these and other variables (age, sex, and body weight) had no significant effect on the dose of LT4 administered or the achieved post-treatment TSH values (data not shown). No specific complaints were reported by the patients. In particular, none of the patients noticed changes in the taste of their breakfast. No adverse events were observed by the investigators. All the patients declared they would prefer to take their daily LT4 treatment directly at breakfast.

Discussion

Current guidelines for the treatment of hypothyroidism by a Task Force of the American Thyroid Association recommend that for optimal and consistent absorption, LT4 should, if possible, be taken at least 30 minutes before breakfast (or at bedtime, at least three hours after the evening meal) (4). This recommendation is based on a small number of studies indicating that concomitant ingestion of LT4 with food (12–15), coffee (13), or fiber and soy products (16,17) is associated with higher serum TSH values in hypothyroid subjects, compared with taking LT4 in a fasting state. However, the Task Force acknowledges that the quality of these studies is only moderate on average, and that the strength of the recommendation is weak (4).

The recent introduction of non-tablet formulations of LT4 in the therapeutic environment seems to call this recommendation into question (18). In a small number of hypothyroid patients, Vita *et al.* (9) observed that treatment with a soft gel preparation of LT4 (Tiche capsules, IBSA Switzerland) is not associated with reduced absorption of the drug by coffee (14). The same authors observed that the soft gel formulation of LT4 can also circumvent the problem of incomplete absorption of LT4 caused by an increase in gastric pH induced by proton pump inhibitors (19).

The authors first reported on 54 patients who erroneously ingested a liquid LT4 formulation (Tirosint, IBSA Italy) with coffee. After anticipating the time of liquid LT4 ingestion to have been 30 minutes before breakfast, no change in TSH, fT4, and fT3 concentrations was observed (10). It has also been shown that patients who have undergone bariatric surgery (bilio-pancreatic diversion) or total laryngectomy and thyroidectomy could benefit from a liquid LT4 formulation (20), which can be administered directly through a feeding tube, with no need for an empty stomach. (21). Further, along this line of reasoning, Brancato *et al.* suggested that a LT4 oral solution consumed within an hour before breakfast could have an increased absorption rate in comparison to LT4 tablets, especially in the presence of other factors interfering with LT4 absorption (22).

The main result of the present randomized, placebo-controlled, double-blind crossover trial involving patients with previously untreated acquired hypothyroidism clearly indicates that the administration of the same dose of oral liquid LT4 either at breakfast or in a fasting state, 30 minutes before breakfast, has indistinguishable effects on the thyroid hormonal profile. This finding, coupled with the unanimous preference expressed by patients for taking the medication directly at breakfast, may represent a distinct advantage of the liquid LT4 formulation compared with traditional LT4 tablets, the absorption of which appears to be erratic when ingested together with food and/or beverages, as reported by Perez *et al.* in a recent study (15). It is widely accepted that adherence to medical recommendations, especially with regard to drug therapy, is challenging (8), and well-documented cross-sectional surveys of patients taking LT4 have shown that between 40% and 48% are either over- or undertreated (2,6). In particular, a significant number of patients find it difficult to comply with LT4 therapy, as they have to postpone their breakfast by 30–60 minutes (9).

Giusti *et al.* recently reported that patients found the LT4 tablet formulation more agreeable than liquid ones (23). It can be speculated that this is partly because tablets may be easier to manage than vials, but it should also be considered that in the study by Giusti *et al.*, the patients added liquid LT4 to a separate glass of water, with a relatively unpleasant taste when compared with direct addition to usual breakfast beverages.

The present clinical observation with patients taking the drug mixed with coffee and other hot beverages suggests that neither high temperatures (i.e., coffee, milk, cappuccino, or hot tea) nor acidity (i.e., orange juice) alter the molecular properties or stability of LT4. Studies on stability carried out with tablet formulations have shown that sodium LT4 rapidly degrades at 60–80°C (24,25). Indeed, an Italian espresso coffee is served at similar temperatures (26). Very recently, Bernareggi *et al.* addressed this issue, demonstrating that liquid LT4 is stable after 20 minutes in milk, tea, coffee, and cappuccino at 50°C, as well as in orange juice at room temperature (27).

One important feature of the present study is that it couples a rigorous study design to a real-life approach in respect of usual breakfast habits and intake of drugs and supplements, which remained unchanged throughout the study. Actually, no influence of breakfast composition or co-treatment with other drugs (including PPI) on TSH levels was observed.

An important issue that has not been directly addressed by the present study is the question of whether liquid LT4 may have distinct advantages over tablet preparations in terms of clinical outcomes, beyond timing of treatment. Negro *et al.* reported interesting data in this respect, showing that administration of a liquid LT4 formulation compared with tablets resulted in a significantly higher number of hypothyroid patients who remained euthyroid over a 12-month follow-up, with a significant reduction of variability in TSH values (28). It has also been observed in a retrospective series of 369 elderly hypothyroid patients treated with LT4 over a five-year period that the prevalence of subclinical or overt hyperthyroidism was significantly reduced in subjects treated with liquid LT4 compared with those treated with tablets (29). This is of particular interest in elderly patients, where the increased risk of developing heart disease, osteoporosis, bone fracture, and cognitive impairment is well documented among subclinical hyperthyroid subjects (15,30–33).

The liquid formulation is currently only available in Italy. This could represent a limitation, since all the clinical studies have been conducted in this country, among people belonging to the same ethnic group, with similar breakfast habits. Accordingly, further studies performed in other countries are needed.

In conclusion, the present study suggests that a liquid LT4 formulation can be ingested directly at breakfast, thus potentially improving therapeutic compliance. This observation is of considerable clinical relevance, given that subjects who do not comply with LT4 therapy requirements are more likely to show variability in TSH concentrations and consequent unwanted effects.

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Author Disclosure Statement

No conflicting financial interests exist.

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