Thyroid Research

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Are liquid levothyroxine formulations comparable? The LETI study

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Abstract

Background Liquid ethanol-containing levothyroxine (e-LT4) is known to circumvent malabsorption induced by food, drugs, or pathological conditions. Recently a new ethanol-free formulation of liquid levothyroxine (ef-LT4) has been commercialized. No studies have compared e-LT4 with ef-LT4. The aim of the present study is to compare thyroid hormone profile in patients treated with e-LT4 and ef-LT4.

Material and methods We retrospectively retrieved thyroid hormonal profile and clinical data of 48 patients diagnosed with hypothyroidism who had been on stable treatment with an e- LT4 formulation at the same dosage for at least one year and who decided to switch to ef-LT4 for tasting issue.

Results A significant increase in TSH levels was observed after 6 months on ef-LT4 treatment (2.5 ± 0.8 mIU/ml vs. 3.1 ± 1.0 mIU/ml, respectively, $p < .001$), while fT4 decreased [1.2 ng/dl (IQR 1.1–1.4) vs. 1.1 ng/dl (1.0–1.2), respectively, $p = .047$], maintaining the same dosage of LT4. In 31 patients, for whom data were available 12 months after the switch, TSH further increased (2.50 ± 0.9 mIU/ml at baseline vs 3.2 ± 0.9 mIU/ml after 6 months vs 3.5 ± 0.9 mIU/ml at 12 months, $p < .001$) and fT4 decreased [1.2 ng/dl (IQR 1.1–1.4) vs. 1.1 ng/dl (IQR 0.9–1.3) vs 1.0 ng/dl (IQR 0.9–1.1), $p = .008$].

Conclusion ef-LT4 formulation seems to be less effective compared to e-LT4 over time. However, further prospective cross-sectional studies, performed in large sets of patients, even on concomitant therapy with interfering drugs, are needed.

Keywords Liquid levothyroxine, Hypothyroidism, Ethanol, Levothyroxine

Introduction

Hypothyroidism is a common condition characterized by thyroid hormone deficiency. It is readily diagnosed and managed but can be potentially fatal in severe cases if untreated. Primary hypothyroidism can result from various conditions, such as Hashimoto's thyroiditis, thyroidectomy, and radioactive iodine ablation therapy [1]. The prevalence of overt hypothyroidism in adults ranges from 0.1% to 2%, whereas the prevalence of subclinical hypothyroidism is higher, ranging from 4 to 10% of adults, with a potentially higher frequency in older women [2–4].

Treatment of hypothyroidism with replacement doses of thyroid hormone is lifelong, and levothyroxine (LT4) is

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the drug of choice [5]. There has been significant progress in the field of thyroid hormone therapy over the past century, from hypodermic injections of sheep thyroid gland extracts to desiccated thyroid extract, tablets, and novel liquid formulations both [6]. Despite the apparent ease of managing LT4 treatment, it has a narrow therapeutic index [7, 8]. Consequently, almost 50% of treated patients exhibit an abnormal thyroid hormone profile after one year of treatment, potentially leading to iatrogenic complications or symptoms of hypothyroidism [9, 10].

Indeed, liquid formulations have demonstrated numerous advantages compared to tablets. Clinical data have shown that therapy with liquid LT4 dissolved in a solution of 85% glycerol and 96% ethanol (Tirosint®, IBSA, Switzerland) provides better thyroid hormone control and requires less frequent thyroid-stimulating hormone (TSH) level monitoring in replacement or suppression therapy [11–13]. Additionally, it is well established that liquid formulations can circumvent malabsorption induced by food, drugs, or pathological conditions [14–17]. Notably, the novel formulation can be taken in a non-fasting state, making adherence to treatment easier and significantly improving the quality of life [18]. However, we are still far from achieving precision medicine, even though recent advancements, such as an innovative device delivering the daily amount of LT4 calculated based on body weight, make it possible to dream about it [6].

The advantages of soft gel capsules compared to tablets have also been reported in a few studies. They combine the practicality of tablet formulations with the pharmacokinetic qualities of liquid ones, resulting in better gastrointestinal absorption compared to tablets [15, 19, 20].

Recently, a new ethanol-free formulation of liquid LT4 has been commercialized (Levotirsol®, IBSA, Switzerland). To the best of our knowledge, no studies have compared ethanol-containing liquid LT4 with the ethanol-free version. Therefore, the aim of the present study was to compare TSH and free thyroxine (fT4) concentrations in patients treated with ethanol-containing and ethanol-free LT4 formulations.

Material and methods

Patients' selection and clinical data collection

We retrospectively reviewed the medical records of patients diagnosed with hypothyroidism due to autoimmune thyroiditis who had been on stable treatment with an ethanol liquid LT4 (e-LT4) formulation at the same dosage for at least one year and who decided to switch to an ethanol-free (ef-LT4) oral solution at the same dosage, as they found the e-LT4 distasteful, between September 2023 and May 2024. We selected patients with TSH within the laboratory reference range on e-LT4, who were instructed to take the treatment in a fasting state, 30 min before breakfast. Patients receiving any medications known to interfere with LT4 absorption [21] were excluded from the study. TSH and fT4 levels were recorded 12 months and immediately before the formulation change, as well as 6 months after the switch. In a subset of patients, hormonal status was available also after 12 months after switch. All the patients reported that the blood sample was collected before having taken LT4. Before enrollment in the study, all the patients were checked to ensure they had not changed their dosage during the study period.

During the same study period, the shelf life of ef-LT4 and e-LT4 was shortened from 18 months to 5 and 7 months, due to a warning from the producer about potential instability of the glycerol used in the formulations. For this reason, to verify whether TSH remained stable, we added two control groups of patients taking e-LT4 (ce-LT4) and ef-LT4 (cef-LT4) within the same study period, matched for TSH levels, who continued using the two formulations at the same dosage for at least 12 months.

Demographic and anthropometric data, TSH and fT4 levels, and weekly LT4 requirements were collected anonymously in an electronic database. The study (ASST_BS_LETI) was approved by the Ethics Committee Lombardia 6 (no 6358).

Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of data distribution. Normally distributed data were reported as mean ± standard deviation (SD), non-normally distributed data were reported as median and interquartile range (IQR). The Mann–Whitney U test was used to assess differences in medians between groups, the 2-tailed Student's T-test was used to assess differences in means, as appropriate. Changes in TSH levels throughout the study were evaluated using a repeated measure one-way repeated measures ANOVA with Bonferroni post-hoc tests; since fT4 data did not follow a normal distribution, a Friedman test with Dunns post-hoc tests were performed. A p-value < 0.05 was considered statistically significant.

The sample size was calculated by considering the score in the GPower 3.1.5 program. Statistical analysis, based on pilot data from patients taking L-T4 for thyroiditis, indicated that 50 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 0.4 mIU/L.

The statistical analyses were conducted using SPSS version 26.0 software (SPSS, Inc., Evanston, IL, USA) and R

software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

The study results are reported in compliance with the STROBE reporting guidelines for cross-sectional studies, with the checklist provided in Supplementary file 1.

Results

A total of 48 patients (65% females) diagnosed with autoimmune thyroiditis, with a mean age of 34.1 ± 4.9 years old, were enrolled. All the subjects showed elevated serum concentrations of thyroid peroxidase antibodies [484 ± 196 IU/mL (normal range: < 60 IU/mL)] and coarsened, hypoechoic, and hypervascularized thyroid gland at ultrasound evaluation. In deep, the mean age of patients was superimposable among sex (33.6 ± 5.4 vs. 34.9 ± 3.9, female vs. male, $p = 0.091$).

The median weekly LT4 dosage was 525 µg (IQR 478.1–650), with no differences between female and male [525 µg (IQR 475–600) vs. 650 µg (IQR 500–743.8), respectively, $p = 0.241$], whereas the mean daily LT4 dosage/kg was 1.4 ± 0.3 µg/kg during all the study spam ($p = 0.348$). In detail, serum TSH levels of patients on e-LT4 at recruitment were comparable to those from 12 months earlier (2.5 ± 0.8 mIU/ml vs. 2.4 ± 0.8 mIU/ml, respectively, $p = 0.586$), such as fT4 [1.2 ng/dl (IQR 1.1–1.4) vs. 1.2 ng/dl (IQR 1.1–1.4), respectively, $p = 0.999$].

A significant increase in TSH levels was observed after 6 months on ef-LT4 treatment respect to recruitment (3.1 ± 1.0 mIU/ml vs. 2.5 ± 0.8 mIU/ml vs., respectively, $p < 0.001$), with 6 (12.5%) patients showing a TSH outside normal range, while fT4 decreased [1.1 ng/dl (IQR 1.0–1.2) vs. 1.2 ng/dl (1.1–1.4), respectively, $p = 0.047$]. In deep no significant difference of daily LT4 dosage/kg was observed after 6 months on ef-LT4 treatment respect to recruitment ($p = 0.719$) (Table 1).

Moreover, for 31 patients (65% females) serum TSH and FT4 values were available 12 month after the therapeutic switch (Fig. 1). In detail, a significant increase of a serum TSH levels was observed along the study spam (2.50 ± 0.9 mIU/ml on e-LT4 at recruitment vs. 3.2 ± 0.9 mIU/ml on ef-LT4 after 6 months and 3.5 ± 0.9 mIU/ml after 12 months, $p < 0.001$) (Fig. 1a). In the same way, fT4 levels decreased [1.2 ng/dl (IQR 1.1–1.4) vs. 1.1 ng/dl (IQR 0.9–1.3) and 1.0 ng/dl (IQR 0.9–1.1), $p = 0.008$] (Fig. 1b). Again, no significant difference of daily LT4 dosage/kg was observed during the study spam (1.4 ± 0.3 µg/kg at recruitment vs. 1.4 ± 0.3 µg/kg after 6 months vs. 1.4 ± 0.4 µg/kg after 12 months, ($p = 0.999$). Finally, we divided the patients based on their baseline TSH levels to analyze the real impact of the absorption rate in two groups: patients with TSH ≤ 2.5 mIU/ml (Group 1) and Group 2 with TSH > 2.5 mIU/ml (Table 2). Specifically, both Group 1 and Group 2 showed a significant worsening of TSH levels after the switch ($p < 0.001$).

In addition, we enrolled in the same period 49 (67% female) ce-LT4 and 48 (63% female) cef-LT4 patients to verify potential bias due to the producer declared instability of glycerol used in both formulations; the control groups are matched based on TSH levels ($p = 0.999$). All the patients taking the same formulation at the same dosage for a superimposable time. No significant differences of serum TSH levels were observed both in ce-LT4 (2.5 ± 0.8 mIU/ml vs. 2.7 ± 0.7 mIU/ml, $p = 0.833$) and cef-LT4 (2.5 ± 0.7 mIU/ml vs. 2.6 ± 1.7 mIU/ml, $p = 0.919$) patients along the study spam.

Discussion

Levothyroxine replacement therapy is experiencing worldwide growth, particularly in the United States and Europe, especially among the elderly population [22]. Despite its widespread use, cross-sectional surveys of patients taking levothyroxine have shown that between 40 and 48% are either over-treated or under-treated [9, 10, 23]. Many explanations can be given for this. Firstly, numerous conditions are known to interfere with LT4 absorption by primarily affecting gastric pH, particularly with tablets [21]. In fact, LT4 absorption mainly occurs in the jejunum and ileum [24], and studies on LT4 tablets have shown that its absorption is maximal when the stomach is empty, demonstrating the key role of gastric

Table 1 Serum TSH, fT4 levels and LT4 dosage/Kg during the study spam

	e-LT4 (−12 months) (A)	e-LT4 (at recruitment) (B)	ef-LT4 (after 6 months) (C)	*p*			
N	48	48	48	A vs. B vs. C	A vs. B	A vs. C	B vs. C
LT4 dosage/kg	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	0.348	0.999	0.449	0.719
TSH (mIU/ml)	2.4 ± 0.8	2.5 ± 0.8	3.1 ± 1.0	< .001	0.586	< .001	< .001
fT4 (ng/dl)	1.2 (IQR 1.1–1.4)	1.2 (IQR 1.1–1.4)	1.1 (IQR 1.0–1.2)	0.077	0.999	0.071	0.047

One-way repeated measures ANOVA and Bonferroni post-hoc test or Friedman and Dunns post-hoc tests as appropriated

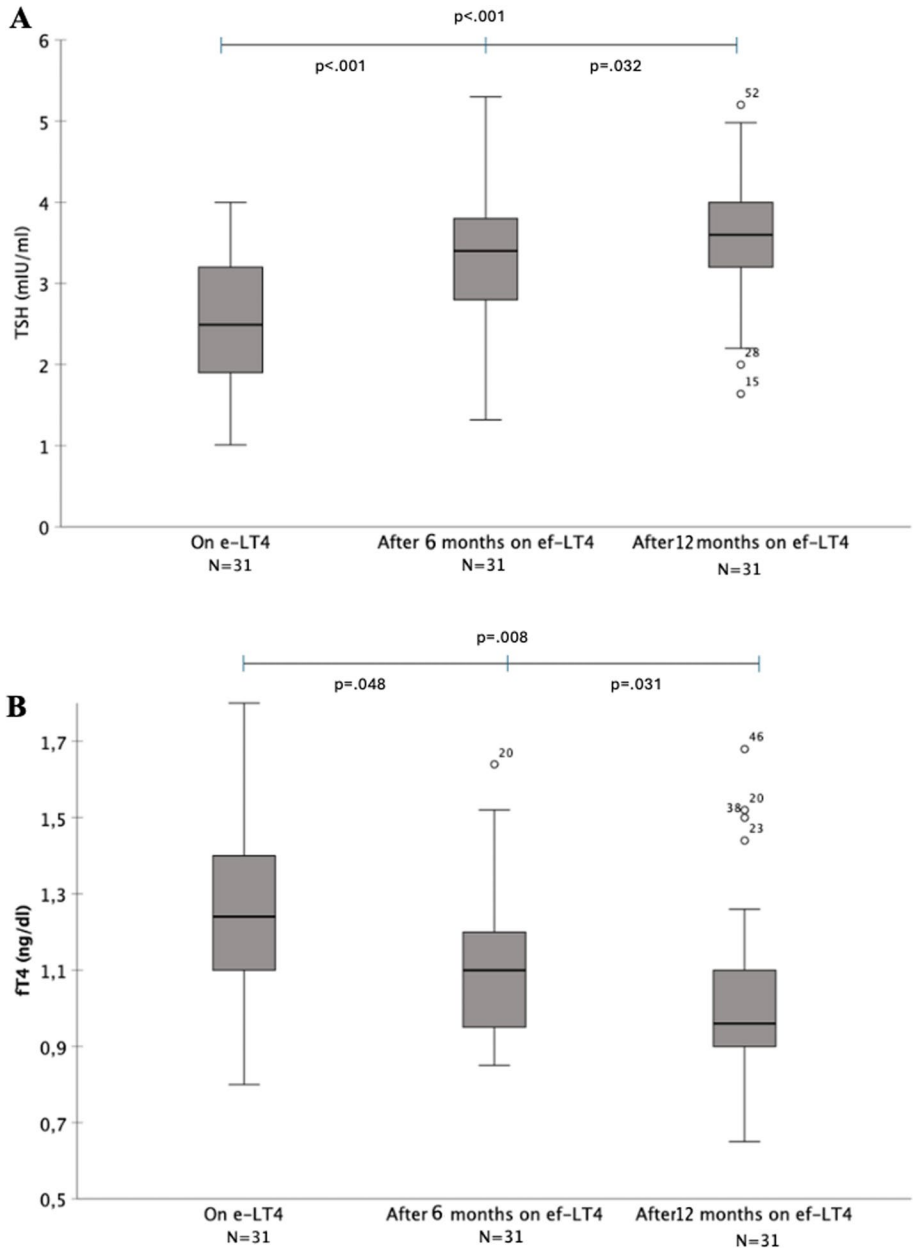

Fig. 1 TSH (**a**) and fT4 (**b**) values of 31 patients at enrollment, 6 months and 12 months after the switch from e-LT4 to ef-LT4. Results of One-way repeated measures ANOVA and Bonferroni post-hoc test or Friedman and Dunns post-hoc tests as appropriated

acidity in this process [15, 21]. Hence, patients with gastrointestinal disorders such as coeliac disease, *Helicobacter pylori* infection, and atrophic gastritis, or those with jejunoileal bypass surgery, require higher daily doses of LT4 [21]. The same has been shown for food and drugs such as coffee, dietary fiber, proton pump inhibitors, calcium carbonate, and ferrous sulfate supplementation [21]. In agreement, ATA Guidelines suggest taking LT4 in a fasting state in the morning or at bedtime, away from interfering drugs [5].

The therapeutic environment has changed with the advent of novel formulations in recent years. Several studies have demonstrated that novel formulations containing ethanol can circumvent the LT4 malabsorption issue [15]. Moreover, it is well known that patients on therapy with novel formulations have a better quality of

Table 2 Serum TSH, fT4 levels and LT4 dosage/Kg during the study spam according to baseline TSH levels

		e-LT4 (at recruitment) (A)	ef-LT4 (after 6 months) (B)	ef-LT4 (after 12 months) (C)	*p*			
N		31	31	31	A vs. B vs. C	A vs. B	A vs. C	B vs. C
LT4 dosage/kg	TSH ≤ 2.5 mIU/ml *N* = 15	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	0.754	0.719	0.682	0.813
	TSH > 2.5 mIU/ml *N* = 16	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	0.824	0.892	0.806	0.759
TSH (mIU/ml)	TSH ≤ 2.5 mIU/ml *N* = 15	1.8 ± 0.4	2.0 ± 0.5	3.1 ± 1.1	< 0.001	< 0.001	< 0.001	0.004
	TSH > 2.5 mIU/ml *N* = 16	3.2 ± 0.5	3.3 ± 0.6	3.7 ± 0.7	0.032	0.071	0.009	0.014
fT4 (ng/dl)	TSH ≤ 2.5 mIU/ml *N* = 15	1.3 (IQR 1.2–1.4)	1.2 (IQR 1.1–1.3)	1.2 (IQR 1.1–1.3)	0.053	0.065	0.042	0.063
	TSH > 2.5 mIU/ml *N* = 16	1.2 (IQR 1.0–1.3)	1.1 (IQR 1.0–1.3)	1.0 (IQR 0.9–1.2)	0.034	0.032	0.021	0.047

One-way repeated measures ANOVA and Bonferroni post-hoc test or Friedman and Dunns post-hoc tests as appropriated

life [18], partly due to the possibility of taking the therapy with breakfast [14], which improves adherence. Many drops make an ocean, and the future challenge is represented by tailored therapy. However, we are still far from the possibility of administering the right dosage to the right patient, although the dream is becoming more attainable [6].

Indeed, a novel ethanol-free formulation has been commercialized with a wide range of intermediate dosages, making the administration of effective therapy easier. Taking in account the clinical data suggesting the superiority of e-LT4 compared to tablets [11–13, 16, 17, 19, 20, 25–28], it is reasonable to think the same might apply to ethanol-free LT4 (ef-LT4). However, to the best of our knowledge, no non-inferiority study between e-LT4 and ef-LT4 has been conducted. Indeed, only two studies have compared liquid ethanol-free formulations to tablets with discordant results [29, 30].

Bornikowska et al. showed in a single-site study that taking ef-LT4 provided higher efficacy, a better thyroid hormone profile, and a greater improvement in quality of life [29]. The TSH profile was similar between the two groups (ef-LT4: 1.71 vs. Tablets: 1.64 mIU/L, $p = 0.773$, respectively), but fT4 levels were higher (15.96 vs. 14.13 pmol/L, $p < 0.001$, respectively) [29]. Conversely, Markantes et al. in a prospective randomized crossover phase III study showed that ef-LT4 is therapeutically equivalent to tablets [30].

On the contrary, many studies have investigated TSH levels by switching LT4 tablet to e-LT4. The meta-analysis by Virili et al., mainly obtained from studies enrolling patients with known causes leading to LT4 malabsorption, showed that the pooled mean difference of TSH value between tablet LT4 and e-LT4 formulation was −4.23 mIU/L ($p < 0.0001$) [13]. Based on these data, it is reasonable to speculate that e-LT4 is superior to ef-LT4 in terms of hormonal profile.

Our data, even if obtained in a small set of patients, are the first suggesting that ef-LT4 is less effective than e-LT4 after 6 and 12 months from the switch. The deterioration appears to worsen over time (Fig. 1). If this data were to be validated in larger prospective studies, how can we explain it? In other words, the possible open-label questions are: why might ethanol-free formulations have reduced absorption? Can ethanol play a fundamental role in the absorption of LT4? Indeed, ethanol is a widely used pharmaceutical excipient in oral formulations, serving as a co-solvent that increases the solubility of poorly soluble drugs [31]. Ethanol stimulates gastric acid secretion, increases mucosal and microvascular permeability in the small intestine, and reduces the motility of the small intestine through its direct effect on the muscular intestinal layer and its toxic effect on the vagus nerve [31]. Thus, it is reasonable to think that ethanol can improve LT4 absorption, and it is plausible that the capability to circumvent malabsorption is mediated precisely by ethanol. On the other hand, many patients dislike the presence of ethanol, at least for palatability, because of the taste it imparts, as well evidenced by Guglielmi et al. in 10.7% of patients [18]. This was also the reason why the enrolled patients decided to switch from e-LT4 to ef-LT4. Palatability studies on ef-LT4 are needed.

This study has a few limitations, including its retrospective nature, and the relatively small patient cohort. Nevertheless, the data provide a real-life experience from a tertiary level Thyroid Unit with extensive experience in LT4 treatment, primarily using the liquid formulation

[11, 12, 14, 16, 17, 32, 33]. Importantly, the data obtained at 12 months of ef-LT4 treatment confirmed and highlighted the increasing TSH trend. Secondly, we cannot exclude that the TSH increase is due to a thyroiditis worsening reducing the residual function. Long longitudinal studies performed in athyreotic patients are needed to investigate this issue. Finally, during the study period, the shelf life of ef-LT4 and e-LT4 was shortened from 18 months to 5 and 7 months, for a potential instability of the glycerol used in the formulations. However, the producer supplied the pharmacies, which distributed the drug on a limited basis to ensure it was consumed before its expiration date. Therefore, the data we reported should not be affected by this possible bias, as also demonstrated in the control groups.

Conclusion

Ethanol-free LT4 formulation seems to be less effective compared to ethanol containing LT4 over time. However, further prospective cross-sectional studies, performed in large sets of patients, even on concomitant therapy with interfering drugs, are needed. We suggest promptly checking serum TSH if a patient switches from e-LT4 to ef-LT4.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
EG: Writing—Original Draft; VM: Material preparation, data collection and analysis; IP: Writing—Review & Editing; EG: Writing—Review & Editing; IS: Material preparation, data collection and analysis; MU: Material preparation, data collection and analysis; RM: Writing—Review & Editing; CC: Writing—Review & Editing, supervision; CC: study conception and design, supervision, Writing—Review & Editing. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

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