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Liquid and softgel capsules of l-thyroxine results lower serum thyrotropin levels more than tablet formulations in hypothyroid patients

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ABSTRACT

Objective: Evidence indicates that L-T4 in liquid and softgel capsule are absorbed better than tablets in hypothyroid patients, even when patients are under medications that impair the intestinal absorption of L-T4. However, no study has evaluated all three L-T4 formulations in the same hypothyroid patients. This study aims to fill this gap. The outcome was the degree of TSH change in the liquid and softgel formulations, using tablet L-T4 as the reference, regardless of sequence of formulation and regardless of whether patients were co-ingesting with interfering medications.

Methods: We recorded serum TSH levels in two groups of L-T4 replaced patients with primary hypothyroidism (23 subjects who did not co-ingest interfering medications, and 20 subjects who did). Either group of patients took one formulation of L-T4 at a time with variable sequences. In the first group, the median durations of exposure to tablet, liquid or softgel L-T4 were 14, 9 and 10 months, respectively. In the second group the corresponding durations were 13, 11 and 10 months, during which patients co-ingested interfering medications.

Results: In the 23 patients, there were 78, 74 or 101 TSH determinations during liquid, softgel capsule or tablet L-T4 regimens. Serum TSH levels associated with liquid, capsule or tablet L-T4 were 1.62 ± 0.51 , 1.77 ± 0.44 mU/L ($P = 0.049$ vs liquid) or 2.38 ± 0.69 mU/L ($P < 0.0001$ vs liquid or capsule). Rates of TSH ≤ 2.50 mU/L were 97.4% (liquid), 95.9% (softgel) or 64.4% (tablet, $P < 0.0001$ vs liquid or capsule). Rates of TSH ≤ 4.12 mU/L were 100%, 100% or 98.0%.

In the 20 patients, the corresponding TSH determinations were 56, 57 and 41, and corresponding TSH levels were 2.74 ± 0.98 , 2.70 ± 0.79 or 7.53 ± 2.82 mU/L. Rates of TSH ≤ 2.50 mU/L were 51.8% (liquid), 47.4% (capsule, $P = 0.64$) or 2.4% (tablet, $P < 0.0001$ vs liquid or capsule). Rates of TSH ≤ 4.12 mU/L were 92.8% (liquid), 94.7% (capsule, $P = 0.68$) or 12.2% (tablet, $P < 0.0001$ vs liquid or capsule).

Conclusions: L-T4 ingested as liquid solution or softgel capsule is more bioavailable compared to L-T4 ingested as tablet, and it is slightly superior to capsule L-T4 only in the absence of co-ingestion of interfering medications.

Introduction

Levothyroxine (L-T4) is the recommended replacement thyroid hormone for both primary and central hypothyroidism [1]. The overwhelming majority of hypothyroid patients are treated with the classic L-T4 formulation, the tablet. Approximately 20% of patients with primary hypothyroidism [1,2] and approximately 40% of patients with central hypothyroidism [2] are undertreated. Relatively frequent reasons for undertreatment are inappropriate ingestion of tablet L-T4 with food or shortly after a meal (almost always at breakfast), ingestion with certain beverages, or impaired intestinal absorption caused by

medications [1–3]. In primary hypothyroidism, undertreatment is revealed by increased serum levels of TSH despite therapy [1–3]. In central hypothyroidism, whose monitoring is based on serum levels of free T4 (FT4) rather than TSH, undertreatment is revealed by serum FT4 levels that remain below the midnormal range value for the assay used [2,4].

There is abundant evidence showing that under the said dietary, pharmacologic or digestive system-associated conditions of undertreated primary hypothyroidism, switch from the tablet to either liquid or softgel capsule (so-called novel formulations) normalizes serum TSH levels [2,3,5–19]. Evidence for lower TSH levels, in both replacement

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and TSH-suppressive settings, under the novel formulations compared to the tablet formulation has also been obtained in the absence of those conditions [20–28] and, for sake of completeness of information, in central hypothyroidism [29]. All this evidence stems from the more favorable pharmacokinetics profile of the two novel formulations compared to the tablet formulation [3,30–32].

We are unaware of studies on hypothyroid patients, as opposed to healthy volunteers, who were exposed to all three formulations at different times so as to fairly evaluate which novel formulation was associated to lower TSH levels compared to the tablet. Thus, we wished to perform this study, and elected to run it in two different types of patients: one not co-ingesting interfering drugs, and one co-ingesting such drugs.

Patients and methods

As the Italian group who started and continue testing the possible benefit of the novel formulations of L-T4 compared to the classic tablet formulation in real-life settings [5,8–15,33], a number of hypothyroid patients are referred to us for undertreated primary hypothyroidism while under tablet L-T4 or for beginning replacement therapy if other physicians plan to prescribe medications known to impair the intestinal absorption of L-T4 or to otherwise affect TSH levels (e.g., corticosteroids, carbamazepine). Upon explanation of a summary of the literature on the novel formulations [see Introduction] and discussion with the patients, either type of patients is left free to choose between the oral solution and the softgel capsule L-T4. Since 2012, the oral solution is available in predosed ampoules of various strengths, all containing L-T4 in a 1.0 ml solution made of 95% ethanol and 86% glycerol. A few years later, capsules of different strengths were marketed in Italy. The soft gel capsule contains L-T4 dissolved in 86% glycerol that is coated with a gelatin shell. Both formulations are produced and marketed by IBSA Farmaceutici Italia Srl, the Italian branch of IBSA Institut Biochimique, Lugano, Switzerland. Brand-name was also the tablet formulation (either IBSA or Merck Serono, Rome, Italy).

To run this prospective study, we took advantage of the said availability of hypothyroid patients at our center. We also took advantage from the fact that, after the softgel capsule was marketed in Italy following the oral liquid solution, some patients found more practical to switch from the oral solution (which initially had replaced the tablet) to the softgel capsule. Basically, some patients preferred to avoid the inconvenience of breaking the vial containing the liquid solution, squeeze it thoroughly in a glass containing water, stir and then swallow. Other reasons for preferring initially the capsule over the oral solution or for switching to the capsule from the oral solution were the more recent introduction in the market (which patients interpreted as indicating more advanced technology), the absence of ethanol, the smaller package or the temporary unavailability of the liquid solution in local pharmacies.

Other patients, who initially had opted for the capsule, then opted for the liquid formulation. Reasons to switch from the softgel to the liquid formulation were that only the latter is fully reimbursed by the Italian health system, or the temporary unavailability of the capsule in local pharmacies. The lack of reimbursement of the softgel capsule and the temporary unavailability of either novel formulation in local pharmacies were reasons for return to the tablet.

In brief, we had the possibility of having patients taking, at different times, each of the three formulations of L-T4, and in variable sequence.

In line with previous studies by our group [5,8–15,33], to form the final cohort of 43 patients described here (not co-ingesting [$n = 23$; 18 women and 5 men] or co-ingesting [$n = 20$; 16 women and 4 men] medications that interfere with the intestinal absorption of L-T4), we requested to maintain the daily dose of L-T4 and the same local laboratory for measurement of serum TSH. This daily dose of L-T4 was 96 and 107 μg in the 23 and 20 patients, respectively. We requested a minimum of two TSH measurements under each formulation. The first

measurement of TSH following each switch occurred 6–8 weeks after each transition. Again as per previous studies, for patients who were under medications impairing the intestinal absorption of L-T4, we requested that such medications continued to be taken at the same dose and interval from L-T4. For this last group of patients, frequent contacts over the phone with the family physicians ensured that such consistency was maintained throughout the follow-up. When starting the first formulation of L-T4, age of the 23 patients was 34–72 years (54.0 ± 11.7 [median = 55]) in the 23 patients, and 33–74 years (59.4 ± 10.9 [median = 61]) in the 20 patients.

In both the 23 patients and the 20 patients, the outcome was the degree of TSH change in the liquid and softgel formulations, using tablet L-T4 as the reference, regardless of sequence of formulations.

Statistics

Continuous variables are presented as mean \pm SD, and median. Differences between means were handled by the two-tailed Mann-Whitney test due to the nongaussian distribution of serum TSH. Categorical variables are presented as proportions (%), and their differences handled by the two-tailed χ^2 or Fisher's exact test. Per previous studies by our group [5,8–15,33], proportions were % TSH levels considered to be target levels, viz. ≤ 2.50 mU/L or ≤ 4.12 mU/L.

P values below 0.05 were considered to be statistically significant, while P values between 0.05 and 0.10 were considered to be borderline significant.

Results

Patients under no interfering medications

Individual data are shown in Fig. 1. Six patients (26.1%) had overlapping TSH levels with any formulation. In the remaining 17 patients, the tablet lagged behind either novel formulation by being associated with the highest serum TSH levels. Particularly, 11 patients showed similar TSH levels upon comparing the liquid with the softgel capsule formulation (1.77 ± 0.52 vs 1.85 ± 0.47 mU/L, $P = 0.45$). All other 6 patients, had lower TSH levels under the liquid L-T4 than under the softgel L-T4 (1.30 ± 0.45 vs 1.76 ± 0.43 mU/L, $P = 0.0039$). In brief, disregarding tablet L-T4, 17 patients (73.9%) had similar TSH levels under either novel formulation, while the remaining 6 (26.1%) had lower TSH levels under the liquid L-T4.

Aggregate data are summarized in Table 1, with details for the sequence groups given in Supplementary Tables 1 and 2. Regardless of sequence in L-T4 formulations, the highest TSH levels were associated with the tablet. In each of the five sequence groups, TSH levels never differed significantly between the two novel formulations. However, when the five groups were pooled making possible to compare a large number of TSH determinations, then the liquid formulation-associated TSH levels were barely significantly greater than the capsule counterpart (1.62 ± 0.51 vs 1.77 ± 0.44 mU/L, $P = 0.049$) (Table 1).

For the clinical purpose of the daily practice, in Table 1 it is more relevant to look at the proportions of serum TSH levels ≤ 4.12 mU/L. Almost all TSH levels associated with the tablet (98.0%) adhered to this threshold, not significantly different from all TSH levels associated with the tablet or the capsule (100%). Two-thirds of the serum levels of TSH measured while under the tablet (64.4%) adhered to the threshold of ≤ 2.50 mU/L, significantly less than almost 100% of the TSH levels under other the solution (97.4%) or the capsule (95.9%).

Patients under medications interfering with L-T4 intestinal absorption

Individual data are shown in Fig. 2. Among the 13 patients who took all three formulations, none had overlapping serum TSH. Indeed, tablet L-T4 lagged behind either novel formulation. Upon comparing the solution with the capsule, similar levels of TSH were observed in 10

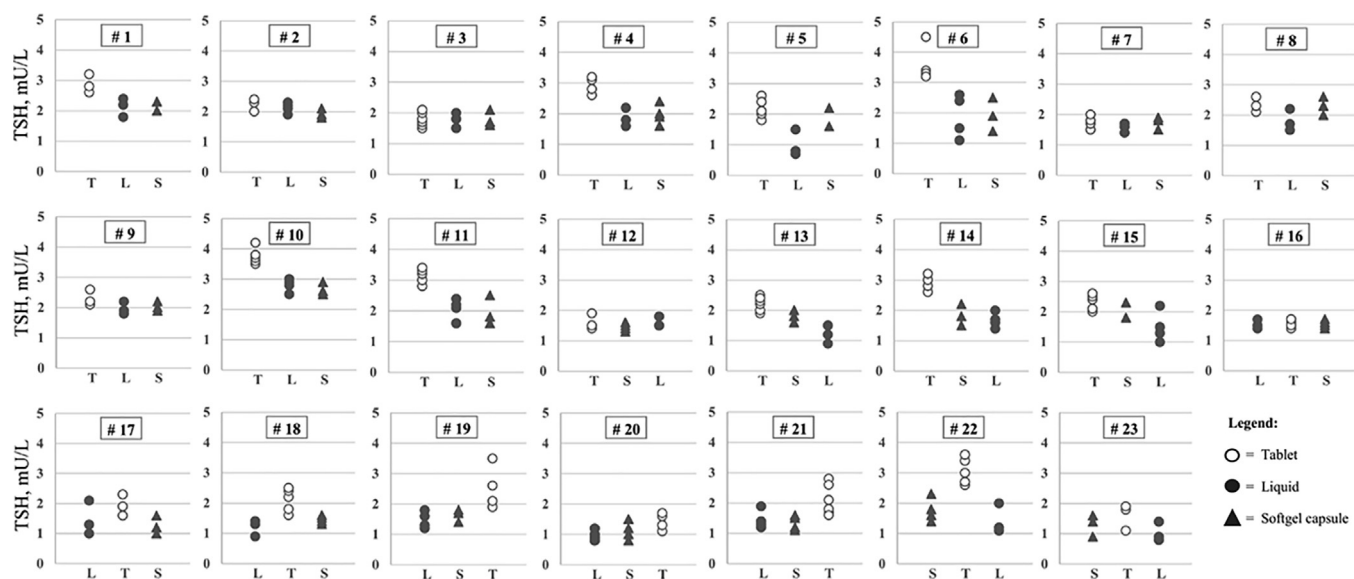


Fig. 1. Serum TSH levels in 23 hypothyroid patients under the three formulations of L-T4 (each at a different time) and who were not simultaneously taking medications known to interfere with the intestinal absorption of L-T4 or anyhow affect serum TSH levels. For details, see [Tables 1 and 2](#). Note that cases no. 2, 3, 7, 12, 16 and 23 had similar TSH levels with any of the three formulations. In cases no. 1, 4, 6, 9, 10, 11, 14, 17, 18, 19 and 21, serum TSH levels were similar under liquid or softgel capsule L-T4. Instead, in cases no. 5, 8, 13, 15, 20 and 22, serum TSH levels were lower under the liquid compared to the softgel capsule formulation. Of the remaining patients, all but two (cases no. 19 and 20) had similar levels of TSH under the two novel formulations. In cases no. 19 and 20, TSH level were lower under the liquid formulation.

patients (2.70 ± 1.13 vs 2.54 ± 0.73 mU/L, $P = 0.54$). In two patients, serum TSH levels were lower under the liquid formulation (2.18 ± 0.51 vs 3.60 ± 0.33 mU/L, $P = 0.035$), while in one patient the opposite occurred. In the 7 patients who took only the two novel formulations, TSH levels were similar (2.98 ± 0.66 [liquid] vs 2.99 ± 0.65 mU/L [capsule], $P = 0.97$), with two exceptions (case no. 19 and 20). In these two patients, TSH levels were lower under the solution than under the capsule (2.07 ± 0.22 vs 2.47 ± 0.28 , $P = 0.046$).

In sum, disregarding tablet L-T4, 16 patients (80%) had similar TSH levels under either novel formulation of L-T4, while 4 (20%) had lower TSH levels under the liquid L-T4. Again, this is in line with the corresponding rates of 73.9% and 26.1% in patients who did not co-ingest interfering medications.

Aggregate data are summarized in [Table 2](#), with details for the sequence groups given in [Supplementary Tables 3 and 4](#). Data are in line with those described above for patients unexposed to inhibitors of the intestinal absorption of L-T4. The highest serum TSH levels, and significantly so when compared with either novel formulation of L-T4, were associated with tablet L-T4. On the other hand, serum TSH associated with liquid L-T4 were superimposable to those associated with softgel L-T4 (2.74 ± 0.98 vs 2.70 ± 0.79 mU/L, $P = 0.81$). Much

greater than these two TSH levels were those associated with tablet L-T4 (7.53 ± 2.82 mU/L), in sharp contrast with the minimal increment of tablet-associated TSH levels compared with either liquid or capsule-associated TSH levels in the patients who did not co-ingest interfering medications ([Table 1](#)). This highlights how sensitive to medication-induced L-T4 malabsorption is tablet L-T4.

Approximately one in 10 TSH assays under tablet L-T4 fell within the threshold of 4.12 mU/L, significantly less than nine in 10 TSH assays under either liquid or softgel L-T4 ($P = 9.6 \times 10^{-17}$ or $P = 6.6 \times 10^{-18}$; [Table 2](#)). Thus, there was no difference between these two novel formulations. The significant difference between tablet and the two novel formulations, and the lack of difference between each of the two novel formulations held upon using the lower threshold of ≤ 2.50 mU/L ([Table 2](#)).

Overall, the data presented herein are congruent with our previous studies [8,10,13] that contrasted the tablet with the liquid formulation. No studies have been run until now on cohorts of patients under medications impairing the intestinal absorption of L-T4 and switched from the tablet to the softgel capsule.

Table 1

Serum TSH levels or proportions of TSH levels adhering to the specified thresholds of target levels in 23 hypothyroid patients under three formulations of L-T4 (each at a different time) and who were under no drug known to impair L-T4 absorption or anyhow affect serum TSH levels.

	Tablet (n = 101)	Liquid (n = 78)	Softgel capsule (n = 74)
m ± SD [median]	2.38 ± 0.69 [2.3] P = 9.6 × 10⁻¹³	1.62 ± 0.51 [1.6] P = 0.049	1.77 ± 0.44 [1.7] P = 2.9 × 10⁻⁹
TSH threshold			
≤ 2.50 mU/L	65 (64.4%)	76 (97.4%)	71 (95.9%)
≤ 4.12 mU/L	99 (98.0%) $\chi^2 = 28.8$, P = 8.0 × 10⁻⁸ , OR = 0.05 [95% CI, 0.01–0.2]	78 (100%) $P = 0.67$, OR = 1.61 [95% CI, 0.3–9.9]	74 (100%) $\chi^2 = 24.6$, P = 7.0 × 10⁻⁷ , OR = 0.08 [95% CI, 0.02–0.3]

For details on groups of patients based on sequence of transition from one formulation to another, see [Supplementary Tables 1 and 2](#).

In the tablet column, comparison is with liquid L-T4, while in the liquid column comparison is with capsule L-T4, and in the softgel capsule column is with tablet L-T4. For comparison of proportions, statistics is by the Fisher's exact test if no χ^2 value appears. P values printed boldface indicate statistically significant difference ($P < 0.05$ minimum).

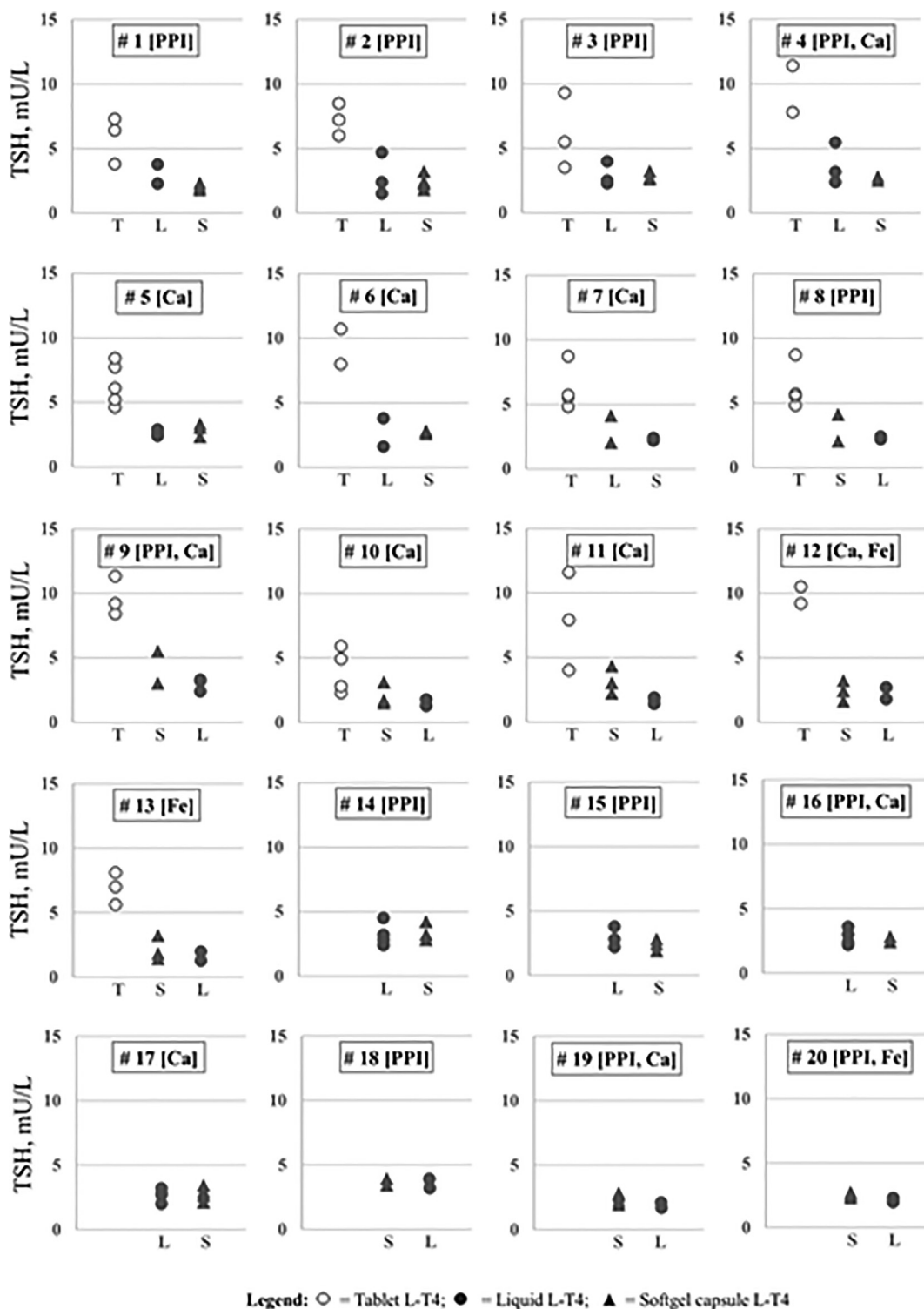


Fig. 2. Serum TSH levels in 20 hypothyroid patients under the three formulations of L-T4 (each at a different time) and who were simultaneously taking medications known to interfere with the intestinal absorption of L-T4. For details, see [Supplementary Tables 3 and 4](#). Note that of the 13 patients who were under all three formulations, 10 (cases no. 1, 2, 3, 5, 6, 7, 8, 10, 12 and 13) had similar TSH levels under the liquid or softgel capsule formulation, while in two patients (cases no. 9 and 11) TSH levels were lower under the liquid formulation, and in one (case no. 4) the opposite occurred. Hence, as observed in the 23 patients not coingesting interfering drugs (Fig. 1), there was no patient with lower TSH levels under softgel L-T4 compared to liquid L-T4.

Discussion

We are unaware of previous studies comparing three formulations of L-T4 in the same hypothyroid patients who were unexposed or exposed simultaneously to medications known to impair the intestinal

absorption of L-T4. Upon enrolling 84 healthy subjects, 4 randomized, 2-treatment, single-dose (600 mcg L-T4), 2-way crossover bioequivalence studies were conducted in order to compare the pharmacokinetics of L-T4 oral solution vs. tablets and soft gel capsules [31]. All three pharmacokinetics indices (area-under-the-concentration-time-curve

Table 2

Serum TSH levels or proportions of TSH levels adhering to the specified thresholds of target levels in 20 hypothyroid patients under three formulations of L-T4 (each at a different time) and who were coingesting one or more drugs known to impair L-T4 absorption.

m ± SD [median]	Tablet (n = 41) 7.53 ± 2.82 [7.8] P = 1.5 × 10⁻¹⁴	Liquid (n = 56) 2.74 ± 0.98 [2.5] P = 0.81	Softgel capsule (n = 57) 2.70 ± 0.79 [2.6] P = 5.0 × 10⁻¹⁵
TSH threshold			
≤ 2.50 mU/L	1 (2.4%) P = 3.1 × 10⁻⁸, OR = 0.02 [95% CI, 0.003–0.2]	29 (51.8%) $\chi^2 = 0.22$, P = 0.64, OR = 1.19 [95% CI, 0.6–2.5]	27 (47.4%) P = 2.3 × 10⁻⁷, OR = 0.03 [95% CI, 0.004–0.2]
≤ 4.12 mU/L	5 (12.2%) P = 9.6 × 10⁻¹⁷, OR = 0.01 [95% CI, 0.003–0.04]	52 (92.8%) P = 0.72, OR = 0.72 [95% CI, 0.1–3.4]	54 (94.7%) P = 6.6 × 10⁻¹⁸, OR = 0.008 [95% CI, 0.002–0.03]

For details on groups of patients based on sequence of transition from one formulation to another, see [Supplementary Tables 3 and 4](#).

In the tablet column, comparison is with liquid L-T4, while in the liquid column comparison is with capsule L-T4, and in the softgel capsule column is with tablet L-T4. For comparison of proportions, statistics is by the Fisher's exact test if no χ^2 value appears. P values printed boldface indicate statistically significant difference (P < 0.05 minimum).

[AUC], maximum concentration or peak [C_{max}], and time of maximum concentration [T_{max}]) were in favor of the liquid solution. Indeed, AUC_{0-48h} was 1862 ± 439 vs 1752 ± 445 (capsule) vs 1632 ± 424 ng * h/ml (tablet), C_{max} was 71.4 ± 16.0 vs 68.0 ± 15.9 vs 67.6 ± 20.9 ng/ml, and T_{max} 1.96 ± 1.07 vs 2.38 ± 1.58 vs 2.25 ± 0.99 h [31]. Because of the extreme sensitivity of serum TSH to small changes in circulating T4 (a hormone with an half-life of 7 days) and because of the daily ingestion of L-T4, the average 14% or 7% greater AUC_{0-48h} associated with liquid or capsule L-T4 compared to tablet L-T4 [31] (averages that one can assume would occur daily in L-T4 replaced hypothyroid patients) would translate into decreases in serum TSH having the greatest magnitude under a liquid L-T4 replacement regimen and the lowest magnitude under a tablet L-T4 replacement regimen. The average 6.3% greater AUC_{0-48h} associated with liquid L-T4 compared to softgel L-T4 (averages that one can assume would occur daily in L-T4 replaced hypothyroid patients) might translate into decreases in serum TSH having greater magnitude under liquid L-T4 compared to softgel capsule L-T4.

While our study indicates that, in the aggregate, liquid and softgel capsule L-T4 appear to be comparable in patients with primary hypothyroidism under replacement therapy regardless of co-ingesting medications that impair the intestinal absorption of L-T4, nevertheless one-fourth to one-fifth of these patients show better absorption of liquid L-T4 compared to softgel L-T4.

As it can be easily deduced upon comparing [Table 1](#) with [Table 2](#), [Supplementary Tables 1 and 2](#) with [Supplementary Tables 3 and 4](#), and [Fig. 1](#) with [Fig. 2](#), the two novel formulations are not totally refractory to the impaired L-T4 absorption exerted by certain medications. The 56 TSH determinations associated with liquid L-T4 in the interfering drugs-exposed patients averaged 2.74 ± 0.98 mU/L, significantly greater than 1.62 ± 0.51 mU/L of the 78 TSH determinations associated with liquid L-T4 in the unexposed patients. Also, in the first group of patients the proportion of TSH levels ≤ 2.50 mU/L was significantly lower than in the second group (51.8% vs 97.4%). Similar considerations apply to the TSH levels associated with the softgel formulation (2.70 ± 0.79 vs 1.77 ± 0.44), with 47.4% vs 95.9% rates of TSH levels ≤ 2.50 mU/L.

The increase of serum TSH, even within the normal reference range, caused by co-ingestion of medications impairing the intestinal absorption of L-T4 is not a trivial issue. Recently, in a study on 50 postmenopausal women under replacement therapy with tablet L-T4 [14], the subsequent supplementation with calcium carbonate (taken 2 h after L-T4) caused serum TSH to increase from 1.93 ± 0.51 to 3.33 ± 1.93 mU/L (P < 0.001) over a follow-up period of 2.3 ± 1.1 years. Paralleling this increase, and line with the literature summarized in Ref. [14], there was a significant increase (P < 0.001) in total cholesterolemia (CHOL), fasting glycemia (FG), systolic blood pressure (SBP) and diastolic blood pressure (DBP). In the 9 women with

calcium-induced tablet L-T4 malabsorption (based on TSH levels that increased above 4.12 mU/L), the elevation of TSH, CHOL, FG, SBP and DBP was of greater magnitude than in the whole group of 50 women. In parallel, there were significant increases in CHOL, SBP and DBP. It was estimated that, for every 1.0 mU/L increase in serum TSH within the range of 0.85–6.9 mU/L, CHOL, FG, SBP and DBP increased by 12.1 mg/dl, 3.12 mg/dL, 2.31 mmHg, and 2.0 mmHg, respectively [14].

In summary, in line with previous literature [2,3,5–33], our data point to greater bioavailability of the L-T4 ingested as oral solution or softgel capsule compared to L-T4 ingested as tablet. Such greater bioavailability is appreciable even when the intestinal absorption of L-T4 is challenged by the ingestion of certain medications (proton pump inhibitors, calcium salts, iron salts). In line with a study on healthy volunteers [31], the oral solution is slightly better absorbed than the softgel capsule.

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Disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcte.2019.100204>.

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