Oral L-thyroxine liquid versus tablet in patients submitted to total thyroidectomy for thyroid cancer (without malabsorption): a prospective study.

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Running title: Liquid L-T4 in thyroid cancer patients.

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Funding: The authors have nothing to declare.
Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract

Objective. No consistent data are present in literature about the effectiveness of Levothyroxine (L-T4) liquid formulation in patients without malabsorption after thyroidectomy. The aim of this study is to compare the effectiveness of L-T4 liquid formulation, with L-T4 tablets, in thyroid cancer patients after thyroidectomy (without malabsorption or drug interference).

Methods. One hundred-five patients were recruited; 52 patients were treated with liquid L-T4 formulation, while 53 with L-T4 tablets, at the same dosage (1.5 mcg/kg/day). Patients started to assume the drug the day after surgery, 30 min before breakfast. In both groups circulating levels of thyrotropic hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were dosed at week 6 (1^{st} control), and then at week 12 (2^{nd} control).

Results. We obtained significantly lower TSH values in the liquid L-T4 group patients, compared to the tablet L-T4 group, at the 1^{st} control ($P<0.05$), and at the 2^{nd} control ($P<0.01$), while FT4 and FT3 levels were not significantly different. Hypothyroid range (TSH>3.6 mcU/mL) was significantly more prevalent in the patients treated with L-T4 tablet.

Conclusions. A better control of TSH was observed in thyroidectomized patients (without malabsorption, gastric disorders, or drug interference) with liquid L-T4 regimen.

Keywords: liquid L-T4, thyroid cancer, total thyroidectomy, TSH, thyroxine absorption

Level of evidence: NA

Introduction

Hypothyroidism is a widespread clinical entity especially among middle-aged and elderly people, and it is well treated with Levothyroxine (L-T4) [1,2].

After an adequate low pH-dependent melting process in the gastric environment, the L-T4 tablets, when given per os, are mainly (70%) absorbed by duodenum, jejunum and ileum [3,4].

Several gastro-intestinal diseases and swallowed substances can interfere with the correct L-T4 absorption [5], as for example: lactose intolerance, intestinal parasitic diseases, *Helicobacter pylori*-associated gastritis, autoimmune gastritis or presence of parietal cells autoantibodies, celiac disease, bariatric surgery, and coffee [6-10].

Beyond the classical tablet form, nowadays new formulations of thyroxine, such as soft gel capsule and oral solution, can be prescribed.

Several studies have demonstrated that we could reach, in both adults and children, higher percent of L-T4 absorption when it is given in liquid solution rather than in solid tablet [11].

Physicians usually attempt to achieve the desired thyroid-stimulating hormone (TSH) range by increasing the L-T4 daily prescription, even in those patients with concomitant factors (drugs, bariatric surgery or coffee consumption) that can alter the L-T4 tablets absorption. In vivo studies have proved how L-T4 oral solution can overcome this malabsorption issue. This new formulation shows to be also proper in patients unlikely to change their routine or with solid dysphagia [12-14].

The liquid formulation has been shown to overcome: 1- the food and beverages interference with L-T4 tablets absorption, caused by food at breakfast [15]; 2- malabsorption induced by the increased gastric pH, resulting from atrophic gastritis, or due to proton-pump inhibitors [16]; 3- malabsorption after bariatric surgery [17]; 4- malabsorption induced by lactose intolerance, or drug interference [18-20].

Finally, liquid L-T4 is more active than tablets in the control of TSH in hypothyroid patients without malabsorption, drug interference, or gastric disorders, leading to hypothesize a higher absorption of liquid L-T4 also in these patients [21,22].

However, until now, to the best of our knowledge, no consistent data are present in literature about the effectiveness of L-T4 liquid formulation in patients immediately after thyroidectomy for thyroid cancer.

The aim of this study is to compare the effectiveness of L-T4 liquid formulation, with L-T4 tablets, in patients operated for thyroid cancer, when absorption impairment or drug interference have been ruled out.

Patients and methods

This is an observational, prospective study, conducted in patients with L-T4 regimen, as substitutive therapy after total thyroidectmy for thyroid cancer, from January 2015 to December 2016.

Inclusion criteria were: a- patients affected by differentiated papillary of follicular thyroid cancer operated for total thyroidectomy [the decision making process for the surgery was made following the Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer (DTC) [23] (Thyr3- Thyr4- Thyr5)] b- age of 18-75 years; c- TSH levels at last control (within 1 month before operation) of 0.5-4 mIU/mL, without L-T4 therapy; d- patients consent to partecipate in the study.

Exclusion criteria were: 1- serious psichiatric disorders; 2- inability to understand the aim of the study and to adhere it; 3- inability to give an acceptable consent; 4- abuse of alchool or drugs; 5-patients in whom histological examination did not confirm the suspicious of thyroid

cancer; 6- allergy or intollerance to the considered drugs; 7- previous neoplasia during therapy in the last 5 years; 8- hepatitis C or B; 9- altered liver function tests; 10- renal impairment [Modification of Diet in Renal Disease (MDRD) < 30 ml/min/1.73 mq]; 11- history of atrial fibrillation or other tachyarrhythmias, coronary artery disease (CAD); 12- severe anemia [haemoglobin (Hb) < 10 gr/dL)]; 13- previous or concurrent atrophic gastritis, *H. Pylori*-associated gastritis, celiac disease, intestinal malabsorption, lactose intolerance; 14- earlier bariatric or intestinal or gastric surgery; 15- pregnancy; 16- concurrent therapy with proton pump inhibitors, or antiacids, beta-blockers, raloxifen, lithium, cholestyramine, interferons, amiodaron, orlistat; 17- urinary iodine > 250 mg/dL.

Other gastrointestinal diseases were assessed in patients to prevent bias in the evaluation of T4 malabsorption: 1- excluding anemia deriving from VitB12 or iron deficiency; well-established uninvestigated dyspepsia, associated with fullness, bloating, or burning; or a combination of these conditions; or diarrhea; 2- evaluating the presence of *H. pylori* antigen in the stool [4]. Patients with positive results were excluded from the study.

The study involved 105 patients, 53 of whom treated with L-T4 in tablets, and 52 with liquid L-T4 (Tirosint® vial, IBSA Farmaceutici Italia), at the same dosage (1.5 mcg/kg/day).

Patients gave consent to take thyroxine on fasting, avoiding meals or drinks apart from water for at least 30 minutes (before breakfast) after L-T4 therapy in tablets or in the liquid formulation. Circulating levels of TSH, free thyroxine (FT4) and free triiodothyronine (FT3) were dosed after 6 weeks (1^{st} control), and 12 weeks (2^{nd} control) from thyroidectomy. The local Ethical Committee accepted the study.

Circulating levels of FT4 (normal range, 0.7-1.7 ng/dL), FT3 (normal range, 2.7-4.7 pg/mL), and TSH (normal range, 0.4-4 mIU/mL) were assessed in all blood samples by electrochemiluminescence immunoassay (Roche Corporation, Indianapolis, IN, USA). The

concentration of each hormone was calculated as a mean of two blood samples collected before assuming the L-T4 daily dose.

Data analysis

Values are given as mean ± SD for normally distributed variables, or as median and [interquartile range; IQR1-IQR3]. For normally distributed variables [age and body mass index (BMI)], one-way ANOVA was used to compare group values. Bonferroni-Dunn test or Fisher PLSD were utilized for post-hoc comparisons on normally distributed variables. For not normally distributed variables (as L-T4 dose, TSH, etc.), Kruskal Wallis test (> 3 groups) or Mann Whitney test (2 groups) were used. χ^2 test was applied to compare proportions.

Results

Among the enrolled patients treated with liquid or tablet L-T4, none were lost at follow-up.

The 105 patients were evaluated both after 6 weeks, and 12 weeks from thyroidectomy [87 females, 18 males; mean age 48 ± 15.7 years; 96 with papillary thyroid cancer, and 9 with follicular thyroid cancer]; without any significant difference in the 2 groups (**Table 1**).

The first evaluation was made after 6 weeks from the initial thyroidectomy (41 ± 5 days), while the second evaluation was made after 12 weeks (85 ± 7 days). Body weight was not significantly changed (BMI, base 24.5 ± 2.8 kg/m^2, 1st control 24.4 ± 2.7 kg/m^2, 2nd control 24.5 ± 2.5 kg/m^2); without any significant difference in the 2 groups.

TSH levels were significantly lower in patients treated liquid L-T4, compared to those treated with the tablet formulation, at the 1st control ($P<0.05$), and at the 2nd control ($P<0.01$) (**Figure 1**). FT4 and FT3 levels were not significantly changed (data not shown). No differences in TSH were reported in patients aged ≤ 50, or > 50 years.

The prevalence of patients in the hypothyroid range (TSH>3.6 mcU/mL) was significantly higher in the L-T4 tablet group (7, 13.5%), with respect to the liquid L-T4 group (1, 1.8%) (P=0.029).

Discussion

These data demonstrate for the first time the effectiveness of liquid L-T4 over the solid form to achieve the desired TSH levels in patient who had undergone total thyroidectomy because of thyroid cancer.

Considering that the drug dosage was the same between both groups, we suppose that the different TSH level could be associated with a higher absorption of L-T4 in the liquid formulation; the underlying mechanisms is not well-known yet [11].

The low pH value of the gastric environment is mandatory for the correct melting of L-T4 tablets and its solubility could be impaired by several factors [19,20,24,25]. Therefore we have recruited patients without malabsorption or gastric diseases, nor drug interference.

Previous analysis established that liquid L-T4 does not require acid dissolution in the stomach but it can directly pass through gut mucosa showing quicker absorption time (area under the curve from 0 to 2 h wider than 50%; time to maximum concentration faster by a mean of 30 min), and overall better pharmacokinetics profile [26-29].

The L-T4 oral solution contains also alcohol, which allows the drug to be delivered directly to the highly vascularized buccal mucosa, and reaching straight the systemic bloodstream bypassing the gastrointestinal tract [30], even if we need more studies to elucidate this process.

Other studies have evaluated liquid L-T4 in patients with thyroid cancer.

A first study evaluated the tolerability and efficacy of a new formulation of liquid L-T4 vs. the previous tablet formulation in 59 patients with cured DTC. Hormonal and clinical evaluations were performed before and 70 days after patients were switched from tablet to liquid L-T4 formulation, without changes in daily dose. No change in TSH, thyroid hormones or thyroglobulin (Tg) was noted during the study [12].

A second study evaluated the TSH variability of patients affected by DTC treated with liquid L-T4 formulation or in tablet form. Patients were randomized (1:1) to receive treatment of hypothyroidism with liquid L-T4 (51 patients) or tablet form (51 patients). The first check-up evaluation was made from 8 to 12 months after 131I remnant ablation. TSH values were established again after further 12 months. A significant increase in TSH levels (median) was observed in patients taking tablets, as compared to those taking liquid formulation. These data suggest that the use of L-T4 liquid formulation, as compared to that of tablets, resulted in a significantly higher number of DTC patients maintaining TSH values in range for the American Thyroid Association (ATA) risk score, reducing TSH variability over the time [31].

However, to the best of our knowledge, this is the first study that evaluated liquid L-T4 in patients with thyroid cancer immediately after total thyroidectomy. Our data show that the use of L-T4 liquid formulation, as compared to that of tablets, resulted in a significantly higher number of DTC patients maintaining TSH values in the normal range after thyroidectomy.

The importance of TSH suppression in general and the degree of suppression in particular in preventing recurrence and adverse clinical events have been taken into account in the recently updated guidelines from the ATA which indicate that in many patients, the serum TSH should be maintained between 0.1 and 0.5 mU/L, taking into account the initial ATA risk classification, Tg level, its trend over the time, and the risk of TSH suppression [32]. However, the potential benefits of reaching the therapeutic goal must always be balanced against

possible adverse effects of subclinical thyrotoxicosis including exacerbation of angina in patients with ischemic heart disease, increased risk for atrial fibrillation in older patients, and increased risk of osteoporosis in postmenopausal women.

In conclusion, on the whole, our data support a better control of TSH values in thyroidectomized thyroid cancer patients (without malabsorption, gastric disorders, or drug interference) in liquid L-T4 regimen, with respect to L-T4 in tablets.

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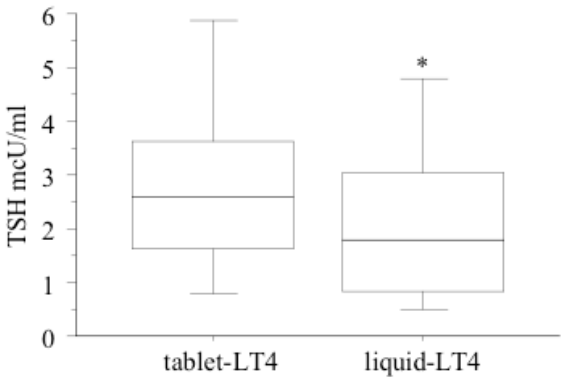
Figure Legends

Figure 1. TSH values were significantly lower in the liquid L-T4 group, compared to the tablet L-T4 group at the 1st control (* = P<0.05) (**Figure 1A**), and at the 2nd control (* = P<0.01) (**Figure 1B**).

Table 1. Demographic data patients treated with liquid L-T4 or tablet L-T4.

	Liquid-LT4	Tablet-LT4	P value
dosage	1.5 mcg/kg/day	1.5 mcg/kg/day	
number	52	53	
female/male	44/8	43/10	0.635
age	49 ± 16.3	47 ± 15.4	0.684
papillary/follicular cancer	49/3	47/6	0.309

A


TSH mcU/ml
6
5
4
3
2
1
0
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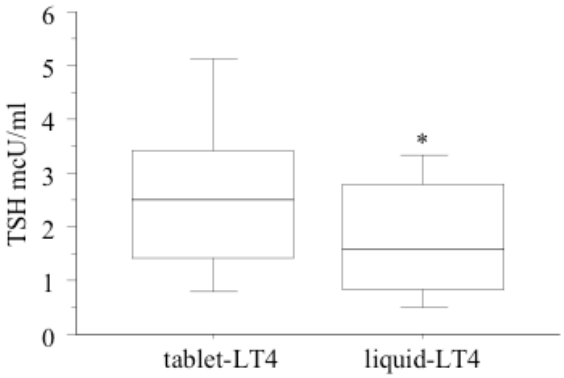
tablet-LT4
liquid-LT4

B


TSH mcU/ml
6
5
4
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tablet-LT4
liquid-LT4

Figure 1