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ENDOCRINE TRIALS

Comparative study between the effects of replacement therapy with liquid and tablet formulations of levothyroxine on mood states, self-perceived psychological well-being and thyroid hormone profile in recently thyroidectomized patients

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Abstract Following thyroid surgery, levothyroxine therapy is used to replace deficient thyroid hormones and prevent postoperative thyroid hypofunction. We compared the effects of replacement therapy with either liquid or tablet formulation of levothyroxine on mood states, self-perceived mental well-being and thyroid hormone profile in recently thyroidectomized patients. Profile of mood states, General Heath Questionnaire 12-items and thyroid hormone profile were assessed in recently (5–7 days) thyroidectomized patients at baseline and 2 months after randomization to replacement therapy with either liquid ($n = 77$) or tablet ($n = 78$) formulation of levothyroxine. After 2 months under levothyroxine replacement treatment, significant improvements of Positive Affect Scale ($p < 0.001$) and Negative Affect Scale ($p < 0.001$) of Profile of mood states, as well as of General Heath Questionnaire 12-items ($p < 0.001$) were observed in the study population. However, there were greater variations observed in patients assigned to liquid levothyroxine formulation in comparison to those who were assigned to levothyroxine in the form of tablet (time × treatment interaction: Positive Affect Scale of Profile of mood states, $p = 0.030$; Negative Affect Scale of Profile of mood states, $p < 0.0001$; General Heath Questionnaire 12-items, $p = 0.003$). As expected, circulating TSH levels significantly decreased ($p < 0.001$) while FT3 and FT4 levels significantly increased ($p < 0.0001$ for both) under levothyroxine replacement therapy. These changes were significantly greater in patients treated with liquid levothyroxine formulation (time × treatment interaction: TSH, $p = 0.011$; FT3, $p = 0.016$; FT4, $p = 0.028$). Our data indicate a greater efficacy of liquid formulation of levothyroxine in ameliorating mood states and self-perception of mental well-being and thyroid hormone profile after 2 months of replacement therapy in recently thyroidectomized patients.

Keywords Thyroid replacement therapy · Mood states · Mental well-being · Insulin resistance

Introduction

Total thyroidectomy is currently the preferred treatment for thyroid cancer, and is increasingly performed also in cases of benign diseases [1]. Indeed, total thyroidectomy has the advantage of reducing/avoiding the risk of disease recurrence and reoperation [1]. In addition, it is safe and associated with a low incidence of lifetime disabilities [1–3].

Following thyroid surgery, thyroid hormone replacement therapy is used to replace deficient thyroid hormones and prevent postoperative thyroid hypofunction [4–6]. The goal of post-thyroidectomy replacement therapy is to restore thyroid function, avoiding oversubstitution and undersubstitution by beginning with an ideal dose of levothyroxine (L-T4) within 7 days after surgery [7]. An optimal thyroid hormone replacement should be able to restore thyroid-stimulating hormone (TSH) concentrations to a normal value, with normal or slightly increased serum

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thyroxine concentration [8]. Some patients experience difficulties in achieving an adequate thyroid hormone profile under replacement therapy [4] and often display significant impairment in psychological well-being [9] and other symptoms suggestive of L-T4 undersubstitution, such as slow speech, depression, weight gain, alertness, insomnia and fatigue [4].

L-T4 is the mainstay used worldwide to replace deficient thyroid hormones [8]. L-T4 is the levorotatory isomer of thyroxine, which is biochemically and physiologically identical to the natural hormone [10]. The classical formulation of L-T4 is a tablet containing a sodium salt of L-T4 together with different excipients [11]. A number of endogenous or exogenous conditions affect the intestinal absorption of L-T4. The former include gastrointestinal diseases [12–15] and gastrointestinal modifications after bariatric surgery [16]. The latter include beverages [17, 18] and drugs [15]. The maximum absorption of L-T4 occurs after the overnight fasting in the morning. The lowest occurs when the drug is taken together with breakfast [19, 20].

Recent evidence has demonstrated a more favorable pharmacokinetic profile of the liquid and soft gel formulations of L-T4 in comparison to the traditional tablet form, allowing better L-T4 absorption [21, 22]. Indeed, these new L-T4 formulations bypass the pH-depending dissolution phase, and are less dependent on the binding with sequestrants in the intestinal lumen [21]. Thus, the liquid formulation of L-T4 is more effective than the tablet formulation in improving thyroid hormone profile independently of the timing of administration with respect to breakfast [23, 24], as well as the presence of potential causes of malabsorption [25, 26]. These pharmacokinetic peculiarities of liquid formulation should allow a more rapid achievement of the condition of euthyroidism in thyroidectomized patients and might favor, therefore, a more rapid return to the state of preoperative health.

Starting from this background, the present study aimed to evaluate whether liquid and tablet formulations of L-T4 could differently influence mood states, self-perception of well-being and thyroid hormone profile in patients undergoing hormone replacement therapy after total thyroidectomy for the management of benign thyroid diseases.

Materials and methods

Patients

A total of 166 consecutive thyroidectomized patients (age >18 and <65 years) from our Endocrine Surgery Unit were enrolled from February 2014 during a recruitment period of 18 months. The participants were selected from among a total of 416 thyroidectomized patients according to the following exclusion criteria: thyroidectomy for thyroid malignancy, presence of clinical conditions associated with an increased demand for L-thyroxine (pregnancy, malabsorption, atrophic gastritis) or concomitant use of drugs that interfere with the pharmacokinetics of L-T4 and thyroid function; presence of psychiatric disorders or other significant comorbidities including heart, brain and kidney diseases, decompensated diabetes mellitus, chronic alcoholism. Enrolled patients were randomized within 5-7 days after the total thyroidectomy to receive L-T4 replacement in liquid or tablet formulation. The dose of L-T4 was individualized on the basis of the body weight of the patients (about 1.6 mcg/kg of body weight per day). The participants received uniform instructions on the daily fasting ingestion of both L-T4 formulations; in particular, participants were informed to take the drug early in the morning, at least 60 min before consumption of any solid and/or liquid food, including coffee [19, 20].

The study was approved by the local Ethics Committee, and written informed consent to participate was obtained from each participant. The study has been registered as EudraCT Number 2013-002139-15.

Study design and outcomes

This was a prospective randomized unicentric trial with blinded assessment of clinical and laboratory data and blinded data analysis (Prospective, Randomized, Open study with Blinded Evaluation of end-points—PROBE). The primary outcome was the measure of changes of the mood states, as assessed by the Profile of Mood States (POMS) questionnaire administered 2 months after initiation of replacement treatment, separately considering the two components of the questionnaire that explore positive affect and negative affect, respectively (explained below). Secondary outcomes were the measure of changes of self-perceived mental well-being (assessed by General Health Questionnaire-12 items—GHQ-12), symptoms/signs of hypothyroidism (assessed by questionnaire ad hoc), thyroid hormone profile and metabolic parameters at 2 months after initiation of L-T4 replacement treatment.

Clinical and laboratory evaluations

All patients, at the time of randomization to one of two replacement treatments of thyroid function and then at 2 months follow-up, underwent a complete clinical evaluation, and blood samplings for the determination of circulating levels of TSH, free T3 (FT3), free T4 (FT4) and metabolic parameters including lipid profile and plasma concentrations of glucose and insulin. Questionnaires to

assess mood states, psychological well-being and clinical symptoms of thyroid hypofunction were also submitted to all the participants at these times.

Measures of mood states, self-perceived mental well-being and symptoms

The POMS is a widely used tool in assessing mood states [27] that has already been validated for Italy [28]. Higher scores reflect mood decrements, except for the vigor subscale, where higher scores reflect improved mood. Taking into consideration the two components characteristic of the POMS that measure negative affect and positive affect, respectively, the data collected with the questionnaire were analyzed both as global score and by separately considering a Negative Affect Scale (NAS-POMS, 48 items, score ranging from 0 to 192) and a Positive Affect Scale (PAS-POMS, 10 items, score ranging from 0 to 40) (Online resource 1).

GHQ-12 is a relevant instrument for measuring psychological well-being [29]. It has been extensively evaluated in terms of validity and reliability as a one-dimensional indicator of the severity of psychological morbidity [30], and it has already been validated for Italy [31] (Online resource 2).

A validated questionnaire was used for monitoring the symptoms of hypothyroidism [32].

Laboratory analysis

Blood samples were drawn from each participant after an overnight fasting period for determining the circulating levels of thyroid hormones, glucose and insulin, and lipid profile. TSH, FT3, FT4 and insulin were measured by COBAS 600 (Electrochemiluminescence Technology, Roche Diagnostics, Mannheim, Germany). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated according to the following formula: fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5.

Statistical analysis

The study was based on an estimated sample size of 200 subjects, with a ratio of 1:1 for the two treatment groups, which has been calculated to be adequate to achieve 90 % power to detect a small effect size (Cohen's *f*: 0.20), and an α of 0.05 for the changes of POMS scores evaluated at 2 months after the initiation of treatment. The prespecified expected duration of enrollment was 18 months; the study was concluded at this time after verification that the enrolled population was enough to warrant a statistical power >80 %. SAS version 9.4 was used to perform statistical analysis. Baseline comparisons between continuous variables were performed with the Wilcoxon rank sum test after evaluation of conformation to normal distribution with the Shapiro-Wilks test. χ^2 test was used to compare categorical variables. To evaluate differences between treatments during time, a two-way repeated-measures analysis of variance with the general linear model procedure was used. Analysis was performed on variables logarithmically transformed to enhance the symmetry of variables. Spearman non-parametric correlation was used to evaluate correlations between variables. If it is not otherwise specified, data are presented as mean ± SD.

Results

Baseline characteristics of study population

Five patients assigned to liquid L-T4 and six patients assigned to tablet L-T4 were lost at follow up due to personal reasons. Thus, the analysis was carried out in 155 patients (77 treated with liquid and 78 treated with tablet L-T4 formulation). The two study groups were comparable with regard to gender, age, anthropometric characteristics, blood pressure levels, thyroid hormone concentrations, and metabolic profile (Table 1). Baseline global POMS score as well as PAS-POMS and NAS-POMS scores were also similar in the study groups (Table 1). Finally, GHQ-12 and symptoms scores were matchable in the two study groups (Table 1). Taken together, these data indicate an adequate randomization procedure.

Measures of mood states, self-perceived mental well-being and symptoms

After 2 months of L-T4 replacement treatment a significant improvement of both PAS-POMS (time effect: $p < 0.001$) and NAS-POMS (time effect: $p < 0.001$) was observed (Fig. 1a, b, respectively). A significant time × treatment interaction for both these parameters was oberved with a greater improvement of these scores in patients assigned to liquid L-T4 formulation (Fig. 1a, b, respectively). A slight but significant (time effect: $p = 0.015$) change of global POMS score was also observed under L-T4 replacement therapy without significant differences between the two treatment groups (-4.4 ± 9.5 for liquid L-T4 and -2.9 ± 9.9 for tablet L-T4, respectively; time × treatment interaction: $p = 0.126$). GHQ-12 score significantly (time effects: $p < 0.001$) improved under L-T4 replacement treatment, with greater changes observed in patients assigned to liquid L-T4 formulation (Fig. 1c). A slight but significant (time effect: $p < 0.001$) change of symptoms score was also observed under L-T4 replacement therapy without significant differences among the two treatment groups (-0.8 ± 0.8 for liquid L-T4 and -0.7 ± 1.0 for tablet L-T4, respectively; time × treatment interaction: $p = 0.700$).

Table 1 Baseline general characteristics of the study participants distinguished according to the treatment assigned

	Liquid L-T4 ($n = 77$)	Tablet L-T4 ($n = 78$)	p value
Gender (m/f)	12/65	12/66	0.973
Age (years)	51.1 ± 13.0	51.1 ± 12.6	0.804
Weight (kg)	71.1 ± 15.1	72.8 ± 15.0	0.396
BMI (kg/m^2)	26.4 ± 4.9	26.4 ± 5.1	0.936
SBP (mmHg)	125.7 ± 10.0	125.5 ± 9.1	0.890
DBP (mmHg)	77.0 ± 6.2	77.9 ± 6.9	0.274
TC (mmol/L)	4.7 ± 0.8	4.8 ± 0.9	0.775
LDL-C (mmol/L)	2.9 ± 0.7	2.9 ± 0.9	0.967
HDL-C (mmol/L)	1.3 ± 0.3	1.2 ± 0.3	0.221
TG (mmol/L)	1.3 ± 0.5	1.4 ± 0.6	0.461
Glucose (mmol/L)	4.8 ± 1.0	4.8 ± 0.9	0.090
Insulin (mU/L)	11.8 ± 8.5	11.6 ± 7.2	0.590
HOMA-IR	2.6 ± 2.4	2.5 ± 1.8	0.556
TSH (μU/mL)	8.6 ± 5.8	7.8 ± 4.2	0.669
FT3 (pg/mL)	2.0 ± 0.6	2.2 ± 0.8	0.253
FT4 (pg/mL)	9.0 ± 3.2	9.4 ± 3.6	0.350
POMS global	43.6 ± 23.4	42.9 ± 25.0	0.819
PAS—POMS	16.5 ± 6.5	17.1 ± 8.5	0.828
NAS—POMS	27.0 ± 23.4	25.8 ± 27.3	0.356
GHQ-12	23.5 ± 4.5	23.0 ± 5.2	0.193
Symptoms scale	2.9 ± 1.2	2.6 ± 1.3	0.411

Plus–minus values are means ± SD

Continuous variables were compared by Wilcoxon rank sum test while χ^2 test was used to compare categorical variables

$p < 0.05$ is considered a statistically significant difference

L-T4 levothyroxine, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *HOMA-IR* homeostasis model assessment–insulin resistance, *TSH* thyroid-stimulating hormone, *FT3* free T3, *FT4* free T4, *POMS* Profile of Mood States, *PAS* Positive Affect Scale of POMS, *NAS* Negative Affect Scale of POMS, *GHQ-12* General Health Questionnaire-12 items

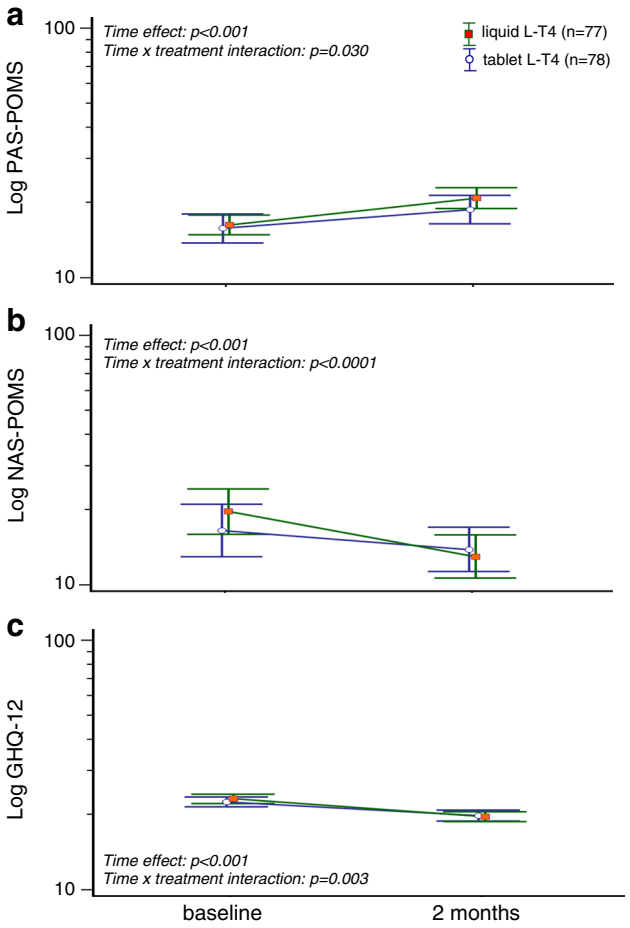

Fig. 1 Changes of the scores of Positive Affect Scale (PAS-POMS, **a**) and Negative Affect Scale (NAS-POMS, **b**) of POMS and General Health Questionnaire-12 items (GHQ-12, **c**) after 2 months under replacement treatment with either liquid or tablet levothyroxine (L-T4) in recently thyroidectomized patients. Data are presented as mean (symbols) and 95 % CI (bars). Differences between treatments were analyzed by two-way repeated measures analysis of variance (ANOVA)

Thyroid hormone profile

After 2 months under L-T4 replacement therapy, TSH concentrations significantly decreased (time effect: $p < 0.001$), whereas FT3 (time effect: $p < 0.0001$) and FT4 (time effect: $p < 0.0001$) concentrations significantly increased (Fig. 2a–c, respectively). A significant time × treatment interaction for all these parameters was observed, indicating a different degree of variation of thyroid hormone profile in the two study groups (Fig. 2a–c).

Anthropometric characteristics, blood pressure and metabolic profile

Body weight and body mass index remained unmodified under L-T4 replacement treatment (Table 2). Slight, although statistically significant, variations of blood pressure values, lipid profile and blood glucose levels were observed under L-T4 replacement therapy, but no significant time × treatment interactions were found (Table 2). Significant reductions of both insulin concentrations and HOMA-IR were also observed after L-T4 replacement, with the evidence of a significant time × treatment interaction for both these parameters indicating a different degree of variation in the two study groups (Table 2).

Relationship between the assessed variables

Considering the study population as a whole, changes of TSH levels under L-T4 replacement therapy were

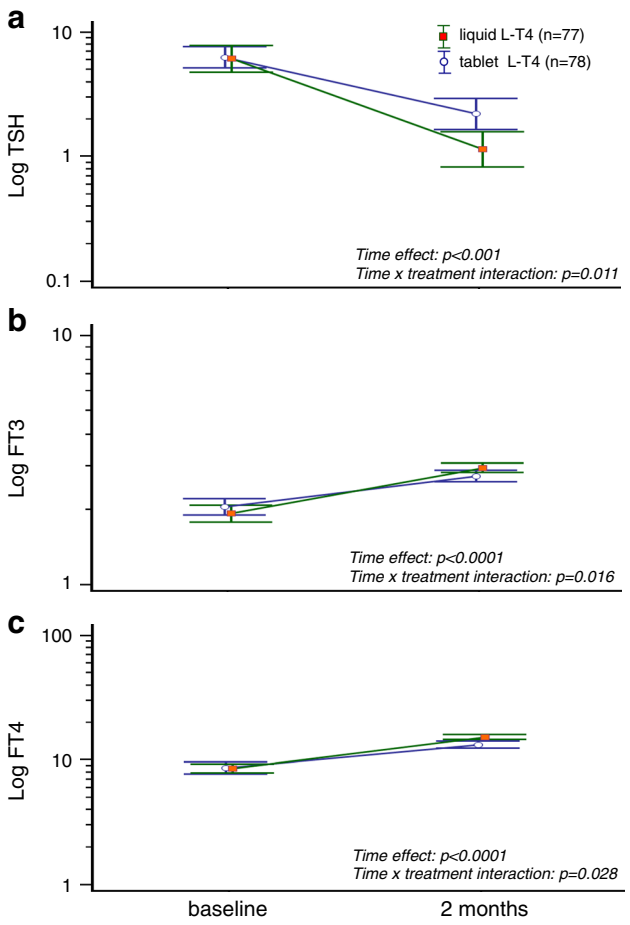

Fig. 2 Changes of thyroid-stimulating hormone (TSH, **a**), free T3 (FT3, **b**) and free T4 (FT4, **c**) concentrations after 2 months of replacement treatment with either liquid or tablet levothyroxine (L-T4) in recently thyroidectomized patients. Data are presented as mean (symbols) and 95 % CI (bars). Differences between treatments were analyzed by two-way repeated measures analysis of variance (ANOVA)

significantly correlated with those of FT3 and FT4 (Table 3). A significant correlation between the changes of FT3 and FT4 levels was also observed (Table 3). Weak, although significant, correlations were found between changes in PAS-POMS score and the variations of circulating levels of FT3 and FT4, whereas no significant relationships were found between the other measures of mood states and mental well-being, and changes of thyroid hormone concentrations during replacement therapy (Table 3).

Discussion

We investigated the effects of replacement therapy with either liquid or tablet formulation of L-T4 on mood states

Table 2 Changes of anthropometric characteristics, blood pressure levels and metabolic parameters during the study period in the two treatment groups

	Liquid L-T4 (n = 77)	Tablet L-T4 (n = 78)
Weight (kg)	Time effect: $p = 0.113$; time × treatment interaction: $p = 0.149$	
Baseline	71.1 ± 15.1	72.8 ± 15.0
2 months	71.1 ± 15.5	73.1 ± 14.6
BMI (kg/m^2)	Time effect: $p = 0.253$; time × treatment interaction: $p = 0.327$	
Baseline	26.4 ± 4.9	26.4 ± 5.1
2 months	26.4 ± 5.0	26.4 ± 4.9
SBP (mmHg)	Time effect: $p = 0.029$; time × treatment interaction: $p = 0.560$	
Baseline	125.7 ± 10.0	125.5 ± 9.1
2 months	126.2 ± 8.6	126.5 ± 8.6
DBP (mmHg)	Time effect: $p = 0.023$; time × treatment interaction: $p = 0.664$	
Baseline	77.0 ± 6.2	77.9 ± 6.9
2 months	77.8 ± 5.6	78.4 ± 6.5
TC (mmol/L)	Time effect: $p = 0.001$; time × treatment interaction: $p = 0.416$	
Baseline	4.7 ± 0.8	4.8 ± 0.9
2 months	4.9 ± 0.8	4.9 ± 1.0
LDL-C (mmol/L)	Time effect: $p = 0.019$; time × treatment interaction: $p = 0.611$	
Baseline	2.9 ± 0.7	2.9 ± 0.9
2 months	3.0 ± 0.8	3.0 ± 0.9
HDL-C (mmol/L)	Time effect: $p = 0.0002$; time × treatment interaction: $p = 0.466$	
Baseline	1.3 ± 0.3	1.2 ± 0.3
2 months	1.4 ± 0.4	1.3 ± 0.3
TG (mmol/L)	Time effect: $p < 0.0001$; time × treatment interaction: $p = 0.660$	
Baseline	1.3 ± 0.5	1.4 ± 0.6
2 months	1.2 ± 0.5	1.2 ± 0.6
Glucose (mmol/L)	Time effect: $p = 0.001$; time × treatment interaction: $p = 0.410$	
Baseline	4.8 ± 1.0	4.8 ± 0.9
2 months	5.0 ± 0.7	5.1 ± 0.7
Insulin (mU/L)	Time effect: $p < 0.0001$; time × treatment interaction: $p = 0.010$	
Baseline	11.8 ± 8.5	11.6 ± 7.3
2 months	8.8 ± 5.0	11.1 ± 7.0
HOMA-IR	Time effect: $p = 0.036$; time × treatment interaction: $p = 0.011$	
Baseline	2.6 ± 2.4	2.5 ± 1.8
2 months	2.0 ± 1.2	2.6 ± 1.8

Plus–minus values are means ± SD

Differences between treatments were analyzed by two-way repeated-measures ANOVA. $p < 0.05$ is considered a statistically significant difference

L-T4 levothyroxine, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *HOMA-IR* homeostasis model assessment–insulin resistance

Table 3 Relationship between changes (Δ) of thyroid hormones and measures of mood states and mental well-being in the whole study population

	ΔTSH	ΔFT3	ΔFT4	ΔPOMS	ΔPAS	ΔNAS	ΔGHQ-12
ΔTSH	r 1.000	$r -0.392$, $p < 0.0001$	$r -0.417$, $p < 0.0001$	$r -0.100$, p 0.217	$r -0.090$ p 0.263	$r -0.069$ p 0.392	$r -0.114$ p 0.157
ΔFT3	$r -0.392$, $p < 0.0001$	r 1.000	r 0.736, $p < 0.0001$	r 0.067, p 0.409	r 0.244, p 0.002	r 0.069, p 0.392	r 0.023, p 0.776
ΔFT4	$r -0.417$, $p < 0.0001$	r 0.736, $p < 0.0001$	r 1.000	$r -0.018$, p 0.820	r 0.180, p 0.025	$r -0.137$, p 0.089	$r -0.053$, p 0.513

Relationship between variables was assessed by Spearman non-parametric correlation

TSH thyroid-stimulating hormone, *FT3* free T3, *FT4* free T4, *POMS* Profile of Mood States, *PAS* Positive Affect Scale of POMS, *NAS* Negative Affect Scale of POMS, *GHQ-12* General Health Questionnaire-12 items

and psychological well-being in recently thyroidectomized patients for benign thyroid diseases. We utilized sensitive, validated measures for mood states and self-perceived mental well-being, which are likely to be affected by the altered thyroid status. We also analyzed the effects of L-T4 replacement therapy on thyroid hormone concentrations and metabolic profile.

Our study was based on the hypothesis of an influential role of changes of thyroid hormone profile in mood states and self-perceived well-being under L-T4 replacement therapy after total thyroidectomy. This question is quite debated since previous studies reported decreased [33, 34] or unchanged [35] quality of life in subjects receiving L-T4, at least at suppressive dose. In addition, some studies reported decrements in health status or mood in endogenous subclinical dysfunction [36, 37], while others did not find any relevant change in mood due to endogenous subclinical thyrotoxicosis [38, 39].

In the current study, significant improvements of measures of mood states were observed after 2 months under L-T4 replacement treatment. In particular, items of POMS exploring positive affect were significantly improved, while items exploring negative affect were significantly reduced. Also, psychological well-being, as assessed by GHQ-12, significantly improved after L-T4 treatment. A slight but significant change of symptoms score was also observed under L-T4 replacement therapy. Interestingly, the improvement of the measure of both mood states and mental well-being was more evident in patients receiving L-T4 in liquid formulation than in those who were treated with L-T4 replacement in tablet form. Interestingly, also the improvement of thyroid hormone profile during L-T4 replacement treatment was more evident in patients treated with the liquid formulation, as indicated by the greater reduction of TSH levels and the greater increase in FT3 and FT4 concentrations observed in patients treated with liquid L-T4 formulation.

Taken together, our findings lead to hypothesize, firstly, that L-T4 replacement therapy could have influenced mood states and psychological well-being in our thyroidectomized patients and, secondly, that the differences observed between the two study groups with regard to the changes of these variables under L-T4 replacement therapy could depend on the different pharmacokinetic profile of the two tested formulations of L-T4.

With regard to the first hypothesis, although it has been hypothesized that self-knowledge of a thyroid disease confers itself a lower health status and mood regardless of thyroid status [40], it has been also observed that circulating levels of TSH represent an independent predictor of negative affectivity and anxiety in young gynecological–endocrinological patients [41]. In addition, a study by Valizadeh et al. [42] described a small but

significantly higher reduction in anxiety/insomnia in patients with primary hypothyroidism treated with the combination of levothyroxine and liothyronine in comparison to those who were assigned to receive the usual dose of levothyroxine, suggesting that these disturbances related to thyroid dysfunction could be differently affected by different intervention strategies. Although no clinically relevant correlations between the degree of improvement of the measures of mood states and mental well-being, and the variations of circulating levels of thyroid hormones were found in our study, we do not think that it weakens our hypothesis since the deep influential role of thyroid hormones in a broad range of physiological variables, including metabolic profile, is well recognized, which, in turn, could influence the mood states and psychological well-being of patients. It is worth mentioning in this regard the improvement of insulin sensitivity that we observed during L-T4 replacement treatment because of the well-established influence of insulin sensitivity on brain function [43]. These findings agree with previous evidence described in patients with either subclinical [44] or overt hypothyroidism [45], and suggest an influential role of L-T4 replacement therapy in glucose metabolism. Interestingly, as for the measures of mood states and psychological well-being, also the variation of insulin resistance index was more evident in patients treated with liquid L-T4, mainly because of a greater reduction of insulin levels. Notably, this greater efficacy of liquid L-T4 in improving insulin sensitivity has been observed in subjects with an HOMA-IR in the range of normality and without evidence of a relevant weight excess. Interestingly, Morelli et al. [24] have recently found no differences in quality of life in hypothyroid patients who achieved superimposable TSH concentrations under replacement therapy with liquid formulation of L-T4 regardless of the timing of ingestion of the drug, i.e., either at breakfast, or 10 or even 30 min before breakfast. Despite the different approach used to measure general health and the different duration of follow-up, the results of this elegant report seem to reinforce our hypothesis of an influential role of L-T4 replacement therapy in mood states and psychological well-being after thyroidectomy.

Our second hypothesis seems quite convincing since the general characteristics of the two treatment groups at baseline were quite similar. In addition, all the participants received an L-T4 dose tailored on the basis of their body weight. Thus, the different influence on thyroid hormone profile observed after 2 months under either liquid or tablet formulation of L-T4 could be likely related to the different pharmacokinetic profiles of the two tested formulations. In this regard, an oral solution of L-T4 has been reported to have better pharmacokinetics indices in comparison to the tablet formulation [21]. Unlike the tablet formulation, the oral solution does not need a dissolution phase in an acid ambient, thus being able to directly permeate through the intestinal epithelium [21]. According to this, Yue et al. [46] have shown that L-T4 in the liquid formulation peaks in blood faster than in the tablet. This peculiarity make the oral solution less susceptible to the interference exerted by food or drugs that affect the gastric pH [21]. In this regard, it has been demonstrated that mere consumption of coffee at breakfast can impair tablet L-T4 absorption by binding to L-T4 [18], whereas the efficacy of liquid L-T4 on thyroid hormones does not significantly change when the drug is consumed with water shortly before coffee, or poured into the coffee, or consumed 30 min before coffee [47]. In addition, liquid L-T4 has been proven to be stable in hot beverages usually consumed at breakfast [48]. According to these advantageous pharmacokinetic characteristics of liquid L-T4, Brancato et al. [49] have reported a significant decrease of serum TSH levels in the large majority of patients who used to take L-T4 30–35 min before breakfast, and who were switched from tablet to oral L-T4 solution. In this regard, it is important to emphasize that in our study all participants received uniform instructions on the daily fasting ingestion of both formulations of L-T4, and on the interval between the liquid or tablet therapy and food consumption in order to exclude, or at least minimize, the influence of food on L-T4 absorption.

The last interesting finding of our study was the slight but significant change of lipid profile after L-T4 replacement therapy with an increase of both LDL and HDL cholesterol, and a decrease of tryglycerides without evidence of any difference between the two L-T4 formulations. These findings seem to suggest an influential role of L-T4 replacement therapy in lipid metabolism in recently thyroidectomized patients, even in the presence of a substantially normal lipidemic pattern. In this regard, controversy surrounds the issue of whether levothyroxine treatment can affect lipid profile in patients with subclinical hypothyroidism, with evidence suggestive of either a neutral [50] or a favourable [51, 52] effect of L-T4 treatment on lipid profile. We do not have information about lipid profile before thyroidectomy in our patients, and thus we cannot speculate about a possible transient derangement of lipid profile following thyroid hormone deprivation due to thyroidectomy. However, a rapid deterioration of lipid profile after thyroidectomy in patients with overt transient non-autoimmune hypothyroidism has been described, which was reversed by the restoration of euthyroid status through L-T4 replacement treatment [53].

The potential clinical relevance of this study should be considered because our findings have been obtained in a real-world context, and this makes our findings potentially extendable to the general population. It is worth mentionng in this regard that we explored several aspects of the potential influence of L-T4 replacement therapy on mood

states and subjective well-being by using the standardized and validated intruments that are widely used in this setting.

In conclusion, our study provides the first evidence that liquid L-T4 replacement therapy could be more effective in improving mood states and self-perception of well-being in patients recently thyroidectomized for benign thyroid diseases. This effect might depend on a more favorable pharmacokinetic profile of liquid formulation of L-T4, making it less susceptible to factors potentially affecting esogenous L-T4 bioavailability [21, 54]. This peculiarity of liquid formulation of L-T4 can lead to a more homogenous effect of this replacement therapy on thyroid hormone profile, thus allowing to more rapidly achieve an adequate thyroid hormone profile in thyroidectomized patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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