Advancements in the treatment of hypothyroidism with L-T4 liquid formulation or soft gel capsule: an update.

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Abstract

Introduction. The most recent advance concerning levothyroxine (L-T4) therapy is the development of novel oral formulations: the liquid preparation, and the soft gel capsule.

Areas covered. This review evaluates the most recent clinical studies about these new formulations. The liquid formulation has been shown to overcome: 1-the food and beverages intereference with L-T4 tablets absorption, caused by food or coffee at breakfast; 2-malabsorption induced by the increased gastric pH, resulting from atrophic gastritis, or due to proton-pump inhibitors; 3-malabsorption after bariatric surgery. The use of liquid L-T4 has been studied also in pregnancy, newborns and infants, suggesting a better bioequivalence than tablets. Finally, liquid L-T4 is more active than tablets in the control of thyroid-stimulating hormone (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. Few studies have evaluated soft gel L-T4 with promising results in patients with malabsorption related to coffee or gastritis.

Expert opinion. Liquid L-T4 (and soft gel capsules) are more active than the tablet L-T4 in the control of TSH in hypothyroid patients with gastric disorders, malabsorption, or drug interference, but also in patients without absorption disorders.

Keywords: bariatric surgery, drug interference, gastritis, liquid L-T4, L-T4, malabsorption, PPI, soft gel L-T4, tablet L-T4.

List of Abbreviations

AITD: Autoimmune Thyroid Diseases

BPD: Biliary Pancreatic Diversions

CD: Celiac Disease

CH: Congenital Hypothyroidism

Cmax: Maximum Concentration Observed

DTC: Differentiated Thyroid Cancer

HP: Helicobacter pylori

IH: Improper Habit

LI: Lactose Intolerance

L-T4: levothyroxine

PH: Proper Habit

PPIs: Proton-Pump Inhibitors

RYGB: Roux-en-Y gastric bypass

T4: Thyroxine

T3: Triiodothyronine

Tmax: Time at which the maximum concentration is observed

TRH: Thyrotropin-Releasing Hormone

TSH: Thyroid-Stimulating Hormone

1. Introduction

Levothyroxine (L-T4) is a synthetic hormone, with a chemical structure identical to thyroxine (T4), produced naturally by the thyroid, and it is used for the substitutive therapy of conditions associated with hypothyroidism. Iodine is transported into the thyroid cells, and thyroid hormones that are produced and secreted from the gland in physiological conditions are about 80-90% T4 and 10-20% triiodothyronine (T3). Deiodinase enzymes convert T4 to T3, which is a major source of T3 (85%) in peripheral tissues [1].

T3 is about four or even ten times more effective than T4, that functions as a prohormone [2-7].

Thyroid hormone controls energy metabolism, protein synthesis, and body's sensitivity to other hormones. Cells of the fetal brain are a major target for action of T3 and T4, that play an important role in brain maturation [8].

Hormonal output from the gland is regulated by thyroid-stimulating hormone (TSH) that is produced by the pituitary, which is regulated by thyrotropin-releasing hormone (TRH), produced by the hypothalamus [9].

On the other side thyroid hormones have a negative feedback on pituitary: in fact TSH production is suppressed when the free T4 (FT4), or free T3 (FT3) levels are high. The negative feedback occurs on the hypothalamus, too.

Hypothyroidism is more common in women and in people over 60 years [10].

Clinical hypothyroidism, in Western countries, occurs in about 0.4% of population [11], while subclinical hypothyroidism **(that occurs when serum TSH concentrations are raised and serum thyroid hormone concentrations are normal)** is present in 4-8% of people [11]. In countries with severe iodine deficiency, a low iodine intake with the diet is the most common cause of hypothyroidism [11,

12], while in developed countries (with mild iodine deficiency, or sufficient iodine intake), the most common causes of hypothyroidism are autoimmune thyroiditis [13, 14], or previous treatment with radioiodine, or thyroidectomy.

Drugs are an emerging cause of primary hypothyroidism, for example, tyrosine kinase inhibitors [15].

Central hypothyroidism, due to injury to the hypothalamus or the anterior pituitary gland, is less frequent [16]. The diagnosis of hypothyroidism can be performed with blood tests measuring TSH and T4 levels.

L-T4 is used also at TSH-suppressive doses for the therapy of patients with thyroid cancer with the aim to slow/arrest its growth [17]. While, the use of L-T4 at TSH-suppressive doses for the therapy of nodular goiter is still debated [18].

After that L-T4 was first isolated in 1914 from porcine thyroid extracts by Kendall [19], animal (porcine or porcine plus bovine) desiccated thyroid, containing a combination of T4 and T3, was the only therapy of hypothyroidism until the mid-1950s, when synthetic L-T4 was developed and introduced in the therapeutical use [20]. Pure synthetic L-T4 became available in the tablet formulation [20]. In the latest guidelines for the therapy of hypothyroidism, the 22.4 recommendation states that "there is no evidence to support using desiccated thyroid hormone in preference to L-thyroxine monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism" [11].

However, many studies have shown that in patients with L-T4 monotherapy the whole symptomatology of hypothyroidism is not corrected in 100% of patients, and that about 5 - 10% of them still have residual symptoms [21].

It was shown that combined infusion of L-T4 plus liothyronine, rather than L-T4 alone, is the only way of restoring the concentrations of T4, and T3 in circulation and

in all tissues of thyroidectomized rats [22]. However in a systematic review of all the published controlled studies comparing treatment with L-T4 alone with combinations of L-T4 plus liothyronine in hypothyroid patients, only in one study out of nine the combined therapy appears to have beneficial effects on the mood, quality of life, and psychometric performance of patients over L-T4 alone [21].

For these reasons, the Authors suggest that until clear advantages of L-T4 plus liothyronine are demonstrated, the administration of L-T4 alone should remain the treatment of choice for replacement therapy of hypothyroidism [22].

The debate is still ongoing [23].

The tablet formulations of L-T4 contain a stable salt, sodium L-T4, together with a variety of excipients [24]. After the ingestion, a dissolution phase of the tablet is necessary to remove sodium, converting L-T4 into a lipophilic molecule; the tablet dissolution needs the acid gastric pH [25]. Then L-T4 reaches the duodenum and jejunum, where it is absorbed. When ingested with water, the absorption is greater in the first three hours, in particular within the second hour [26-28]. In the absence of factors that alter L-T4 absorption, about 70% of tablet L-T4 is absorbed. It has been shown a decrease of tablet L-T4 bioavailability of about 4% for an increase of 10 years of age, so the percentage of L-T4 absorption is decreased in the elderly [26, 29].

The intestinal L-T4 absorption varies with the timing of ingestion, with the maximum absorption occurring in the morning after overnight fasting, while the lowest occurring when L-T4 is ingested together with breakfast [27, 30].

Dietary fibre and espresso coffee interfere with the absorption of L-T4 [31].

L-T4 malabsorption is also reported in malabsorptive disorders such as Helicobacter pylori (H. pylori - HP) infection, atrophic gastritis, inflammatory bowel disease, celiac disease (CD), and lactose intolerance (LI). Many commonly used drugs, as

ferrous sulphate, sucralfate, raloxifene and proton-pump inhibitors (PPIs), bile acid sequestrants, calcium carbonate, phosphate binders, aluminium-containing antacids, have also been shown to interfere with the L-T4 absorption [32].

Demand for bariatric surgery has risen and bariatric patients often have **medication** malabsorption. In a recent review [33] evidence for diminished drug absorption was found in different types of bariatric surgery, such as: jejunoileal bypass, gastric bypass/gastroplasty and biliopancreatic diversion. Drugs that are lipophilic and undergo enterohepatic recirculation exhibited the greatest malabsorption: among them the most consistent evidence was found for L-T4, and cyclosporine [33].

Drugs could impair L-T4 absorption both by increasing the gastric pH (e.g., the PPIs [32, 34]) preventing the dissolution of tablet L-T4, or by binding L-T4 into insoluble complexes (e.g., calcium or iron salts [32, 35]).

L-T4 treatment is contraindicated in patients with overt or subclinical hyperthyroidism, tachiarrythmias, acute myocardial infarction [36], and a history of hypersensitivity to the inactive ingredients of the formulation.

In the elderly, in patients with adrenal impairment, with myocardial ischemic disorders, with arrythmias, or epilepsy [37], L-T4 treatment should not be started at full replacement dose, and monitored carefully.

Adverse effects associate with L-T4 treatment are the expression of iatrogenic hyperthyroidism (due to overtreatment), and include general, gastrointestinal, cardiovascular, neuromuscular and dermatological signs [11].

Since the different manufacturing of L-T4 and different composition of excipients may affect L-T4 tablets intestinal absorption, the American Thyroid Association has advocated that the patients “take always the same brand of L-T4” [38].

L-T4 can be administered in refractory hypothyroidism [39, 40], or in the myxedematous coma [41] by the intravenous or the intramuscular route.

2. Body

2.1 Pathogenesis of L-T4 tablets malabsorption

Food and beverages can interefere with L-T4 tablets absorption. L-T4 is normally taken before breakfast. Recently a prospective, randomized, open-label, crossover study was carried out to compare usual L-T4 administration while in a fasting state with administration during breakfast. TSH was higher for levothyroxine administered with breakfast than while fasting (2.89 vs 1.9 mIU/L). The Authors concluded that it is recommendable to take L-T4 while fasting in patients in whom a specific serum TSH goal is required [42]. Benvenga et al. have recently shown that L-T4 assumption ten minutes before drinking coffee also reduces its absorption [31].

Furthermore, many gastric or intestinal disorders can influence the L-T4 tablet absorption [43].

The L-T4 tablets solubilization is altered by a decrease of gastric acidity. In fact, in patients with HP gastritis, atrophic gastritis (or both), with impaired acid secretion, it has been shown that the daily L-T4 requirement was higher (by 22 to 34%) [25] than in controls with normal gastric pH. The production of ammonia in HP infection, and hypocloridria induced by atrophic gastritis, increase the gastric pH, reducing the stomach ability to dissolve tablets. Moreover the increased pH alters the ionization and tridimensional structure of L-T4, reducing the efficiency of intestinal absorption [44, 45].

Also the PPI may reduce absorption of L-T4 [34]. The effect of PPIs was evaluated on circulating TSH in 37 patients with hypothyroidism and normal TSH receiving L-T4

replacement therapy. Results showed that the mean change in TSH in the study group from before to 2 months after the beginning of PPI treatment (0.69 +/- 1.9 μIU/mL) was higher than in controls (0.11 +/- 1.06 μIU/mL). The **Authors** suggested that patients with hypothyroidism during L-T4 therapy and PPI may need additional thyroid hormones testing and adjustment of the L-T4 dose [34].

Intestinal disorders can also impair the L-T4 tablet absorption, and an increased need for L-T4 has been described [46].

CD is a gluten intolerance of the mucosa of small intestine [46], that has a spectrum of clinical features from asymptomatic forms to overt disease [47, 48], and it is classified into five phenotypes [49].

The association of different autoimune disorders is well known [12, 50-52].

CD and autoimmune thyroid diseases (AITD) are cognate diseases [53, 54], with a prevalence of CD in patients with AITD of 2-5%, and that of AITD in CD patients up to 30% [54]. Case reports have shown an increased need of L-T4 in CD [55, 56].

Recently the L-T4 dosage in hypothyroid patients with AITD and atypical CD has been studied in 35 patients, in comparison with patients with AITD only. If CD patients were not correctly treated with a strict gluten-free diet, the L-T4 dosage needs to be increased by up to 50% [57]. Because of the high prevalence of CD in AITD patients, it is recommended to consider the presence of an underling intestinal disorder when patients on chronic L-T4 treatment exhibit a need for an increased dosage [57].

LI may require an increased dose of tablet form of L-T4 [58-60].

Recently the replacement L-T4 dose has been studied in 34 hypothyroid AITD patients with LI and not-compliant with a lactose-free diet. In patients with isolated

AITD, a median T4 dose of 1.31 μg/kg/d was necessary, while in 29 patients with LI a median T4 dose of 1.81 μg/kg/d (+38%) was necessary [61].

Both a lactose-free diet and a lactose-free L-T4 formulation can be administered to restore euthyroidism [62].

The prevalence of LI in adult patients is 7-20%, but the association with resistance to treatment with oral L-T4 is unusual. However, in these patients an individually tailored T4 dose is recommended.

The pathogenic mechanism leading to increased L-T4 need in LI patients is not clear. Three possible mechanisms have been advocated: 1- undigested lactose increases the fluid in the intestinal lumen [63], accelerating intestinal transit time and decreasing the binding between lactose and enzyme [62]; 2- a faster intestinal transit reduces the bioavailability of L-T4 [64]; the different microbiota of LI patients may impair the absorption of nutrients and drugs [63, 65].

In the last years, the request for bariatric surgery is raised [66-68], and about 180 000 surgeries are performed in US each year [69]. Different kinds of operations exist: a- exclusively restrictive (gastric banding, gastroplasty); b- restrictive with limitation of digestive capacity (sleeve gastrectomy); c- restrictive/malabsorptive (gastric bypass); d- exclusively malabsorptive (biliopancreatic diversion, jejunoileal bypass). Malabsorptive procedures can cause nutritional deficiencies [70], or drug malabsorption [71].

People with severe obesity treated with bariatric surgery often have drug malabsorption, since the major part of oral agents are absorbed principally in the small intestine, bypassed in different bariatric procedures. Other factors impairing drug absorption are: **reduced mucosal exposure**, and alterations in drug solubility and dissolution, **due to** an altered intestinal pH [71].

After bariatric surgery, patients show a reduced L-T4 absorption [33, 72, 73].

2.2 Novel oral L-T4 formulations

The most recent advance concerning L-T4 therapy is the development of novel oral formulations: the liquid preparation, and the soft gel capsule.

The soft gel capsule contains, in an outer gelatine shell, L-T4 dissolved in glycerine [74]. This structure warrants a rapid dissolution in the acid gastric environment, and prevents binding with other substances in the jeunal lumen (for example, coffee, calcium or iron salts).

The liquid formulation is composed of L-T4, glycerine and ethanol. The most important advantage of the oral solution, compared to the tablets, is that it does not need a gastric phase of dissolution [4].

This review evaluates the most recent papers about these new formulations.

2.3 L-T4 solution, or capsule, pharmacokinetics studies in normal subjects

One of the initial studies evaluated the relative bioavailability of T4 sodium and liothyronine sodium (T3), administered in single doses as oral solution (drops) and tablet forms in 24 healthy volunteers [75]. A single oral dose of 100 μg (1 ml or 1 tablet) of T4 were administered with a randomized, crossover design and T4 or T3 serum concentrations were measured. After administration of liquid T4 oral solution, Cmax (maximum concentration observed), AUC0-t [AUC up to the last measurable concentration (otherwise called AUClast)] and Tmax (time at which the maximum concentration is observed) were similar to those obtained with L-T4 tablets. These results demonstrated the similar bioavailability of the T4 oral solution and the corresponding tablet forms and suggested that they are bioequivalent [75].

In another study, the bioavailability of the L-T4 tablet and that of a reference oral solution were compared under fasting conditions in 24 healthy volunteers. The L-T4 90% confidence limits for the studied pharmacokinetic parameters AUC(last) and Cmax resulted within the limits for bioequivalence [76].

More recently, to understand the potential advantages of a L-T4 oral solution vs tablets or soft gel capsules, the results of 4 randomized, 2-treatment, single-dose (600 mcg levothyroxine), 2-way crossover bioequivalence studies in 84 healthy subjects were analyzed [77]. T4 was measured in serum samples collected before drug administration and until 48-72 h post-dose. Mean pharmacokinetic parameters for tablets, capsules and solution were, respectively: area-under-the-concentration-time-curve from 0 to 2 h (ng*h/mL)=68, 64, 99; area-under-the-concentration-time-curve from 0 to 48 h (ng*h/mL)=1 632, 1 752, 1 862; Cmax (ng/mL)=67.6, 68.0±15.9, 71.4±16.0; Tmax (hours)=2.25, 2.38, 1.96. These parameters were not statistically different between the formulations, however a faster absorption for the L-T4 solution was observed. The solution appears to reach systemic circulation quicker, probably because dissolution is not needed, before absorption starts in the jeunum [77].

2.4 Liquid L-T4 and interaction with food

The most important advantage of the liquid L-T4 solution is the possibility of administration in patients who are not able to swallow tablets or capsules. Pirola et al. compared thyroid hormones and TSH in patients administered with L-T4 in tablets or liquid formulation with an enteral feeding tube [78]. Twenty patients submitted to total thyroidectomy and laryngectomy were treated with L-T4 [in tablets (Group T) or liquid formulation (Group L)] with enteral feeding tube the day after surgery. Tablets were smashed before administration and enteral feeding was ceased for 30 min before

and after L-T4 treatment, while the liquid formulation could be put into the nasoenteric tube immediately. No difference of thyroid hormones and TSH was in patients of Group L or in Group T. Preparation and administration of liquid L-T4 was preferred by nurses. These results demonstrated that liquid L-T4 could be administered through feeding tube improving the preparation and administration of therapy by nurses [78].

The interference of foods with L-T4 abosrption has been studied in other studies.

In a first study, Cappelli et al. evaluated retrospectively patients on liquid L-T4 therapy, whether they consumed L-T4 at breakfast or 30 min before it [79]. No significant difference in TSH, or thyroid hormones was observed when they consumed L-T4 at breakfast or when they consumed it 30 min before breakfast at 3 and 6 months. The Authors suggested that liquid L-T4 formulations might diminish the problem of L-T4 malabsorption caused by food or coffee at breakfast when using L-T4 in tablet [79].

Another study evaluated the equivalence of administering liquid L-T4 with breakfast or 10 min before breakfast [80]. This study had a crossover design AB/BA where A stays for L-T4 with breakfast and B for L-T4 10 min before breakfast. Fifty-nine hypothyroid patients were assigned to one of the two treatments, and evaluated for TSH levels at the end of each period. The mean TSH was 1.52 μU/ml when L-T4 was administered with breakfast and 1.46 μU/ml when it was taken 10 min before, regardless of treatment sequence. This study suggested a therapeutic equivalence between liquid L-T4 administration at breakfast or 10 min before breakfast [80].

Cappelli et al. more recently conducted a double-blind, randomized, placebo-controlled, crossover trial in 77 hypothyroid patients randomly assigned to receive liquid L-T4 either at least 30 minutes before breakfast, or at breakfast [81]. No

statistically significant differences in TSH, or thyroid hormones levels were observed when L-T4 was taken at breakfast or 30 minutes before. This study suggested that a liquid L-T4 formulation can be ingested directly at breakfast, potentially improving therapeutic compliance [81].

2.5 Liquid L-T4 in impaired gastric acidity

Vita et al. studied whether a liquid formulation of L-T4 would correct L-T4 malabsorption induced by PPIs, with a prospective observational cohort study in 24 consecutive adult patients who had absorption of tablet L-T4 impaired by PPIs. The patients were switched from the tablet to the oral solution L-T4 at the same daily dose. Serum TSH was lower with the oral solution than with the tablet formulation (1.7 vs 5.4). These data demonstrated that liquid L-T4 is able to overcome L-T4 malabsorption induced by the increased gastric pH due to PPI therapy [82].

As previously shown L-T4 malabsorption is a potential trouble in patients with autoimmune atrophic gastritis. In a recent study five patients with autoimmune gastritis, with TSH levels in the hypothyroid range during the treatment with L-T4 tablets, were switched to receive an oral L-T4 liquid formulation at the same dose. Serum TSH levels were normalized in all patients after the switch to an oral L-T4 liquid formulation, at the same dose. In four patients who were switched back again to L-T4 tablets, with the same dosage, a worsening in TSH occurred. Such data lead to hypothesize that the L-T4 oral liquid formulation might bypass the pH alteration due to atrophic gastritis [83].

2.6 Liquid L-T4 in malabsorption

Drug malabsorption is a potential concern after bariatric surgery. Pirola et al. [84] presented 4 cases of hypothyroid patients who had TSH in the euthyroid range with L-T4 tablets prior to Roux-en-Y gastric bypass (RYGB) surgery, who developed elevated TSH after the surgery. In all these patients upon the switch to an oral liquid formulation with the same L-T4 dose, TSH levels were normalized [84].

More recently our group has studied 17 cases of hypothyroid patients, who were well replaced with thyroxine tablets (for > 1 year) to euthyroid TSH levels before surgery [13 RYGB; 4 biliary pancreatic diversions (BPD)], who developed from 3 to 8 months after surgery a high TSH [85]. Patients were then switched from oral tablets to a liquid L-T4 formulation (with the same dosage). TSH declined significantly in patients treated with RYGB, and in the ones treated with BPD (RYGB group, TSH μIU/mL: 7.58 vs 3.808; BPD group, TSH μIU/mL: 8.82 vs 3.12), 2-3 months after the switch. These results demonstrated that liquid L-T4 could avoid the problem of malabsorption in patients with BPD, confirming preceding studies in patients submitted to RYGB, and leading to suggest that the L-T4 oral liquid formulation could circumvent malabsorption after bariatric surgery [85].

2.7 Liquid L-T4 in pregnancy and infancy

In pregnant women, whose daily dose is higher because of higher requirements, serum TSH and FT4 should be monitored monthly, and TSH goals are trimester dependent [11].

A study evaluated the need and the magnitude of L-T4 increase in hypothyroid pregnant women on liquid L-T4 compared to tablet formulations [86]. During pregnancy 7/17 (41.2%) of the women had to increase the dosage of L-T4 while on L-T4 replacement therapy with tablets, vs 1/14 (7.1%) of those treated with liquid

formulation. Daily L-T4 was significantly increased in the tablet group only. This study suggested that pregnant women on optimal therapy before pregnancy require an increase of L-T4 dosage more often when on a tablet than liquid formulation [86].

In children daily L-T4 dosage is calculated according to age. In newborns and infants L-T4 tablets are usually crashed and given with liquids.

The use of L-T4 as liquid solution has been studied also in newborns and infants.

Liquid L-T4 solution was administered to 28 consecutive newborns with primary congenital hypothyroidism (CH). TSH, T3, T4, FT3 and FT4 were measured before therapy and during follow-up up to 2 years. The median time of normalization of TSH (< or =6 mU/l) was 1-2 weeks. The initial dose necessary to normalize TSH was not lower when a liquid solution is used in comparison with tablets [87].

In a second study [88] 42 consecutive infants with CH were subdivided into 2 homogeneous groups in order to investigate the effects of liquid (drops) and tablet formulations of L-T4. Infants with CH were randomly subdivided in group 1 (receiving the liquid formulation) or group 2 (receiving tablets), and thyroid function tests were done before the start of the therapy, and at 15 and 30 days and at 3 and 6 months after its beginning. After 15 days of therapy, serum TSH became normal in 8/9 patients belonging to group 1 and in 5/9 to group 2. During the follow-up, a higher number of patients with suppressed TSH levels was present in group 1 than group 2. Considering these results, it seems that no complete bioequivalence between drops and tablets exists, particularly in infants with severe CH [88].

A further study [89] compared the effects of liquid and tablet formulations of L-T4 in 78 newborns with CH: 39 patients received liquid L-T4 (group A) and 39 patients received tablets (group B). FT4 concentration normalized before 10 days of treatment in all patients. Normalization of TSH concentration was achieved after 7-10 days of

therapy in 87% of group A and in 82% of group B. Group A patients had significantly lower TSH values compared with those of group B at 10 days and 7 months of treatment, despite similar L-T4 dose and FT4 concentration. This study confirmed the efficacy and safety of both formulations, however the TSH inhibition trend when using liquid L-T4 is suggested to be linked to a higher absorption in comparison to the tablets [89].

2.8 Comparison of liquid formulation vs tablets in adult hypothyroidism

Fifty-three outpatients administered with L-T4 replacement therapy (within 1 h before breakfast) who switched from L-T4 tablets to an oral L-T4 solution at the same daily dose were evaluated, reporting a significant reduction of TSH level 60 to 90 days upon the switch [90]. In the patients whose TSH declined, an increased frequency of factors interfering with L-T4 absorption was shown; such factors are absent in our patients [90].

Another study by Negro et al. [91] investigated whether L-T4 liquid formulation (drops or monodose vials) is able to affect TSH stability values and evaluated its usefulness in maintaining the TSH level into the normal range with respect to tablets. One hundred hypothyroid patients on replacement treatment with L-T4 liquid solution were enlisted to belong to the Liquid Group, and 100 hypothyroid patients taking L-T4 tablets to the Tablet Group. TSH levels were abnormal **(TSH>3.6 mU/L)** in 19 patients of the Tablet Group and in 8 of the Liquid Group, at the follow-up visit. Patients of the Tablet Group had higher daily and weekly L-T4 dose per kilogram. These results indicated that L-T4 liquid formulation is more efficacious to maintain the euthyroidism in hypothyroid patients [91].

Giusti et al. [92] studied the tolerability and efficacy of the liquid L-T4 vs the previous tablet formulation in a cohort of 59 patients with cured differentiated thyroid cancer (DTC). No change in TSH, thyroid hormones or thyroglobulin was evidenced during the study. At the end of the study subjective symptoms had diminished significantly and 73% requested to remain on the liquid formulation. It was suggested that liquid L-T4 seems to be a valid alternative to tablet formulation in DTC patients [92].

A more recent study of our group [93] aimed to compare the effectiveness of L-T4 liquid formulation with L-T4 tablets, in hypothyroid patients without malabsorption or drug interference. We recruited 152 patients without malabsorption or drug interference. Patients were switched from L-T4 tablets, to liquid L-T4 at the same dosage, 30 min before breakfast. Circulating TSH, FT3 and FT4 were measured after 1-3 months (first control) and 5-7 months (second control) from the switch. TSH significantly declined vs the basal value after the switch to liquid L-T4 both at 2 and 6 months; FT4 and FT3 did not significantly change. The reported data first demonstrate that liquid L-T4 is more effective than the tablet formulation in maintaining the control of TSH values in hypothyroid patients without malabsorption, drug interference, or gastric disorders. As the drug dose did not change, we suppose that the TSH declined owing to an increased absorption of L-T4 with the liquid formulation; the mechanisms at the basis of this process need additional investigations [93, 94].

2.9 Soft gel L-T4 clinical studies

Few studies have evaluated soft gel L-T4 in clinical studies.

Vita et al. recruited 8 patients with coffee-associated L-T4 malabsorption including 1 hypothyroid patient [95]. For 6 months, the patients were switched to the capsule maintaining the L-T4 daily dose. Patients took the capsule with water, having coffee 1 h later (proper habit, PH) on days 1-90, or with coffee ≤ 5 min later (improper habit, IH) on days 91-180. In 7 patients, post-switch TSH was 0.41 (PH) vs 0.28 pre-switch (PH), and 0.34 (IH) vs 1.23 (IH) ($p < 0.001$). This study suggested that soft gel capsules can be used in patients who are unable/unwilling to change their IH of taking L-T4 [95].

Another study [96] aimed at comparing soft gel and tablet L-T4 requirements in patients with gastric disorders in 31 patients with gastric-related T4 malabsorption. All patients were in long-lasting treatment (>2 years) with the same dose of L-T4 tablets when treatment was switched to a lower dose of soft gel L-T4 capsules (-17 %), and serum FT4 and TSH were re-evaluated after 3, 6, 12, and 18 months. In 21 patients despite the reduced dose of L-T4, median TSH values were similar at each time point. In the remaining 10 patients TSH levels were significantly higher. The Authors suggest that doses of soft gel L-T4 capsules lower than L-T4 tablet preparation are required to maintain the therapeutic goal in about 2/3 of patients with impaired gastric acid secretion [96].

3. Conclusion

The most recent advance concerning L-T4 therapy is the development of novel oral formulations: the liquid preparation, and the soft gel capsule. The liquid formulation is composed of L-T4, glycerine and ethanol, and it does not need a gastric phase of dissolution [4]. The soft gel capsule contains, in an outer gelatine shell, L-T4

dissolved in glycerine [74], and it is rapidly dissoluted in the acid gastric environment.

Pharmacokinetic studies have shown that the solution appears to reach systemic circulation quicker, probably because dissolution is not needed, before absorption starts in the jejunum [77].

Tablet L-T4 therapy of hypothyroidism can result in a not properly controlled TSH (nevertheless the right L-T4 dosage) in about 10-15% of patients. Many different reasons are related to the inefficiency of L-T4 dosage, such as: a- poor patient's compliance; b- wrong habits, for example taking the L-T4 with coffee breakfast; c- gastric disorders (H. pylori infection, atrophic gastritis) or drugs (PPIs) that impair acidic environment; d- intestinal malabsorption due to celiac disease, or lactose intolerance, or bariatric surgery; e- drugs that reduce the L-T4 intestinal absorption (such as calcium salts and iron salts, or bile sequestrants).

Generally the improper high TSH due to the above mentioned conditions is managed with an increase in L-T4 daily dosage, and subsequent re-evaluation of TSH after 2-6 months.

Increasing L-T4 daily dose may lead to iatrogenic hyperthyroidism that may occur overall when patients cure the underlying disorder (for example with a gluten free diet), or when patients withdraw interfering drugs.

In some categories of patients, L-T4 treatment has to be started and monitored carefully: i) in children, whose daily dose is calculated according to age; ii) in pregnant women, whose daily dose is higher because of higher requirements, and serum TSH and FT4 should be monitored monthly; iii) in the elderly, in patients with adrenal impairment, with myocardial ischemic disorders, with arrythmias, or epilepsy.

The most important advantage of the liquid L-T4 solution is the possibility of administration in patients who are not able to swallow tablets or capsules. It has been recently reported that liquid L-T4 formulation can be administered directly through feeding tube (in patients treated through enteral feeding tube) improving significantly the preparation and administration of therapy by nurses [78].

The liquid formulation has been shown to overcome the food and beverages intereference with L-T4 tablets absorption, caused by food or coffee at breakfast when using L-T4 in tablet [77, 78], potentially improving therapeutic compliance.

L-T4 oral liquid formulation could circumvent malabsorption induced by the increased gastric pH, resulting from atrophic gastritis, or due to PPI therapy [80, 81].

Recent results demonstrated that liquid L-T4 could avoid the problem of malabsorption in patients with BPD, or RYGB, leading to suggest that the L-T4 oral liquid formulation could circumvent malabsorption after bariatric surgery [84].

Moreover, the use of L-T4 as liquid solution has been studied also in pregnancy, newborns and infants, suggesting a better bioequivalence than L-T4 in tablets [86, 88].

Finally, we demonstrated that liquid L-T4 is more effective than L-T4 tablets in maintaining TSH values under control in hypothyroid patients without malabsorption, drug interference, or gastric disorders, suggesting an increased absorption of the oral liquid L-T4 formulation also in these patients [93].

Further studies will be needed to evaluate the role of liquid L-T4 in celiac disease, lactose intolerance, or in patients with other drugs that interfere with L-T4 absorption such as calcium, or iron salts, or bile sequestrants.

Few studies have evaluated soft gel L-T4 in clinical studies with promising results in patients with coffee-associated L-T4 malabsorption or gastric-related T4

malabsorption. However, future studies are in program to evaluate soft gel L-T4 in other conditions of impaired L-T4 absorption.

4. Expert opinion

Tablet L-T4 therapy of hypothyroidism can result in a not properly controlled TSH (nevertheless the right L-T4 dosage) in about 10-15% of patients. Many different reasons are related to the inefficiency of L-T4 dosage, such as: a- poor patient's compliance; b- wrong habits, for example taking the L-T4 with coffe breakfast; c- gastric disorders (H. pylori infection, atrophic gastritis) or drugs (PPIs) that impair acidic environment; d- intestinal malabsorption due to celiac disease, or lactose intolerance, or bariatric sugery; e- drugs that reduce the L-T4 intestinal absorption (such as calcium salts and iron salts, or bile sequestrants). Generally the improper high TSH due to the above mentioned conditions is managed with an increase in L-T4 daily dosage, and subsequent re-evaluation of TSH after 2-6 months. Increasing L-T4 daily dose may lead to iatrogenic hyperthyroidism that may occur overall when patients cure the underlying disorder (for example with a gluten free diet), or when patients withdraw interfering drugs.

The most recent advance concerning L-T4 therapy is the development of novel oral formulations: the liquid preparation, and the soft gel capsule. The liquid formulation does not need a gastric phase of dissolution, while the soft gel capsule is rapidly solubilized in the stomach. Pharmacokinetic studies have shown that the L-T4 solution appears to reach systemic circulation quicker, probably because dissolution is not needed.

The most important advantage of the liquid L-T4 solution is the possibility of administration in patients who are not able to swallow tablets or capsules, such as in patients treated through enteral feeding tube, with a significant improvement in preparation and administration of therapy.

The liquid formulation has been shown to overcome the food and beverages intereference with L-T4 tablets absorption, caused by food or coffee at breakfast when using L-T4 in tablet, potentially improving therapeutic compliance.

L-T4 oral liquid formulation could circumvent malabsorption induced by the increased gastric pH, resulting from atrophic gastritis, or due to PPI therapy.

Recent results demonstrated that liquid L-T4 could prevent the problem of malabsorption in patients with BPD, or RYGB, suggesting that the L-T4 oral liquid formulation could circumvent malabsorption after bariatric surgery.

Moreover, the use of L-T4 as liquid solution has been studied also in pregnancy, newborns and infants, suggesting a better bioequivalence than L-T4 in tablets.

Finally, it has been shown that liquid L-T4 is more effective than L-T4 tablets in maintaining TSH values under control in hypothyroid patients without malabsorption, drug interference, or gastric disorders, suggesting an increased absorption of the oral liquid L-T4 formulation also in these patients.

Further studies will be needed to evaluate the role of liquid L-T4 in celiac disease, lactose intolerance, or in patients with other drugs that interfere with L-T4 absorption such as calcium, or iron salts, or bile sequestrants.

Few studies have evaluated soft gel L-T4 in clinical studies with promising results in patients with coffee-associated L-T4 malabsorption or gastric-related T4 malabsorption. However, future studies are in program to evaluate soft gel L-T4 in other conditions of impaired L-T4 absorption.

Article highlights box

1-The most recent advance concerning L-T4 therapy is the development of novel oral formulations: the liquid preparation, and the soft gel capsule. The liquid formulation is composed of L-T4, glycerine and ethanol, and it does not need a gastric phase of dissolution.

2-The most important advantage of the liquid L-T4 solution is the possibility of administration in patients who are not able to swallow tablets, such as in patients treated through enteral feeding tube.

3-The liquid formulation has been shown to overcome: 1- the food and beverages intereference with L-T tablets absorption, caused by food or coffee at breakfast; 2-malabsorption induced by the increased gastric pH, resulting from atrophic gastritis, or due to PPI therapy; 3-malabsorption in patients with BPD, or RYGB after bariatric surgery.

4-Moreover, the use of L-T4 as liquid solution has been studied also in pregnancy, newborns and infants, suggesting a better bioequivalence than L-T4 in tablets.

5-Finally, it has been shown that liquid L-T4 is more effective than L-T4 tablet in controlling TSH levels in hypothyroid patients without malabsorption, gastric disorders, or drug interference, suggesting an increased absorption of L-T4 with the liquid formulation also in these patients.

6-Few studies have evaluated soft gel L-T4 in clinical studies with promising results in patients with malabsorption related to coffee or gastritis.

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Declaration of interest

The Authors have no conflict of interests to declare.