

GUIDELINES

ETA guidelines for the use of levothyroxine sodium preparations in monotherapy to optimize the treatment of hypothyroidism

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Abstract

Sodium levothyroxine (LT4) as a monotherapy represents the mainstay of treatment of hypothyroidism, and its use has increased over time. Nevertheless, it faces several potential barriers in its 'real life' utilization, and hence its clinical effectiveness may be marred. This is suggested by the frequent situation of patients failing to reach the therapeutic goals of symptom relief and serum TSH control. Thus, an expert task force was approved by the Guidelines Board of the European Thyroid Association to examine the available data and to formulate recommendations based on the available evidence and the experts' deduction. The task force provides a body of suggestions to optimize the levothyroxine treatment in monotherapy, considering the key point in the individualization of treatment. Furthermore, the nutritional, pharmacological and pathological factors, potentially leading to the increased need for levothyroxine, are discussed, with a specific focus on the use of liquid and softgel formulations of the hormone.

Keywords: levothyroxine therapy; hypothyroidism; levothyroxine malabsorption; levothyroxine formulations; patient adherence

Introduction

Sodium levothyroxine (LT4) as a monotherapy represents the mainstay of treatment of hypothyroidism, and its use has been increasing over time reaching a steady state in recent years remaining, however, one of the most prescribed medication worldwide (1). Three main features characterize this therapeutic approach: a) it is usually a lifelong treatment; b) it is a drug with a narrow therapeutic index; c) several interfering factors may

blunt reaching the therapeutic goal, namely a serum TSH level within its reference limits in the absence of signs and symptoms of hypothyroidism. Thus, this 'easy to use' hormone medication faces several potential barriers in its 'real life' utilization, and consequently, its clinical effectiveness may be marred. Indeed, using serum TSH as a marker of adequate thyroid hormones status in LT4-treated primary hypothyroid patients, almost half

of treated patients in the world appear to be under- or over-treated (2). It is worth noting that serum TSH concentrations may be altered by the patient's demographic characteristics and comorbidities, concomitant drug use, assay interference and so on (3, 4). LT4 over-treated patients are exposed to a chronic state of excess iodothyronines in the more sensitive target tissues, mainly the heart and bones (5), while undertreated patients may experience subtle and nonspecific symptoms that are difficult to distinguish from those in many other clinical situations (6). Among them, the most frequently reported ones are cold intolerance, depressed mood, decline in memory, fatigue and muscle weakness (7), affecting their health-related quality of life (QoL). These symptoms are persistently complained by a fraction of patients with serum TSH and thyroid hormones within the reference intervals. These complaints may be due to concomitant comorbidities, psychosocial factors and/or unrealistic expectations toward LT4 treatment (8). This issue is further complicated by the evidence that most cases of primary hypothyroidism are initially mild or subclinical and there is no consensus on when to start treatment (3, 9). In addition, most LT4 users are treated based on a single, mildly elevated serum TSH or even when it is within the reference intervals, often in an inappropriate way (10). Compliance is another challenging aspect of LT4 therapy. Poor adherence to treatment has been considered for long time as the main cause of LT4 treatment failure (11). Nowadays, we know that other causes may be equally relevant, as in the case of nutritional, pharmacological or pathological interferences (12, 13, 14). Novel formulations of LT4 were made available by pharmaceutical companies aimed at overcoming these issues (15). Keeping this information in mind, it has become clear that a guideline to optimize the treatment with levothyroxine monotherapy is needed, even in a situation where other treatment options are available. Methodology used in this guideline is provided as Supplementary Material (see section on [Supplementary materials](#) given at the end of the article)

Issues about the drug

The pharmaceutical form of thyroxine available is the levothyroxine sodium salt pentahydrate (LTSS), introduced in 1949 (16). Levothyroxine sodium shows a markedly increased solubility and more reliable intestinal absorption compared to the free acid form of T4, and it is now the active pharmaceutical ingredient (API) of T4 tablets (17). The discovery in 1970 that the prohormone T4 is efficiently enzymatically converted to T3 by endogenous deiodinases (18) in athyreotic patients resulted in a switch to T4 monotherapy during the next four decades: indeed, daily administration of the long-lived prohormone T4 ($t_{1/2} \sim 7$ days) avoided post-absorptive high T3 peaks associated with unwanted side effects of the short-lived T3 ($t_{1/2} \sim 1$ day) (19).

T4, oxidatively coupled from two iodinated L-tyrosine amino acid residues, contains three charged functional groups at physiological pH: two of them are acidic (the side chain carboxylate and the 4'-phenolic group) and the other one is basic (the protonated side chain amine), as characterized by their different pKa-values (20). Based on environmental pH, the T4 may exist in different ionization states from cationic prevailing in acid conditions to di-anionic at more basic pH (21). In addition, the solubility of LT4 decreases from medium at pH 1 to 3, reaching a much lower level at pH 7, and then increasing again at more basic pH values in solution (22).

Thyroid hormones and their metabolites are very hydrophobic, a feature increasing with higher iodination grade and poorly soluble at neutral physiological pH. They are more soluble and more stable in solution at alkaline pH. At very low pH, their solubility increases too, while decomposing more rapidly then. Despite the classification of LT4 as a Class III drug (relatively high solubility and low permeability compounds) by Biopharmaceutics Classification System (BCS), several other factors markedly impact on the solubility and/or stability of the active ingredient, such as excipients in its pharmaceutical formulation (23, 24). A detailed comparative analysis of common drug excipients on stability and potency of LT4 (25) revealed the best outcome for binary mixtures with dibasic calcium phosphate combined with a basic 'pH modifier' (sodium carbonate, sodium bicarbonate, or magnesium oxide). A further factor influencing stability and decomposition of LTSS is the gradual loss of the non-stoichiometric number of five crystal water molecules yielding LT4 monohydrate. This process already occurs under realistic storage conditions, and along with light exposure and high temperatures, may contribute to the chemical decomposition of LT4 (26).

LT4 is even one of the most frequently recalled products from the market in several countries, mostly for issues in maintaining potency during the shelf life (26). A case series article reported some clinical evidence of the refractoriness of hypothyroidism due to improper storage of tablet levothyroxine (27). Moreover, being characterized by a narrow therapeutic index, FDA restricted the potency range for marketed products to $100 \pm 5\%$ of the labeled amount (<http://www.fda.gov/cder/drug/infopage/levothyroxine/qa.htm>). However, it is known that chemical equivalence does not automatically correspond to bioequivalence, which is determined by pharmacokinetic tests on healthy volunteers (28) but may differ from actual bioequivalence in patients in different clinical settings (29). Considering that the LTSS ranks among the top ten medically prescribed drugs worldwide, the safety, stability and reliability of T4 preparations are highly demanding for production, storage, shelf life, distribution and use of this medication by patients living under different socio-economic and regional conditions.

Recommendation 1

The progressive dehydration of the active ingredient levothyroxine sodium salt pentahydrate requires careful check of the hormone's storage conditions.

Weak recommendation. Quality of evidence (0000). Agreement 8/8

Issues about the patients

The barely compliant patient

Hypothyroidism often requires lifelong treatment with LT4, for which patients' compliance is essential for therapeutic success, the latter reflected in TSH levels restored to reference interval. Despite WHO stating that the mean adherence rate for long-lasting treatments is about 50%, hypothyroidism treatment has been reported to be one of the clinical conditions for which there is better patient compliance (30). However, in 1991, Ain *et al.* explored the issue of patient compliance vs malabsorption of medication in the context of persistent hypothyroidism, and these patients were found to have normal percentage of absorption of LT4 administration (31). Indeed, poor compliance, and often intentional non-adherence, are among the several factors that hamper the achievement of euthyroidism (11). While patient–physician cross-talk must be kept high as long as the treatment is required, nevertheless, the above situation leaves the physicians perplexed, speculating whether their patient's condition may be related to gastrointestinal problems or interference from food and/or other drugs (14). The LT4 absorption test proved to be an effective and safe way to assess refractory hypothyroidism, providing reliable information to distinguish LT4 malabsorption from 'pseudomalabsorption', a condition of intentional or unintentional non-adherence (32). There was some variability about the procedures for LT4 absorption test; namely the dose of levothyroxine and duration of sampling, the frequency of blood collection and the interpretation of the results (32). In fasting patients, 600–2,000 µg are given and the absorption profile via measurement of FT4 level was observed at hourly intervals up to a 6 h period (32). In a cross-sectional study, a total of 100 patients (25 euthyroid, 25 newly diagnosed hypothyroid, 25 treated hypothyroid with TSH within the reference intervals, and 25 hypothyroid subjects with elevated TSH despite an adequate dose of LT4 over more than 6 months) and ten euthyroid subjects with true malabsorption were administered LT4 (10 µg/kg or maximum 600 µg) (33). These authors reported that free T4 increment at 3 h above 5.15 pmol/L had a sensitivity of 97% and a specificity of 80% in excluding true malabsorption. If the test indicates abnormal LT4 absorption upon increasing the dose, it is indicated to start a diagnostic workup for gastrointestinal

malabsorption, as described in (14). Furthermore, a modified 6 h LT4 absorption test was carried out at the Mayo Clinic with patients receiving a weight-based dose of LT4 followed by serial measurements of TT4 and TSH (34). One patient who had known causes of malabsorption exhibited impaired absorption.

Recommendation 2

2a) *When the dose of levothyroxine needed to restore serum TSH within the reference interval exceeds 1.5–1.7 µg/kg/day in adult hypothyroid patients with thyroid in situ or 1.8–2.0 µg/kg/day in thyroidectomized patients, always explore low adherence to treatment or even pseudomalabsorption.*

Strong recommendation. Quality of evidence (0000). Agreement 8/8

2b) *In levothyroxine refractory patients, upon exclusion of nutrients, drugs and known interference from comorbidities, a levothyroxine absorption test should be performed when clinically appropriate.*

Strong recommendation. Quality of evidence (0000). Agreement 8/8

The costs of thyroxine treatment for the health system

Levothyroxine sodium is available in tablet or capsule form as a solution and as powder to be made into a solution; the price may vary depending on the form, insurance, and country. More specifically, hypothyroid treatment that is not covered by insurance typically costs €15–€50 per month or €180–€600 per year, depending on the dosage, form, country, and brand name (35, 36, 37, 38, 39). In addition, the indirect costs of changing brand or formulations (medical costs and higher consumption of healthcare resources) has been recognized ((28, 36), this latter study was funded by industry). Generic levothyroxine is available for the treatment of hypothyroidism; however, potency can vary from manufacturer to manufacturer, and there is also uncertainty as to whether the patient will receive the same generic drug from the same manufacturer each time (37). Switching among generics is not associated with clinically significant changes in TSH level for Brito *et al.* in a study encompassing some 16,000 patients (38) but not for others (28, 37, 39, 40). However, the study from Brito *et al.* was based on 'an administrative claims database linked to laboratory test result'. Therefore, this approach may conceal several confounding issues, and this work was carried out on generic preparations, widely used in US and much less in Europe. To note, authors stated that more than 50% of patients have been treated with 'daily levothyroxine dose of 50 µg or less', a statement that may add uncertainty about the adequacy of treatment. The conclusion of a systematic review highlighted 'the limited and mixed evidence in real-world clinical and economic outcomes for generic

levothyroxine' (37). The effects of switching among brand and generic and from different levothyroxine formulations are also a matter of debate. In European countries, the switch from one levothyroxine brand to another caused some health issues (39). These adverse effects included headaches, muscular fatigue, depression, anxiety, hair loss and insomnia. Owing to some uncertainties regarding the levothyroxine bioequivalence of certain generics to that of branded compounds, some variation in patients' TSH levels were observed (28, 39, 40). Moreover, adherence to a LT4 preparation results in significantly reduced hypothyroidism-related non-drug medical costs and hypothyroidism-related total medical costs (28, 40). Finally, increased healthcare costs have been observed when patients switch from a brand name to generic and a further increase when they frequently change the dose ((36), this study was funded by industry). Patients must therefore be aware that their generic LT4 prescription may be switched at the pharmacy and must ask to remain on the compound at every refill. A Joint Position Statement from the European Thyroid Association (ETA) and Thyroid Federation International (TFI) affirmed that after a formulation change of levothyroxine, bioequivalence does not guarantee continued euthyroidism (39).

Recommendation 3

In patients with optimal biochemical hormonal replacement and no clinical contra-indication, the current treatment should be maintained on the same brand or preparation of levothyroxine. Should any change be necessary and in consideration of the clinical situation, a measurement of FT4 and TSH after 6 weeks is advised.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

The search for a minimal effective dose

Timing of treatment with LT4

Several studies have examined the effect of timing of LT4 ingestion on serum TSH level, considered the best marker of systemic thyroid hormone status. Although there are differences in the exact timings of LT4 administration and the study design, the general inference is that fasting regimens and bedtime regimens are associated with TSH values within the reference intervals. In a study which compared three timing regimens in 65 patients with primary hypothyroidism, a with-breakfast dosing resulted in the highest and most variable TSH levels, while a regimen of LT4 being administered an hour before breakfast was associated with the lowest and least variable TSH; the bedtime LT4 regimen produced values and variability that was in-between the other two

dosing regimens (41). Another 3-period crossover randomized trial in 84 patients with primary hypothyroidism demonstrated no significant differences in serum TSH, FT4 or FT3 levels during 8 weeks of before breakfast, an hour before the main meal or bedtime ingestion of LT4 (42). As primary hypothyroidism is frequently diagnosed and treated in older individuals, the importance of drug scheduling becomes even more important due to issues relating to polypharmacy and drug interactions. A randomized crossover trial in 201 older patients (60 years or older) did not detect any significant differences in the mean TSH levels between an hour before breakfast administration versus an hour after evening meal dosing regimen (43). To note, the lag time between the meal and the levothyroxine ingestion was 1 h, a time in which the digestion process is clearly at the beginning, since the gastric transit time ranges from 2.4 and 3.5 h (44). Furthermore, the characteristics of these polypharmacy patients and the interfering factors were heterogeneous, preventing from draw definite conclusions. The key consideration for selecting a particular time for a patient for taking LT4 should be the regimen that is easy to remember and convenient, and thus potentially increases adherence.

Recommendation 4

The task force recommends that the timing of levothyroxine administration should be in keeping with the patient's lifestyle. The interval between drug and food or drink intake must be not less than 30 min in any case. However, to obtain an optimal therapeutic efficacy, levothyroxine should be consistently taken either 60 min before breakfast or at bedtime (3 or more hours after the evening meal).

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Interference with food

The optimal absorption of LT4 is under fasting conditions, with 62–82% of the dose absorbed during the first 3 h after ingestion (45). Some types of foods and dietary supplements have been reported to reduce LT4 absorption, including soy, coffee, calcium, and grapefruit (14, 46) (Table 1). Notwithstanding that the absorption of oral thyroxine (T4) occurs predominantly in the jejunum and ileum (45), patients with gastric disorders show a requirement for higher T4 doses (47). Evidence has been provided *in vitro* that pH variations of the medium interfere with T4 dissolution (48). The presence of an acidic environment in the stomach enables the disaggregation and dissolution of tablet formulations to occur (49), thus enhancing LT4 absorption at the intestinal level. It is interesting to note that vitamin C can improve LT4 absorption, presumably by providing an acidic gastric environment (50). Natural juices are instead believed to increase pH in

Table 1 Food, beverages and dietary supplements known to interfere with oral thyroxine bioavailability (see ref. 14, 46, 84).

Food, beverages and dietary supplements	Mechanism of interference	Suggestion	Possible switch to softgel or liquid LT4
Dietary fibers (wheat bran)	LT4 binding	Take LT4 at least 4 h before	
Soy	LT4 binding	Take LT4 at least 4 h before; avoid use if possible	
Coffee (espresso, drip coffee)	LT4 binding	Take LT4 at least 1 h before	Softgel
Tea	LT4 binding?	Take LT4 at least 1 h before	
Milk	Calcium and proteins interference	Take LT4 more than 1-2 h before	
Grapefruit juice	Inhibition of intestinal T4 transporters	Take LT4 at least 4 h before	
Papaya	LT4 binding? Alkalinization of gastric juice	Take LT4 at least 4 h before	
Over-the-counter whey and soy protein supplements	Delayed gastric emptying? Inhibitory effect on ileal transporters?	Delay assumption >4 h since ingestion of thyroxine; avoid use if possible	
Calcium salts (calcium carbonate, calcium citrate, calcium acetate)	Ca ⁺⁺ binding LT4 at acidic pH (gastric level)	Take LT4 at least 4-6 h before	Liquid/softgel
Iron salts (ferrous sulfate, ferrous fumarate)	Fe ⁺⁺⁺ binding LT4 at pH 7.4 (intestinal level)	Take LT4 at least 4 h before iron-based preparations	Liquid
Vitamin C	Increased gastric juice acidity in patients with hypochlorhydria		
Nicotinic acid	↓ T4 binding to plasma proteins	Usually changing dose unnecessary	

the stomach and reduce LT4 bioavailability (51). Enzymes such as papain that are present in papaya possibly delay gastric emptying and decrease LT4 bioavailability (52). On this ground, Singh *et al.* (53) reported that both acute and chronic ingestions of calcium carbonate can reduce the *in vitro* bioavailability of T4 by binding it in a dose-dependent fashion at medium pH 2. The effect of administration of LT4 alone or concomitantly with milk was investigated in a study recruiting ten healthy patients (54). Peak serum T4 concentrations and area under the curve (AUC) were found to be significantly lower in patients taking LT4 simultaneously with cow's milk (containing 450 mg calcium) as compared to ingestion of LT4 alone (54). LT4 sequestration is the proposed mechanism for many other food items and coffee. This has been investigated with espresso and American (filter) coffee, without milk, co-administered with LT4 (55). Coffee significantly decreased both the incremental rise (by 36% in hypothyroid patients and 29% in healthy volunteers) and the peak of serum T4 levels by 30 and 19%, respectively, and also delayed the time for T4 to reach the maximum serum level (by 38 and 43 min, respectively). Based on these results, a 1 h break between coffee and LT4 intake is recommended to avoid any interaction. A fiber-enriched diet or fiber supplements may cause malabsorption, as LT4 is non-specifically absorbed by the fibers (56); the latter is likely to delay gastric emptying (56), although this effect is most likely modified by the type of fibers (soluble or insoluble), the quantity of fibers ingested, and the patient's hydration status. Soy protein and soy isoflavones possibly interact with LT4 treatment, although the clinical significance remains uncertain at present (57, 58). Some ingredients of natural juices, particularly grapefruit and apple juice,

may block the organic anion-transporting polypeptide (OATP) family and the monocarboxylate transporter (MCT) family or NTCP (sodium-taurocholate co-transporting polypeptide) carrying LT4 from the small intestine to the circulation (59). Some religious fasting may be mentioned; indeed, TSH increases significantly after Ramadan. No timing schedule provided advantage in maintaining thyroid control (60). The TSH changes during Ramadan may be associated with age (inverse association), weight gain, and the number of non-adherence to LT4 days (61).

Recommendation 5

In a previously well-controlled hypothyroid LT4-treated patient, the finding of an altered thyroid function test (TFT) may be due to a transient interference by some specific food or a changed dietary habit. The task force recommends, in non-pregnant patients, retesting TFT before increasing the dose of LT4.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Minimal effective dose of LT4

The dose of LT4 required to maintain a euthyroid state is one that alleviates symptoms of hypothyroidism and maintains serum TSH level within the reference interval (17). Several factors can affect the dose of LT4 required to maintain a particular patient's TSH within the reference interval. There is consistent evidence that actual body weight/lean body mass/ideal body weight, age, etiology of hypothyroidism, degree of serum TSH elevation pre-treatment, and pregnancy can influence LT4 dose requirement. Despite that, a more accurate

predictor of daily LT4 dose would be the lean body mass (62); its limited availability in most routine clinical settings makes normalization of LT4 dose based on actual body weight easier. Based on body weight, hypothyroid patients with minimal endogenous thyroid function appeared to require LT4 doses between 1.6 and 1.8 µg/kg/day of actual body weight, although some studies estimate higher doses of 2.0–2.1 µg/kg/day for some patient groups (63). However, these reference intervals referred to patients in whom the interference and the comorbidities were not taken into account. Doses of levothyroxine of approximately 1.3–1.5 µg/kg/day were reported to be sufficient in control subjects positively devoid of comorbidity or drug interference (49). According to a RCT study carried out in 75 overt hypothyroid patients, a full starting dose of levothyroxine is safe and may be more convenient and cost-effective than a low starting dose regimen (64) in patients <65 years without heart comorbidities. Older patients with hypothyroidism require lower doses of LT4 to maintain euthyroidism, as lean body mass, iodothyronine metabolism and elimination rate decrease with age (65). In iodine replete populations, serum TSH levels increase after the age of 60 years (66). However, it is not yet clear whether the target serum TSH in older patients on LT4 treatment needs to be altered to reflect this change in the hypothalamic–pituitary–thyroid setpoint (67). In contrast to the consistent results reported in the above studies, the effect of sex, menopausal status, and the presence of the type 2 deiodinase gene (*DIO2*) Thr92Ala polymorphism have not been conclusive (68). With regards to the effect of deiodinase polymorphisms on the LT4 dose required to reach a target TSH concentration, one study showed that individuals with thyroid cancer with the *DIO2*-Thr92Ala polymorphism required a higher dose of LT4 in order to achieve near suppression of their serum TSH levels (69). Another larger study, in contrast, found no effect of this polymorphism on the LT4 dose required to achieve TSH suppression in thyroid cancer patients or TSH within the reference intervals in patients with autoimmune hypothyroidism (70). Given the inconsistencies in the literature, it is not yet feasible to say whether a patient's genetic composition predicts LT4 requirements.

Recommendation 6

When deciding a starting dose of levothyroxine and calculating the daily requirement, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, age, and general clinical context should be considered.

Strong recommendation. Quality evidence. (0000) Agreement 8/8

Side effects of under- and overtreatment

The World Health Organization (WHO) has classed levothyroxine (LT4) as a narrow therapeutic index drug. This is because small changes in LT4 dose can lead to substantial variation in serum TSH levels (71).

Observational studies of LT4-treated patients with hypothyroidism have demonstrated that almost half of the patients have serum TSH levels that are either low or high, indicative of over- or under-replacement (2). Analyses of real-world data from patient registries have demonstrated that the levels of serum TSH outside the reference intervals, in patients with LT4-treated hypothyroidism, are associated with adverse health outcomes, including ischemic heart disease events, cardiac dysrhythmias, fractures, and heart failure (5, 72, 73). These risks were particularly more pronounced in those with serum TSH levels that are consistently at the extremes (<0.1 or >10.0 mU/L). There is robust evidence that serum TSH levels increase slightly with age, particularly after the age of 65–70 years (9, 74). However, it is not clear whether this translates to different target ranges for serum TSH in older patients on LT4 treatment for hypothyroidism (67). Altering the LT4 dose over 6 months does not lead to significant changes in the objective measures of quality of life, mood or cognition (75). However, patients with hypothyroidism appear to prefer perceived higher doses of LT4 despite the lack of objective benefit. Furthermore, adjusting the LT4 dose to manipulate serum TSH levels in and near the limits of the reference range does not have any significant effects on energy expenditure or body weight and composition (76).

Recommendation 7

7a) The task force recommends that the dose of levothyroxine in patients with primary hypothyroidism should be adjusted to aim for a serum TSH level within the population reference interval. Once the target TSH is achieved, complicated regimens and minute adjustments of LT4 dose to improve quality of life or modulate body weight are not useful and not advised.

Strong recommendation. Quality of evidence. (0000) Agreement 8/8

7b) Serum TSH increases with age. Efforts should be made to individualize treatment in accordance with the subject's age and degree of comorbidities. A more relaxed TSH reference interval should be adopted in older people (over age 70) with LT4-treated hypothyroidism.

Weak recommendation. Quality of evidence. (0000) Agreement 8/8

Thyroxine interaction with drugs and polypharmacy

Drug interaction with LT4 absorption

The use of drugs interacting and/or interfering with the different formulations of levothyroxine may represent a significant issue when treating patients in a 'real life' setting. Some exhaustive reviews on this topic contained most of this information (12, 13, 14, 42, 51, 77). Table 2 lists the drugs that are likely to affect LT4 bioavailability, and

Table 2 Drugs known to interfere with oral thyroxine bioavailability and TSH levels (see ref. (12, 14, 84)).

Drugs	Mechanisms of interference	Suggestion
Antacids, sequestering agents and prokinetic		
*PPI (esomeprazole, omeprazole, pantoprazole, lansoprazole)	↓ gastric juice acidity; ↑ UDP-glucuronyltransferase (rats)	Take LT4 at least 4 h before PPI
Cimetidine	↓ gastric juice acidity	Switch to another drug of the same category
Aluminum hydroxide	Al ⁺⁺⁺ binding LT4 at pH 7 (intestinal level)	Take LT4 at least 4 h before
Magnesium hydroxide	Mg ⁺⁺ binding LT4 at pH 7 (intestinal level)	Take LT4 at least 4 h before
Sucralfate	Binding LT4	Take LT4 at least 4 h before sucralfate
Cholestyramine and colessevelam	Binding LT4 at intestinal level; inhibiting enterohepatic recycling	Avoid concomitant use or maximally separate their intake
Sodium polystyrene sulfonate	Binding demonstrated both at pH 2 and 7; inhibiting enterohepatic recycling	Avoid concomitant use or maximally separate their intake
Lanthanum carbonate	Binding LT4? Effects at intestinal epithelium level?	Avoid concomitant use or maximally separate their intake
Sevelamer hydrochloride	Binding LT4?	Avoid concomitant use or maximally separate their intake
Domperidone, metoclopramide	Slightly ↑ TSH	Thyroid function monitoring
Antiepileptic, antipsychotics, antidepressant		
Carbamazepine	Faster catabolism	Thyroid function monitoring – increase dose in thyroidectomized patients
Phenytoin	Faster catabolism; ↓ binding to plasma proteins; ↓ TSH	Thyroid function monitoring – increase dose in thyroidectomized patients
Fluoxetine	?	Thyroid function monitoring
Sertraline	?	Thyroid function monitoring
Phenothiazines, haloperidol	Slightly ↑ TSH	Thyroid function monitoring
Tricyclics	Slightly ↑ TSH	Thyroid function monitoring
Compounds with hormonal and/or anti-hormonal action		
Corticosteroids	↓ TSH	Thyroid function monitoring
Androgens	↓ binding to plasma proteins; ↓ TSH	Thyroid function monitoring – reduce dose
Estrogens	↑ binding to plasma proteins; ↑ TSH	Thyroid function monitoring – increase dose
Tamoxifen	↑ binding to plasma proteins	Thyroid function monitoring – increase dose
GH	Faster T4 metabolism	Thyroid function monitoring
Raloxifene	↑ binding to TBG?	Avoid concomitant use or take LT4 at least 12 h before
Mifepristone	Intestinal malabsorption? – Increased inactivation of T4 via deiodinases?	Thyroid function monitoring – increase dose
Somatostatin analogs	Transiently ↓ TSH	Thyroid function monitoring
α-Methyldopa	Slightly ↑ TSH	Thyroid function monitoring
Bromocriptine and cabergoline	Transiently ↓ TSH	Thyroid function monitoring
Antibiotics and chemotherapy drugs		
Ciprofloxacin	Competition with LT4 for OATP1A2	Avoid concomitant use
Rifampin	Variations in LT4 catabolism? ↑ TBG?	Thyroid function monitoring
Antiretroviral drugs	↑ T4 metabolism	Thyroid function monitoring
TKI (sorafenib, motesanib, imatinib)	↓ conversion T4 to T3; inhibition of T4 transporters	Thyroid function monitoring
Mitotane	↑ binding to plasma proteins; faster T4 metabolism; ↓ TSH	Thyroid function monitoring
Bexarotene	Faster T4 metabolism; ↓ TSH	Thyroid function monitoring
Miscellaneous drugs		
Propranolol	↓ conversion T4 to T3	Thyroid function monitoring
Amiodarone	↓ conversion T4 to T3	Thyroid function monitoring
Lovastatin	↑ T4 catabolism	Change lipid lowering drug
Furosemide, ethacrinic acid	Reduced binding to plasma proteins	Usually changing dose unnecessary
Heparin	↓ binding to plasma proteins	Usually changing dose unnecessary
Salicylates and NSAIDS	↓ binding to plasma proteins	Usually changing dose unnecessary
Metformin	↓ TSH	Thyroid function monitoring
Chromium picolinate	Binding LT4? ↓ intestinal transporters?	Take LT4 at least 4 h before
Orlistat	Binding LT4? ↓ intestinal transit?	Take LT4 at least 4 h before
Simethicone	Binding LT4?	Avoid concomitant use
Clofibrate	↑ binding to plasma proteins	Thyroid function monitoring – increase dose

*Possible switch to softgel/liquid.

consequently, may necessitate modification of dosage requirements.

Most of the commonly prescribed drugs act by sequestering the hormone in the intestinal content, thus considerably decreasing LT4 bioavailability. This mechanism of interference is shared by bile acid sequestrants, such as colestevam, colestyramine, and/or phosphate binders, sevelamer hydrochloride or lanthanum, and even antacids containing aluminum hydroxide or sucralate. These latter, however, may alternatively act by altering gastric acidity (14). Indeed, several studies have demonstrated that patients with decreased gastric acid secretion, owed to the use of proton pump inhibitors (PPIs), may need higher LT4 doses to achieve target TSH levels, long-term PPI administration presenting a heightened risk in these cases (47, 78). A number of drugs, such as phenytoin, carbamazepine, salsalate, salicylate, furosemide, diclofenac, ethacrynic acid, and heparin, have been observed *in vitro* to displace T4 from the distribution proteins, changing the amount of thyroxine bound to plasma protein, while biotin may interfere with some T4 assay systems (79, 80). Ciprofloxacin is a quinolone antibiotic that has been reported to interfere with the intestinal transport of thyroxine, leading to decreased LT4 bioavailability, in contrast to rifampicin, an antibiotic used to treat several bacterial infections, including tuberculosis, which increases LT4 bioavailability (81). On the contrary, vitamin C seems to increase the efficacy of LT4 absorption in a subset of hypothyroid patients with decreased gastric acidity (50). Over-the-counter protein supplements, such as whey protein, can even interfere with LT4 absorption since whey protein appears to delay the responsiveness of organic anion transporters in the ileum (82). Supplements containing ferrous salts or treatment with ferrous preparations decrease LT4 bioavailability by adsorbing LT4 (46). Chromium picolinate supplementation, prescribed to control body weight, has been shown to decrease LT4 bioavailability by up to 17% (83).

In conclusion, the co-prescription of LT4 with several interacting drugs or supplements can frequently lead to decreased LT4 bioavailability, which may often be clinically relevant (84). Clinicians should thus be well-acquainted with all the above-mentioned proven and suspected drug–drug, supplement–drug, and food–drug interactions (Tables 1 and 2).

Recommendation 8

The task force recommends a careful anamnestic interview on the drugs concomitantly used by LT4-treated patients. Ideally, discontinuing the interfering drug, when possible, would be the best option. Otherwise, scheduling an appropriate lag time between levothyroxine and the interfering drug is advisable (see Table 2). In cases of expected interference due to drugs prescribed for more than 2 weeks of treatment, the dose of levothyroxine can be adjusted for the period of treatment.

Strong recommendation. Quality of evidence. (0000) Agreement 8/8

Patients in special situations

Background

Some special patient situations inherently lead to more challenging management of hypothyroidism replacement, and therefore require special attention in order to avoid over- or undertreatment with LT4. Although there are not many peer-reviewed publications in relation to these rare special situations and use of different LT4 formulations, they are worth mentioning, because they are clinically relevant and important for the proper management of patients with hypothyroidism. Based on this lack of scientific evidence, the statements below are mainly expert opinion based.

Pregnancy and oral contraceptive pills

Pregnancy is physiologically associated with a higher requirement of T4 production from the thyroid due to a variety of factors, including increased production of thyroid hormone distribution proteins (mainly TBG) in the liver, delivery of T4 to the growing feto-placental unit and increased degradation of T4 by placental D3. In patients on LT4 replacement therapy, this increased requirement can only be satisfied by an increased replacement dose, with a reduction in the dose to pre-pregnancy values after delivery. However, management of hypothyroidism during pregnancy is still complicated (85, 86). Due to the very high and increasing distribution proteins, a TSH-like effect from HCG, an unstable hypothalamus–pituitary–thyroid balance, and the long physiological half-life of T4, it can be challenging to correctly interpret the most commonly used thyroid function tests TSH and FT4 (87, 88). Serum TSH becomes suppressed at the end of the first trimester, when HCG is high, but should not result in a decrease of LT4 replacement dose; free T4 measurement is often disturbed in the presence of high circulating thyroid hormone-binding proteins, because the methods do not correct the total T4 measured by the platforms in the extreme ends of the correction curve (as is the case for both late pregnancy and high estrogen oral contraceptive drugs). In many of the methods, the failed correction results in falsely high free T4, which should not result in a decreased replacement dose. The safest measurement plan is to measure both total (where trimester-specific references ranges are available) and free T4 and TSH, follow the dynamic changes closely and account for the long T4 half-life and slow TSH reaction to the changes in order to keep the replacement at euthyroid levels. Both ETA and ATA guidelines on this topic have been published (85, 86).

Recommendation 9

9a) The task force recommends monitoring TSH, free and total T4 tests in LT4-treated hypothyroid pregnant women at least in each trimester.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Fertility treatment

Pregnancies induced by assisted reproduction technology involve high dose gonadotropin stimulation of ovulation. A recent systematic review and meta-analysis documents what has long been suspected, that this treatment results in a decrease in free T4 and rise in TSH in women with normal thyroid function before stimulation. This is due to a rapid increase of thyroid hormone-binding protein production that far exceeds the rate of increase in a normal pregnancy, the extent of which is also determined by the duration and intensity of ovarian stimulation (OS) (89). The implication of this procedure for women on LT4 replacement is that increasing the LT4 dose should be considered before commencing the stimulation in order to avoid under replacement at a very critical phase of the pregnancy, also taking into account the long time to obtaining steady state of serum T4 due to the half-life (90). Anticipating the degree of change is difficult and prone to many variables, but we recommend keeping TSH levels <2.5 mIU/L before the start of the OS in women on levothyroxine and planning thyroid function testing 2 weeks after a positive pregnancy test. However, there are no controlled trials with regard to clinical outcome on this topic.

9b) LT4 replacement during fertility treatment with ovarian stimulation might require prior increase of the replacement dose in order to keep TSH levels <2.5 mIU/L and match the LT4 to the very steep rise in thyroid hormone-binding proteins.

Weak recommendation. Quality of evidence (0000). Agreement 8/8

Central hypothyroidism

In hypothalamus–pituitary–hypothyroidism or central/secondary myxedema, the thyroid hypofunction is due to a failure of pituitary TSH production. However, unfortunately, biologically inactive TSH is mostly measurable by the TSH immunoassays, and therefore serum TSH is useless in the diagnosis of central hypothyroidism and in the monitoring of replacement (91). The evidence to support this recommendation is contained within previous ETA guidelines and has not changed (91).

Recommendation 10

The task force recommends that LT4 replacement in central hypothyroidism should be monitored by the measurement of free T4 but not TSH value.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Elderly patients

Several different variations of thyroid pathophysiology have been described in the elderly (92, 93). Reduced lean body mass, reduced T4 absorption and outer ring deiodination as well as the presence of comorbidities and the use of drugs are among them (14, 42, 51). In a population study, 70% of patients >80-years-old showed a serum TSH greater than 4.5 mU/L (97.5 centiles = 7.49 mU/L) (74). An age-specific reference interval should be used to avoid misdiagnosing subclinical thyroid disorders. Therefore, the treatment of elderly patients is usually suggested only for patients showing persistent TSH levels >10 mU/L, while the decision is patient-tailored for TSH levels between 7 and 10 mU/L (9). In the elderly, LT4 treatment should start at low doses (12.5–25 µg/kg/day) depending on the patient's frailty and comorbidities (64). A reduced therapeutic dose of LT4 is suggested in these patients compared to younger subjects (63), but no focused RCTs are available. The detrimental effects of both over- and under-replacement have been reported (94, 95). Therefore, it is of utmost importance to avoid overtreatment of elderly hypothyroid patients on LT4 replacement, and probably rather keep TSH in the higher end of the reference range to protect the aged heart (9, 95).

Recommendation 11

Levothyroxine initiation in older patients with subclinical hypothyroidism with TSH levels between 7 and 10 mU/L should be patient-tailored, and treatment must consider cardiac and bone comorbidities.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Obese patients

In obese patients, a weight-related increase in serum TSH is common, which is not due to glandular failure and returns to normal after weight loss (96). Indeed, the TSH-based diagnosis of subclinical hypothyroidism should be carefully assessed in obese patients. Lean body mass is a major determinant of LT4 treatment (62). However, total body weight is the measurement that is most used in clinical practice, with consequent higher LT4 doses relative to requirements in obese compared with non-obese patients (97). Using BMI adjustment of dose, different ways of calculating the relationship between BMI-related doses had different outcomes in relation to

the achievement of euthyroidism or overdosing, respectively (98). Upon normalization by body weight, the requirement of levothyroxine seemed to be lower than in the non-obese subjects (99).

Recommendation 12

The task force recommends that LT4 treatment dose in obese patients should be carefully adjusted according to body weight, considering the variations of the ratio between lean to fat mass in these patients.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Thyroidectomized patients

After thyroidectomy, a variety of dosing issues with LT4 can occur, depending first of all on the underlying thyroid disease, i.e., cancer, thyroid autoimmunity or non-toxic goiters. Some patients are quite easy to adjust to a correct dose of LT4, i.e., patient operated for an autoimmune thyroid disease (Graves' or Hashimoto), but others may be more challenging, e.g., the case of thyroid cancer surgery. Achieving the correct maintenance dose can thus take some time considering the long half-life of T4. When achieving euthyroid state in these patients is difficult, it may be necessary to look for interfering factors or the presence of autoimmune comorbidities (14, 42, 51). However, quality of life seems to depend more on the degree of hypothyroidism than the level of thyroid surgery (total or partial thyroidectomy) (100). A substantial percentage (from 2/3 to 3/4) of thyroidectomized patients require adjustment of LT4 dose (101). Lean body mass is not the only variable to estimate the therapeutic post-thyroidectomy LT4 dose, owing to the disappearance of thyroidal contribution to circulating T3 (102). Thus, peripheral type 2 deiodinase efficiency becomes relevant in maintaining circulating iodothyronine homeostasis (103). Indeed, low FT3 and an increased FT4/FT3 ratio after thyroidectomy has been reported in about 15% of a large unselected population (102). However, in longitudinal studies, this reduction was not confirmed between pre- and post-thyroidectomy (104, 105). Some studies proposed a scheme to predict the LT4 requirement after thyroidectomy (101). An increased dose up to 25% may be required in thyroidectomized patients to achieve the desired T4 concentration or the target TSH (105, 106). Furthermore, the use of calcium salts in the post-operative period in patients with transient or permanent hypocalcemia results in interference with LT4 absorption (13, 14).

Recommendation 13

The calculation of the LT4 dose in thyroidectomized patients must take into account body weight, underlying thyroid disorder, and the extent of thyroid resection.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Unconscious patients and patients with non-thyroidal illness

Patients in ICU are particularly problematic because they often cannot take tablets orally. In these situations, patients need other routes of administration, either i.v. LT4, or if they have a gastric tube, oral liquid formulation (107). In the monitoring of thyroid replacement, it is important to realize that all patients in ICU have an element of non-thyroidal illness (NTI) (108). This implies, even in replaced patients, a peripheral reduction of conversion of T4 to T3 and an increase to reverse (inactive) T3, which is not routinely measured. Therefore both central and peripheral changes, not related to the replacement itself, may occur. The best strategy is to continue the regular replacement dose and abstain from measurements of thyroid function tests in this situation. Measurements of total and free T3 and T4 and TSH will not reflect the glandular 'thyroid function' of the patients nor of any previously healthy (euthyroid) individuals, but rather the thyroid hormone system, including the extrathyroidal and pituitary contributions (109). The regular replacement dose can be adopted, when the NTI is alleviated.

Recommendation 14

The task force recommends maintaining the LT4 treatment dose in ICU patients and patients with non-thyroidal illness independently from blood tests results, which cannot be interpreted accurately in this situation. If a change in route of administration is required, appropriate dose variation must be applied.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Comorbidities and increased need for oral levothyroxine

A number of disorders affecting the gastrointestinal tract have been referred to as factors interfering with sodium levothyroxine bioavailability, resulting in a spectrum from the need for a modestly increased dose of levothyroxine to frank levothyroxine malabsorption (14). Celiac disease, one of the most common autoimmune disorders in patients with thyroid autoimmunity, may lead to a reduced absorptive surface due to intestinal villi damage and the increased mouth-to-cecum transit time, and the variations in intestinal juice pH, as well (110). In patients with atypical celiac disease, the more frequent form of this disease, an increase of 49% in LT4 requirement, was described that was fully reversed by adherence to a gluten-free diet (110). Lactose malabsorption, the most common disorder affecting levothyroxine bioavailability, has a prevalence of 68% worldwide, although with highly different geographical distribution in different countries (111). The putative reasons leading to levothyroxine

malabsorption are the accelerated intestinal transit and the variations of intestinal environment (e.g., bacterial overgrowth) (112, 113). The median of levothyroxine requirement in patients with lactose intolerance has been estimated to be approximately 31% higher as compared to controls (113). Eliminating the disaccharide from the diet may improve patients' pharmacological thyroid homeostasis (112). The inflammatory injury and the apoptosis of mucosal cells caused by the protozoan *Giardia intestinalis* has been suggested to reversibly affect levothyroxine absorption. (114). A further cause of a reduction of the absorptive intestinal surface is represented by surgical procedures; indeed, a severe reduction of LT4 absorption, independent of the length of residual intestine has been described in patients with short bowel syndrome (115). Even in bariatric malabsorptive procedures, such as jejunum-ileal bypass, a threefold to fourfold higher requirement of LT4 has been demonstrated compared to normal adult patients (116). A defective bile production and secretion has been proposed as one of the mechanisms leading to increased need for LT4 in patients with liver cirrhosis (117). Some case reports also described LT4 malabsorption in patients with cystic fibrosis that was ascribed to pancreatic insufficiency, impaired biliary salt production and anomalies in intestinal transit, as well as the protein wasting disorders (nephrotic syndrome and protein-losing enteropathy) (14). An increased need for levothyroxine has also been observed in patients with ulcerative colitis (118). The levothyroxine requirement was 26% higher in 12 out of the 13 patients with ulcerative colitis examined, even if the disease was in clinical remission. The hypothetical mechanism for the higher

requirement is the small intestine reduced transit time that often characterizes these patients (118). The prototype of an increased need for LT4 is the hypothyroid patient with an impaired gastric homeostasis. Indeed, a study measuring the gastric pH *in vivo* showed a direct correlation between the increasing gastric pH and the patient need for oral thyroxine (49). First described in patients with chronic atrophic gastritis, where the acid-producing parietal cells are destroyed (LT4 need increased from 22 to 34%) (47), the increased gastric juice pH (>2) represents the leading cause of the increased LT4 requirement in patients with all conditions of impaired gastric acidity (47). *Helicobacter pylori* infection and related gastritis represent the prototype of gastric juice alkalization through bacterial urease activity and IL-1 β and TNF- α production (119), and is also a frequent cause of increased need for LT4 (47).

Variations in gastric motility may also increase levothyroxine needs both in the presence of delayed gastric emptying, as in patients with gastroparesis, and in patients with dumping syndrome, a drawback of restrictive and mixed bariatric surgery. However, the lack of normalization by patients' weight often prevented an accurate estimate of LT4 requirement in these surgical procedures (120). However, a median increased need for tablet levothyroxine (+27%) has been described in patients who have undergone RYGB (121). Under these conditions, the main variations of gastric physiology are the reduced volume of water in the restricted stomach, thus interfering with the levothyroxine dissolution process and the higher gastric juice pH (120) (see Table 3).

Table 3 Comorbidities affecting oral LT4 bioavailability and putative mechanisms of interference.

Disorder*	Putative mechanisms of interference	Suggestion	Possible switch to non-tablet LT4
Systemic sclerosis (14)	Esophageal dysmotility (impaired bolus progression)		Liquid
Chronic atrophic gastritis (47)	Increased gastric juice pH		Softgel/liquid
<i>Helicobacter pylori</i> related gastritis (47)	Increased gastric juice pH	<i>H. pylori</i> eradication	Softgel/liquid
Gastroparesis (14)	Delayed gastric emptying		Softgel
Bariatric surgery (116, 120, 121)			Liquid
Restrictive procedures	Gastric mixing, pH and emptying		
Malabsorptive procedures	Intestinal transit time variations, length of bypassed segment		
Celiac disease (110)	Small intestine villous atrophy	Gluten-free diet	
Lactose intolerance (112, 113)	Intestinal transit time variations?	Lactose-free diet	Liquid
<i>Giardia lamblia</i> infestation (114)	Intestinal transit time variations?	<i>G. lamblia</i> treatment	Liquid
Short bowel syndrome (115)	Reduction of intestinal absorptive surface	Teduglutide?	
Cystic fibrosis (14)	Combination of pancreatic insufficiency, reduced biliary salt production, abnormalities in intestinal transit	Pancreatic enzymes?	Liquid
Exocrine pancreatic insufficiency (14)	Steatorrhea	Pancreatic enzymes	
Ulcerative colitis (118)	Intestinal transit time variations?		
Liver cirrhosis (117)	Increased TBG concentrations and defects in bile production and excretion		Liquid
Nephrotic syndrome (14)	Binding of T4 to the excreted albumin		

*References are indicated within.

Recommendation 15

A specific diagnostic workup for transient or persistent interfering comorbidities is advised when the need for a change in LT4 dose is observed over a sustained period of time.

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Role of the main different LT4 preparations

Main different features between tablet and liquid and softgel LT4 preparations

In an attempt to overcome the above-mentioned issues with gastrointestinal absorption (such as intake interference, drug interference, and pH dependence), non-tablet LT4 formulations, i.e., liquid solution (LS) and softgel capsule (SG), have been manufactured and commercialized for clinical practice, although they are not available in every country (13, 107). Tablet LT4 requires disintegration in the gastric lumen, which is significantly dependent on the gastric juice pH (14). Different excipients are contained in both branded and generic LT4 tablets (14). On the other hand, LS of LT4 is prepared with glycerol (and ethanol at the beginning of its commercialization), while SG represents a gelled form of LS and contains LT4 dissolved in water and glycerin (107). LS does not need specific pathways in the gastric lumen to achieve the liberation of LT4, while SG preparation simply requires that the shell melts, which takes a few minutes (122). More specifically, a recent study demonstrated *in vivo* that, unlike tablets, the bioavailability of softgel preparations was independent of gastric juice pH (123). Not surprisingly, it has been demonstrated that athyreotic patients can be initially treated with an SG dose lower than previously stated for tablet preparation (124). In some countries, these non-tablet formulations may be more expensive than the generic, and even than the brand tablets. However, should these formulations be correctly prescribed to the target patients, these costs would be buffered by the reduction of the diagnostic workup (36) needed in patients with suboptimal pharmacological homeostasis.

Recommendation 16

16a) *After counseling patients about the correct use of the LT4 treatment, switching from tablet to liquid solution or softgel capsules LT4 formulations at unchanged dose can be considered in hypothyroid patients with repeated TSH values above the reference range.*

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Available data about the comparison of performance of different formulations of LT4

A number of studies have investigated whether the LS and SG preparations could have a higher or more stable performance than the tablet ones. Notably, most of these studies enrolled patients with suboptimal or clearly increased TSH values during tablet LT4 treatment and with clinical risk factors for malabsorption. Most studies evaluated the changes of TSH after switching from tablet to LS or SG and then after introducing a rigorous patient adherence to the prescription of LT4. From a methodological point of view, performance bias may very well be present in these studies (125, 126, 127). Moreover, patients with potential (36) or definite (128) impaired absorption of LT4 tablets have been included in other studies, acknowledging this as a source of potential selection bias. A meta-analysis specifically focused on this issue was reported by Virili *et al.* (129). This study aimed at investigating whether switching LT4 treatment from tablet to LS improved patients' TSH levels. Six studies were included and the pooled mean reduction of TSH value was 4.23 mU/L (95% CI 3.69 to 4.77) after switching from tablet to LS, with mild heterogeneity among the studies. One RCT found a higher efficacy of LS than tablet LT4 in terms of TSH control in patients ingesting LT4 concomitant with breakfast (130). In summary, sparse RCTs have been published in this field. Most studies collected small series of patients observed for a short period of time, with different and non-comparable designs, and with high risk of selection and performance bias. The issue whether using SG preparation could reduce dose adjustments and improve tolerability and efficacy of LT4 was evaluated in a retrospective study (36). The authors reviewed a series of 99 randomly selected hypothyroid patients who switched from tablet to SG for several reasons (i.e., adverse effects, inadequate biochemical, or hypothyroid symptom control) and found that the rate of LT4 dose adjustment was significantly reduced or absent in most cases, with a concomitant improvement of symptoms control. The worldwide prevalence of gastrointestinal disorders associated with tablet LT4 malabsorption is very high (111). Although most studies investigating the impact of this issue showed improved TSH control after switching patients from tablet to LS or SG LT4, no prospective studies have systematically compared liquid gel formulations of levothyroxine with solid formulations in relation to clinical outcomes.

16b) *Consider using LT4 liquid solution or softgel capsule formulations as first-line in patients at risk of malabsorption of LT4 tablet preparations.*

Strong recommendation. Quality of evidence (0000). Agreement 8/8

Is there a specific group of patients that might benefit from the use of non-tablet LT4 preparation?

Based on the features of non-tablet LT4 preparations and on the available literature, four specific categories of hypothyroid patients can be identified that might benefit from the use of non-tablet LT4 medications. First, hypothyroid patients that have undergone bariatric surgery. These patients have gastrointestinal malabsorption with some differences according to the surgical therapy. As a consequence, they are at a higher risk of malabsorption of tablet LT4. These patients have been shown to have an improvement of TSH values after switching from tablet to LS (131). Second, treating hypothyroid infants and children is a relevant topic in clinical practice. In fact, both administration of LT4 to newborns and achieving an optimal compliance in children can be a challenge. The use of LS showed a good performance in patients of this age group and some advantages with respect to the tablet preparation (132, 133). Third, managing those hypothyroid patients requiring tube feeding during hospitalization in the intensive care unit may be difficult with tablet LT4 preparation. In fact, several complicating issues are present in these patients, including significant interference by other drugs and the efficacy of crushed or powdered LT4 tablet is debatable (134). The last group is represented by those patients with all causes of altered gastric juice pH, as described above

16c) The task force recommends that the above-mentioned categories of hypothyroid patients (with impaired gastrointestinal absorption, enterally fed and infants) may preferentially use liquid LT4 preparations

Strong recommendation. Quality of evidence (0000). Agreement 8/8

A comprehensive synopsis of all recommendations is presented as Supplementary Material.

Summary /key messages

- Sodium levothyroxine has a narrow therapeutic index with relevant side effects derived from over- and undertreatment.
- A significant fraction of patients on levothyroxine does not reach the therapeutic goal (e.g., serum TSH within the reference interval).
- The individualization of treatment is mandatory and should consider target TSH, patients' anthropometric characteristics and the patients' comorbidities.
- Sodium levothyroxine therapy requires an effective doctor–patient relationship to ensure adherence to this chronic treatment.
- The knowledge of the main causes of levothyroxine increased need (nutritional, pharmacological and pathological) is key in selecting the best sodium levothyroxine formulation for the patients.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/ETJ-25-0123>.

Declaration of interest

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