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CONSENSUS STATEMENT

Recommendations for treatment of hypothyroidism with levothyroxine and levotriiodothyronine: a 2016 position statement of the Italian Society of Endocrinology and the Italian Thyroid Association

B. Biondi[1] · L. Bartalena[2] · L. Chiovato[3] · A. Lenzi[4] · S. Mariotti[5] · F. Pacini[6] · A. Pontecorvi[7] · P. Vitti[8] · F. Trimarchi[9]

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Abstract Levothyroxine (L-T4) is recommended as lifelong replacement therapy for hypothyroidism. Recent clinical and experimental data support the addition of levotriiodothyronine (L-T3) treatment in some selected hypothyroid patients when their symptoms persist and their quality of life remains impaired despite adequate L-T4 monotherapy. An increase in L-T3 prescriptions has been recently observed in Italy due to availability of different L-T3 formulations, making it possible to clinicians to prescribe L-T3 alone or in combination with L-T4. The aim of the present position statement was to define the correct clinical indications, schedule, duration of treatment and contraindications of combined treatment with L-T4 and L-T3 in hypothyroid patients in an attempt to guide clinicians and to avoid potential adverse effects of overtreatment.

Keywords Hypothyroidism · Replacement therapy · TSH-suppressive therapy · L-Thyroxine · L-Triiodothyronine · Deiodinases · Clinical symptoms · Quality of life · Cognition · Mood · Depression · Body weight · Heart rate and patient preference for combined therapy · Thyroidectomized patients · Polymorphism in type 2 deiodinase gene

✉ B. Biondi
bebiondi@unina.it; bebiondi@libero.it

L. Bartalena
luigi.bartalena@uninsubria.it

L. Chiovato
luca.chiovato@unipv.it

A. Lenzi
andrea.lenzi@uniroma1.it

S. Mariotti
s.mariotti@unica.it

F. Pacini
pacini8@unisi.it

A. Pontecorvi
alfredo.pontecorvi@unicatt.it

P. Vitti
paolo.vitti@med.unipi.it

F. Trimarchi
francesco.trimarchi@unime.it

[1] Department of Clinical Medicine and Surgery, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

[2] Department of Clinical and Experimental Medicine, ASST dei Sette Laghi, Ospedale di Circolo, University of Insubria, Varese, Italy

[3] Unit of Internal Medicine and Endocrinology, Fondazione Salvatore Maugeri and University of Pavia, Pavia, Italy

[4] Department of Experimental Medicine, Medical Pathophysiology, Food and Science and Endocrinology Section, Sapienza University of Rome, Rome, Italy

[5] Endocrinology Unit, Department of Medical Sciences "M. Aresu", University of Cagliari, Cagliari, Italy

[6] Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

[7] Unità di Endocrinologia, Università Cattolica del Sacro Cuore, Rome, Italy

[8] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[9] Accademia Peloritana dei Pericolanti, Università di Messina, Messina, Italy

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Introduction

Primary overt hypothyroidism is an insidious condition occurring in 1–2 % of individuals residing in iodine-replete populations, more frequently in the elderly and about eightfold to tenfold more commonly in women than in men [1–3]. Overt hypothyroidism is characterized by increased serum thyroid-stimulating hormone (TSH) and decreased serum free thyroxine (FT4) concentrations [1, 2]. Serum total or free triiodothyronine (TT3 or FT3) levels may also be low when thyroid hormone deficiency is more severe [1, 2]. The most frequent cause of spontaneous hypothyroidism in the adult is chronic autoimmune thyroiditis; additionally, hypothyroidism usually occurs after radioiodine treatment or thyroidectomy, may develop following external irradiation of the head and neck, or be drug-induced [1, 2].

Because hypothyroidism is the consequence of an impaired or totally abolished thyroid hormone production, hormone replacement therapy is needed to correct the negative consequences of untreated hypothyroidism on the cardiovascular system (increased risk of atherosclerosis, coronary heart disease, heart failure and ventricular arrhythmias) [1, 4–7] and to control systemic manifestations of thyroid hormone deficiency. Even if the thyroid gland secretes two hormones (T4 and, to a lesser extent, T3), and T3 is the active form in thyroid hormone-dependent peripheral tissues, only levothyroxine (L-T4) is generally used to treat hypothyroidism [2, 8–10]. The large majority (about 85–90 %) of L-T4-treated patients are clinically and biochemically euthyroid and have a good quality of life [2, 8–10]. However, some clinical and experimental data have recently suggested that the addition of levotriiodothyronine (L-T3) treatment may be beneficial in a subset of patients when their symptoms persist and quality of life is impaired despite adequate doses of L-T4 [10, 11].

Need for clinical practice guidelines on combination treatment with L-T4 and L-T3

Because some patients may still feel "always tired" and, more generally "dissatisfied" on appropriate L-T4 replacement [9–11], and clinicians may not offer an acceptable alternative, patients may look for a solution on the Web (see, e.g., www.stopthethyroidmadness.com). Web sites often suggest the use of thyroid L-T3 or thyroid extracts as an alternative to L-T4 for hypothyroidism, but this uncontrolled therapy may be responsible for adverse events and complications [8–11].

Both the American Thyroid Association (ATA) and the European Thyroid Association (ETA) have recently revised their guidelines for treatment of hypothyroidism [8–10]. In Europe, available information shows that L-T3 represents 0.3 % of thyroid hormone prescriptions in the UK [12] and 8.9 % in Germany [13]. Similar findings have been observed in Italy [14]. For all the above-mentioned reasons, the Italian Society of Endocrinology (SIE) and the Italian Thyroid Association (AIT) have deemed it necessary to contribute an official position statement in order to establish the correct clinical indications, schedule, duration of treatment and contraindications of combined treatment with L-T4 and L-T3 in hypothyroid patients in an attempt to guide clinicians and to avoid potential adverse effects of overtreatment. The two societies selected a task force of experts to prepare the document. Each panel member worked without any financial or commercial support.

Literature search

The major source of data acquisition includes PubMed search. We searched for published reports using the search terms: hypothyroidism, replacement therapy with levothyroxine and treatment with levothyroxine and levotriiodothyronine. We added the search records from personal files, references of relevant articles, chapters of major textbooks and review article. The task force assessed study designs, the quality and consistency of the results and the statistical analysis used to evaluate the effects of replacement therapy in hypothyroid patients. The preference was given to randomized controlled trials. Review article, expert opinions and previous guidelines were also considered.

Evaluation system and grading for recommendations

Similarly to previous guidelines, the task force rated the recommendations according to the GRADE system [15]. Level 1 was considered a strong recommendation (for or against), while level 2 a weak recommendation [15].

The quality of the evidence that led to a specific recommendation was rated as follows: +++ (high, level A), ++0 (moderate, level B) and +00 (low, level C) [15].

Thyroid hormone action and metabolism

Thyroid hormones regulate the development and maintenance of the neurocognitive function and of the cardiovascular and musculoskeletal system [1, 4, 5]. In addition, they control kidney function, skeletal growth, bone turnover, glucose metabolism, serum lipids, body weight, mood and fertility [2]. Thyroid hormone production is regulated by a complex interaction between the release of thyroid

hormones to the periphery and the central hypothalamic-pituitary control through a negative feedback loop [11]. Under normal conditions, serum thyroid hormone concentrations result from a dynamic equilibrium between production and secretion of T4 and T3 from the thyroid gland, utilization and catabolism of thyroid hormones, and peripheral conversion of the pro-hormone T4 into the active metabolite T3 or into the inactive reverse T3 by deiodinases [11, 16, 17]. T3 is the biologically active thyroid hormone that binds to thyroid hormone receptors. In healthy individuals, every day 20 % of T3 production derives from direct secretion from the thyroid gland, whereas 80 % is generated in peripheral tissues by monodeiodination of T4 [16].

Available thyroid hormone formulations: pharmacokinetics and pharmacodynamics

L-T4

L-T4 is the current standard treatment for hypothyroidism [8–11, 14]. The daily dose required to normalize serum TSH depends on several factors, including severity of hypothyroidism, patient age, gender, body mass index, pregnancy and concomitant pathological conditions [2]. The half-life of L-T4 is approximately 7 days, with minimal variations in serum thyroid hormone concentrations following a single therapeutic dose [11]. Only a modest 16 % increase in serum FT4 levels (with no change in serum FT3) can be observed in the first 4 h after L-T4 administration [11]. Therefore, L-T4 is safe, well tolerated and usually associated with a good patient compliance [2, 8–11, 14].

In Italy different formulations of L-T4 are available in the form of tablets, oral liquid solutions or soft gelatin capsules [14]. These formulations are therapeutically equivalent by pharmacokinetic analysis [2, 14], although oral liquid and soft gel preparations have a different dissolution and absorption profile [2, 14]. The latter may be useful in patients with malabsorption, lactose intolerance or under treatment with drugs interfering with L-T4 absorption [2, 14, 18].

L-T4 has a narrow therapeutic index with potential clinical consequences after small changes in the daily dose [2]. Variability in dosage, due to poor interchangeability or different absorption profile, may be dangerous, especially in vulnerable populations of patients (children, pregnant women, elderly patients and those with comorbidities) who require an accurate dosage of the drug [19, 20] because subclinical hyper- and hypothyroidism may lead to adverse cardiovascular effects, osteoporosis and cognitive dysfunction [5]. Patients and physicians should be aware of the possible consequences of a change in L-T4 dose by switching between different commercial formulations to avoid potential adverse events [2].

Recommendation 1 on L-T4 therapy (1/+++)

- L-T4 therapy should be considered the standard treatment for patients with hypothyroidism, based on its documented efficacy, long-term experience, favorable biochemical profile and low cost;
- The goal of L-T4 therapy is to restore clinical and biochemical euthyroidism;
- Undertreatment and overtreatment with L-T4 should be avoided due to documented detrimental effects.

Recommendation 2 on the evaluation of TSH fluctuations during L-T4 monotherapy (1/+++)

- Patients, especially those in certain clinical situations (severe hypothyroidism, childhood, pregnancy, old age, thyroid cancer, heart or bone disease), should be advised to avoid switching between different L-T4 formulations;
- Patients should consult their physician if symptoms possibly related to under- or overtreatment occur;
- Inadequate or incorrect L-T4 dosage and/or administration, interferences related to drugs administered for concomitant illnesses and L-T4 malabsorption should be investigated in patients with persistently high serum TSH despite theoretically adequate dose of L-T4.

Thyroid hormone preparations other than L-T4

Other thyroid hormone preparations are commercially available. They include: (A) thyroid extract preparation; (B) L-T3 preparations; (C) preparations containing a mixture of L-T4 and L-T3.

Desiccated thyroid extract

Thyroid extract preparations contain a combination of T4 and T3 in a ratio of twofold-to-threefold higher than that found in human thyroid, as well as other iodinated compounds [2]. They are of animal origin and may be antigenic [2]. Some of these preparations may be appealing for patients because they are presented as more natural, physiological and more efficient than synthetic products. Although some patients prefer thyroid extracts [21], these preparations may account for important adverse events and should, therefore, be avoided [2, 8–10]. Desiccated thyroid extracts of animal origin are not available in Europe, but synthetic preparations, dietary supplementations and nutraceuticals can be easily found and ordered on homeopathic websites. These drugs may be inappropriately advised for

weight loss or improvement of symptoms of hypothyroidism or depression in euthyroid subjects [2].

Recommendation 3 on thyroid extracts, iodine-containing preparations, dietary supplementations and nutraceuticals (1/+++)

- The routine use of thyroid extracts, iodine-containing preparations, dietary supplementations and nutraceuticals is not recommended in hypothyroid patients, because these compounds may result in high serum T3 levels and thereby cause symptoms of thyrotoxicosis;
- Thyroid hormone therapy, iodine-containing preparations, dietary supplementations and nutraceuticals are not recommended in euthyroid individuals with symptoms of hypothyroidism, in obese or depressed patients.

L-T3

The pharmacokinetic characteristics of L-T3 remarkably differ from those of L-T4 [11, 22, 23]. Both drugs are absorbed in the upper gastrointestinal tract, although only 70 % of administered L-T4 is absorbed while L-T3 is virtually completed absorbed. Their absorption requires an acid stomach environment for optimal absorption [22, 23]. However, the half-life of L-T3 is much shorter, and the administration of L-T3 results in significant fluctuations in serum TSH, TT3 and FT3 levels with once daily administration [24]. Even a twice daily administration would result in unacceptable peaks of serum T3 with an approximately 40 % increase in serum FT3 concentrations within the first 4-h after L-T3 administration [23]. Only a thrice daily administration regimen or an extended release L-T3 formulation could provide acceptable serum T3 throughout the 24-h period [23]. Interestingly, pharmacoequivalent doses of L-T4 and L-T3 resulting in superimposable serum TSH levels may be associated with differential responses at the end organ levels, suggesting a distinct tissue pharmacodynamics response [23]. Compared to L-T4 monotherapy in equivalent doses, three daily administration of L-T3 therapy may induce significant weight loss, cholesterol decrease and increase in sex hormone binding globulin levels, suggesting relevant peripheral metabolic effects [23]. Hyperthyroid symptoms may increase significantly after L-T3 administration [24], and persistently elevated serum TT3 and FT3 levels may be a risk factor for the development of atrial arrhythmias and progression of acute myocardial ischemia [25, 26]. No long-term prospective studies have assessed cardiovascular morbidity and mortality during treatment with L-T3. Just one recent retrospective study has reported that the long-term use of L-T3 is not an additional risk factor for atrial fibrillation, cardiovascular disease or fractures in young hypothyroid patients compared to the long-standing use of L-T4 in older patients [27]; however, a significant increased prescription of antipsychotic medication and a trend toward an increased risk of breast cancer have been observed [27]. Therefore, for the time being, the clinical use of L-T3 as monotherapy is not advisable and is only indicated in patients with differentiated thyroid cancer during preparation for radioiodine therapy in order to avoid the adverse effects of prolonged hypothyroidism [2, 8–11].

Recommendation 4 on L-T3 as monotherapy (1/+++)

- The use of L-T3 as monotherapy is not recommended because of its pharmacokinetic profile which results in a relatively short half-life and in wide non-physiological fluctuations in serum TSH and TT3 or FT3 levels;
- Monotherapy with L-T3 may be associated with symptoms of thyroid hormone excess and potential adverse events;
- L-T3 should be reserved for specific conditions such as short-term therapy in patients with differentiated thyroid cancer before radioiodine therapy to reduce the duration of hypothyroidism.

Preparations with a mixture of L-T4 and L-T3

In Italy, some commercially available tablets contain a mixture of synthetic L-T4 and L-T3 doses. They do not provide a correct physiological ratio of the two hormones [11].

Recommendation 5 on tablets containing a fixed combination of L-T4 and L-T3 (1/+00)

- Fixed-combination products containing a mixture of synthetic L-T4 and L-T3 doses should be avoided because their fixed ratio do not allow clinicians to personalize the combined treatment;
- Separate preparations of L-T4 and L-T3 should be used in hypothyroid patients in which combined treatment is indicated.

Effects of combined therapy with L-T4 + L-T3

Experimental evidence

Normal serum T3 concentrations do not necessarily reflect the intracellular T3 content in all tissues because it does not account for the intracellular production and inactivation of T3 via the deiodinase pathways [11, 17]. In experimental studies, hypothyroid rats were infused with either L-T4 or L-T4 + L-T3 and serum and tissue levels of T4 and T3 were measured [28, 29]. No single dose of L-T4

over a wide range could normalize T3 levels simultaneously in plasma and all tissues, except for the brain due to its highly efficient D2 activity [28, 29]. Only the combined therapy with L-T4 + L-T3, in spite of a lower total L-T4 dose, normalized serum and tissue T3 levels, thus indicating that L-T4-treated rats still had tissue hypothyroidism [28]. The increased sensitivity of the hypothalamus to plasma T4 levels may explain why TSH is normalized, despite relatively lower levels of serum T3 [17]. A recent animal study confirmed that thyroidectomized rats have low levels of serum T3 and a high T4/T3 ratio during L-T4 monotherapy [30]. In addition, tissue markers of T3-responsiveness, such as mitochondrial content and α-glycerophosphate dehydrogenase activity, as well serum cholesterol levels were normalized only in rats receiving combination therapy [30]. Therefore, these studies in the animal models suggest that L-T4 replacement therapy resulting in a high ratio of T4 to T3 and low serum levels of T3 is associated with tissue hypothyroidism, especially at the level of liver and skeletal muscles. Combined therapy with L-T4 and L-T3 normalizes tissue and circulating T3 with lower doses of L-T4.

Clinical evidence

Despite restoration of biochemical euthyroidism (normal serum TSH, FT4 and FT3 concentrations), about 15 % of L-T4-treated patients do not reach clinical euthyroidism and continue to complain of symptoms, including difficulty to lose weight, fatigue or chronic malaise, impaired psychological well-being, depression or anxiety. Three large community-based studies reported only a partial recovery of neurocognitive function and psychological well-being in hypothyroid patients treated with L-T4, despite TSH normalization [31–33]. The origin of these symptoms may be different in patients with autoimmune hypothyroidism compared to postsurgical hypothyroidism. Patients with chronic autoimmune thyroiditis may have more residual thyroid tissue that could secrete thyroid hormone (including T3), and their symptoms might be related to the underlying autoimmune condition [10, 11]. Conversely, in athyreotic patients the lack of the 20 % T3 of thyroidal origin might not be compensated by an increased peripheral deiodination of T4 during L-T4 monotherapy [10, 11].

Despite these premises, the majority of clinical trials failed to demonstrate an objective benefit of combination therapy. Three recent meta-analyses of available randomized clinical trials showed no difference in the effectiveness of monotherapy versus combined therapy with regard to bodily pain, depression, anxiety, fatigue, quality of life, body weight, serum lipids psychological and physical well-being, psychiatric symptoms and adverse events [34–36]. Three additional randomized clinical trials were published after these meta-analyses [37–39]. The conclusions were similar, except for a Danish study showing that, despite similar TSH levels, L-T4 + L-T3 combination therapy was better than L-T4 monotherapy in terms of quality of life and depression scores [37]. The results of five crossover studies were evaluated to assess the patient preference for combined therapy versus monotherapy [37, 40–43]. About 48 % of the patients expressed preference for the combined therapy [44]. Similar findings (47 %) were reported in another study with a parallel design [45]. Weight loss might explain the patients' preference for combination therapy in some trials.

Relevant methodological limitations of the available literature data include: (1) small sample size; (2) lack of homogeneity in the population of hypothyroid patients in terms of etiology and severity of hypothyroidism; (3) large variation in the T4/T3 ratio administered usually with a higher ratio than that recommended; (4) low sensitivity of some peripheral parameters of thyroid hormone action; (5) brief duration of combination therapy with the possibility of a carryover effect in the trials with a crossover design [11].

Therefore, it is presently unsettled whether L-T4 + L-T3 combination therapy offers a true advantage over L-T4 monotherapy in terms of improvement of residual symptoms or tissue-specific markers in adult patients with hypothyroidism. Similarly, due to the few available studies, there is no evidence that combined therapy with L-T 4 and L-T 3 is more beneficial than treatment with L-T4 alone in patients with subclinical hypothyroidism, infants and young children [2].

Both ETA and ATA guidelines strongly recommend that L-T4 monotherapy remains the therapy of choice in hypothyroidism because of insufficient evidence of the superiority of combination treatment [8–10]. We agree with this position and support the view that, for the time being, L-T4 + L-T3 combined therapy may offer some beneficial advantage in a small subset of patients.

Recommendation 6 on the use of combined therapy with L-T4 + L-T3 therapy in persistently symptomatic patients with overt hypothyroidism: (2 + 00)

- The routine use of L-T4 + L-T3 combination therapy is not recommended in adult hypothyroid patients due to the insufficient evidence from the available controlled trials and meta-analyses;
- Screening for other autoimmune disorders (such Addison's disease or pernicious anemia) may be considered in selected patients with autoimmune hypothyroidism and persistent non-specific symptoms during L-T4 monotherapy;
- L-T4/L-T3 therapy may be considered as an "experimental approach" in overt hypothyroid patients who

have persistent symptoms despite adequate L-T4 doses resulting in biochemical euthyroidism after exclusion of other specific causes for persistent symptoms. This recommendation is not based on evidence-based data;
- Combined treatment should be discontinued in the absence of clinical improvement;
- Combined therapy is not indicated in patients with subclinical hypothyroidism;
- Treatment with L-T4 + L-T3 is not recommended in pregnant women and children.

Rationale for combined therapy after total thyroidectomy

The peripheral T4-to-T3 conversion should be sufficient for a normal T3 production during L-T4 monotherapy also in athyreotic patients after thyroidectomy [2]. However, recent data support that athyreotic individuals may have subnormal serum T3 levels, despite normal serum TSH levels and relatively higher serum FT4 [11]. A higher FT4-to-FT3 ratio is necessary to achieve normal postoperative T3 levels in patients on L-T4 monotherapy compared with their preoperative values [46]. In a large cross-sectional study of 1811 athyreotic patients, normal TSH levels during L-T4 replacement were associated with free T4 levels above the upper normal limit in 7.2 % of cases, subnormal free T3 levels in 15.2 % and reduced FT3/FT4 ratio in 29.6 % compared to 3.875 euthyroid controls [47]. The FT4/FT3 ratio increased with increasing L-T4 dose, and the widely variable ratio showed a great heterogeneity of peripheral T3 production in athyreotic individuals [47]. Higher FT4, lower FT3 levels and lower FT3/FT4 ratio during treatment with L-T4 were found after total thyroidectomy than after partial thyroidectomy [48, 49], suggesting that T3 production by the remnant thyroid tissue is important to maintain normal postoperative serum T3 levels. It is, however, still unclear whether the relatively lower serum T3 levels in athyreotic patients are clinically relevant and play a causal or a contributing role in the persistence of hypothyroid or non-specific symptoms during L-T4 monotherapy.

Recommendation 7 on combined L-T4 + L-T3 therapy in thyroidectomized patients: (2 + 00)

- Combined treatment is not indicated in patients with residual thyroid tissue after partial thyroidectomy;
- Although there is insufficient evidence to recommend monitoring serum TT3 or FT3 levels in hypothyroid patients during L-T4 monotherapy, serum TT3 or FT3 evaluation and free T4/free T3 ratio should be assessed in athyreotic patients remaining symptomatic during L-T4 therapy;
- Combined therapy may be indicated in thyroidectomized adult patients with persistent symptoms of hypothyroidism and postoperative serum T3 levels and FT3/FT4 ratio lower than their preoperative values during L-T4 monotherapy;
- The L-T4 + L-T3 dose ratio during combined therapy should be between 13:1 and 20:1 by weight. To avoid potential adverse events the starting ratio should be about 17:1;
- L-T4 should be administered once daily, whereas L-T3 preferably twice daily.

Rationale for TSH-suppressive therapy with L-thyroxine in thyroidectomized patients

In some studies, clinical symptoms improved only when serum TSH was suppressed [50]. Small increases in L-T4 dosage close to TSH suppression could increase resting energy expenditure and reduce fat mass in hypothyroid patients [51]. However, other studies did not show during TSH suppression significant differences in clinical variables such as hypothyroid symptoms, well-being or quality of life, lipid profile and body composition [52, 53]. Moreover, low or suppressed serum TSH during replacement L-T4 therapy and high FT4 levels are associated with an increased risk of detrimental effects on bone and heart [54]. Initial TSH suppression <0.1 mIU/L is recommended in high-risk thyroid cancer patients only [54, 55]. For intermediate-risk thyroid cancer patients, initial TSH suppression between 0.1 and 0.5 mIU/L is recommended [54, 55]. TSH-suppressive therapy with L-T4 is not indicated in patients with a low risk of thyroid cancer progression [54, 55].

Recommendation 8 on TSH-suppressive therapy in thyroidectomized patients: (1 + 00)

- Combined therapy is not indicated in high-risk patients with differentiated thyroid cancer. TSH suppression with L-T4 is recommended;
- TSH-suppressive therapy with L-T4 is not indicated in patients with differentiated thyroid cancer with a low risk of cancer progression and in those with a high and intermediate risk of adverse effects;
- High FT4 levels should be avoided in elderly patients receiving long-term L-T4 therapy, independent of the serum TSH value.

Potential adverse events during combined therapy with L-T4 and L-T3

Only a few studies have assessed the cardiovascular and bone effects of combined L-T4 + L-T3 therapy [11]. The

presence of atrial arrhythmias has been reported in over-treated patients during L-T3 treatment [25]. Potential adverse events of combined therapy should be further clarified. Future large prospective randomized controlled trials will be necessary to establish the potential effects of combination treatment on bone and heart and the optimal T4/T3 ratio that could avoid the potential adverse effects of T3 on heart rate and arrhythmias.

Recommendation 9 on potential adverse effects of combined therapy (1/+00)

- Treatment with L-T4 and L-T3 is contraindicated in patients with underlying heart disease, in elderly patients and in those with a history of arrhythmias and chronic ischemic heart disease;
- Combined therapy is contraindicated and L-T4 monotherapy should be administered with caution in patients with abnormal heart conduction pathways, as demonstrated at a standard ECG by a shortened P-R interval, which may help identifying patients predisposed to A-V nodal tachycardia;
- Combined treatment is only advisable in symptomatic adult patients with overt hypothyroidism, and this therapy should be monitored to assess compliance and prevent complications;
- Serum TSH and serum FT3 levels should be measured in the morning before the administration of the daily dose of L-T4 and L-T3;
- Serum T3, FT3 and FT4 levels should be maintained within their respective reference range.
- Cardiovascular evaluation and biochemical markers of osteoporosis should be measured during long-term combined therapy due to the lack of large prospective studies on the potential adverse events;
- Immediate withdrawal of combined therapy should be performed in the presence of adverse events. The onset of atrial arrhythmias or other cardiac events should prompt specific investigations such as ECG, Holter ECG and Doppler ecocardiography.

Thr92Ala polymorphism in type 2 deiodinase gene (*DIO2*) and response to combined therapy

Another factor associated with a positive response to combination therapy in hypothyroid patients is the Thr92Ala polymorphism in type 2 deiodinase gene (*DIO2*) [56]. In a large clinical trial, a common variation in *DIO2* (rs225014) was present in 16 % of individuals [56]. This subpopulation of patients experienced decreased psychological well-being during L-T4 therapy with an improved response to L-T4 + L-T3 combination therapy [56]. This polymorphism is also associated with a number of other metabolic derangements, including insulin resistance and type 2 diabetes mellitus, and mental and psychological disorders [57–63]. Although there are data suggesting that specific polymorphisms of type 2 deiodinase gene might be associated with therapeutic response to combination L-T4 + L-T3 therapy, controlled confirmatory studies are needed.

Patients with polymorphisms in thyroid hormone transporter genes (monocarboxylate transporter 8 and 10, and organic anion polypeptides [OATP] 1C1), which are essential for maintaining the circulating and intracellular homeostasis of thyroid hormones, may complain fatigue and depression [64, 65]. While preliminary studies have not yet shown any effect of combined treatment in these patients, future studies will be needed to confirm these findings.

Recommendation 10 on genetic testing: (2 + 00)

- Currently, there is insufficient evidence to recommend genetic testing as a guiding factor in selecting patients for combined therapy.

Conclusions

L-T4 remains the best and most safe current approach for treating hypothyroidism. The majority of patients are satisfied with this long-life treatment when euthyroidism is reached with L-T4 monotherapy. Management of patients who are dissatisfied and complain of persistent symptoms during L-T4 monotherapy remains an unanswered dilemma. The benefits of combination therapy with L-T4 and L-T3 in these patients are still unproven and should be considered as an experimental approach to improve their quality of life. Benefits and risks of combined therapy should be further investigated. The risk of potential adverse effects is particularly increased when this treatment is inappropriately performed by clinicians who are not expert. Our position statement is in agreement with both the American Thyroid Association (ATA) guidelines for the treatment of hypothyroidism and the European Thyroid Association (ETA) guidelines on use of L-T4 + L-T3 in the management of hypothyroidism and clearly recommend L-T4 monotherapy as the treatment of choice for hypothyroidism, while combination therapy with L-T4 + L-T3 is not routinely proposed. This is mainly due to the fact that the available studies on combination therapy evaluated could not insofar provide a sound support to combination treatment because of

Table 1 Summary of the recommendations

Recommendations statement strength and level of evidence		
Recommendation 1 on L-T4 therapy	Levothyroxine therapy should be considered the routine treatment of patients with hypothyroidism	(1/+++)
	The goal of L-T4 therapy is to restore clinical and biochemical euthyroidism	
	Undertreatment and overtreatment with L-T4 should be avoided	
Recommendation 2 on the evaluation of TSH fluctuations during L-T4 monotherapy	Patients should be instructed to avoid switching between different L-T4 products	(1/+++)
	Inadequate or incorrect L-T4 dosage and/or administration, interferences related to drugs administered for concomitant illnesses and L-T4 malabsorption should be investigated in patients with persistent TSH increased despite over-replacement dose of L-T4 according to their body weight	
Recommendation 3 on thyroid extracts, iodine-containing preparations, dietary supplementation and nutraceuticals	The routine use of thyroid extracts, L-T3 monotherapy, iodine-containing preparations, dietary supplementation and nutraceuticals is not recommended in the management of hypothyroidism and in euthyroid obese or depressed patients.	(1/+++)
Recommendation 4 on L-T3 as monotherapy	The use of L-T3 as monotherapy is not recommended	(1/+++)
	L-T3 generally should be reserved for specific conditions such as short-term therapy in patients with differentiated thyroid cancer before radioiodine therapy	
Recommendation 5 on tables containing a fixed combination of L-T4 and L-T3	Fixed-combination products containing a mixtures of synthetic L-T4 and L-T3 should be avoided	(1 + 00)
Recommendation 6 on combined L-T4/L-T3 therapy in symptomatic patients	The routine use of L-T4 and L-T3 combination therapy is not recommended in hypothyroid patients, in patients with subclinical hypothyroidism, in pregnant women and in children	(2 + 00)
	L-T4 and L-T3 therapy may be considered as an "experimental approach" in overt hypothyroid patients with persistent symptoms despite biochemical euthyroidism	
Recommendation 8 on TSH-suppressive therapy	Combined therapy is not indicated in high-risk patients with differentiated thyroid cancer	(2 + 00)
	High FT4 levels should be avoided in elderly patients	
Recommendation 9 on potential adverse effects of combined therapy	Combined therapy is contraindicated in patients with underlying heart disease, in elderly patients and in patients with a history of arrhythmias, and chronic ischemic heart disease	(1 + 00)
	Combined therapy is advisable in thyroidectomized patients with overt hypothyroidism only	
	Monitoring treatment to assess compliance and to prevent complications is very important	
Recommendation 10 on genetic testing	Currently, genetic testing is not recommended as a guide to selecting patients for combined therapy	(2 + 00)

many inconsistencies and discrepancies [1–3]. We hope that this statement and our recommendations (Table 1) together with other international guidelines will help clinicians in the management of some difficult cases of persistent clinical hypothyroidism despite biochemical euthyroidism.

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Compliance with ethical standards

Conflict of interest The panel members worked on this statement without any financial or commercial support.

Ethical approval This article does not contain any study with human participants or animals performed by any of the authors.

Informed consent No informed consent.

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