Endocrine (2019) 66:18–26
https://doi.org/10.1007/s12020-019-02023-7

REVIEW

Check for updates

Thyroid hormone therapy for hypothyroidism

Bernadette Biondi[1] · David S. Cooper[2]

Received: 21 June 2019 / Accepted: 17 July 2019 / Published online: 1 August 2019

Abstract
The purpose of this article will be to review the basics of thyroid hormone therapy, including various thyroid hormone formulations, the institution and monitoring of thyroid hormone therapy, adverse effects of overtreatment, the management of patients with persistent symptoms despite normal thyroid function tests, and potential new innovations in thyroid hormone therapy. The conclusions support the necessity to personalize thyroid hormone replacement therapy in hypothyroid patients.

Introduction

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3) play a critical role in growth and development, and in adults regulate key metabolic processes affecting virtually every organ system. Hypothyroidism is the result of an insufficient amount of circulating thyroid hormones. In primary hypothyroidism, due to thyroid gland failure, serum thyroid hormone levels are low and pituitary thyrotropin (TSH) levels are elevated, due to the ultrasensitive negative feedback relationship of the hypothalamic-pituitary-thyroid axis. Primary hypothyroidism can be *overt*, where circulating levels of free thyroxine (FT4) are below the lower limit of the reference range, or *subclinical*, where free T4 levels are within the reference range, but lower than they should be for that individual, with consequent mildly elevated circulating TSH levels. Overt hypothyroidism represents severe thyroid hormone deficiency disease that requires mandatory treatment as soon as it is recognized. In contrast, there are continuing debates about whether subclinical hypothyroidism should be treated due to lack of compelling high-level evidence of treatment benefit through randomized controlled trials (RCTs). The purpose of this article will be to review the basics of thyroid hormone therapy, including various thyroid hormone formulations, the institution and monitoring of thyroid hormone therapy, adverse effects of overtreatment, the management of patients with persistent symptoms despite normal thyroid function tests, and potential new innovations in thyroid hormone therapy.

Etiology of hypothyroidism

While iodine deficiency has traditionally been the major cause of hypothyroidism worldwide, in iodine sufficient parts of the world, autoimmune (Hashimoto's) thyroiditis is the primary cause of hypothyroidism in most individuals, especially women. Other causes include congenital absence of the thyroid or inborn errors of thyroid hormone synthesis (dyshormonogenesis), radioiodine therapy for hyperthyroidism, surgical thyroidectomy, various drugs that affect thyroid function or cause thyroid inflammation, and a variety of other rarer causes. While most forms of autoimmune thyroiditis cause hypothyroidism, often this is transient, rather than permanent in patients with mild TSH increase. Central or secondary hypothyroidism, due to hypothalamic or pituitary disease, is a relatively rare cause of hypothyroidism, accounting for <1% of cases.

Epidemiology

Congenital hypothyroidism occurs in ~1/4000 infants [1]. In adults, the prevalence of hypothyroidism in the general

✉ Bernadette Biondi
bebiondi@unina.it
bebiondi@libero.it

[1] Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[2] Division of Endocrinology, Diabetes, and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

population was 7.5% in women and 2.8% in men in the Whickham survey in England [2]. Data from the United States National Health and Nutrition Examination Survey (NHANES) showed a prevalence of 4.6%, with the vast majority of individuals (>90%) having subclinical rather than overt hypothyroidism [3].

Diagnosis of hypothyroidism

Since thyroid hormone effects virtually every organ system, one would expect that severe hypothyroidism would be associated with a host of signs and symptoms that are well-known to all clinicians, reflecting decreased metabolic activity. Unfortunately, many patients with hypothyroidism are relatively asymptomatic, and the symptoms of hypothyroidism are nonspecific and overlap with typical complaints of normal healthy people (e.g., fatigue, weight gain, constipation, dry hair, dry skin, etc.). In one large study, the symptoms of hypothyroidism in persons with mild hypothyroidism were indistinguishable from symptoms found in the general population [1], and this is particularly the case in older persons [2, 3].

The hallmark of the biochemical diagnosis of primary hypothyroidism is a persistently elevated serum TSH level, either in conjunction with a low serum FT4 (overt hypothyroidism) or a FT4 that is within the reference range (subclinical hypothyroidism). Some experts define *mild* subclinical hypothyroidism when the serum TSH is between 4.5 and 9.9 mU/L and *severe* subclinical hypothyroidism when the serum TSH is ≥10 mU/L. In central hypothyroidism, the serum TSH may be low, normal, or even slightly elevated, and serum FT4 levels are below the reference range.

While the biochemical diagnosis of hypothyroidism seems straightforward, there are a number of issues that add to the complexity of diagnosis. First, there is an age-related rise in serum TSH in individuals who have no apparent thyroid disease. In the NHANES study alluded to above [3] the upper limit of the reference range (97.5% confidence interval) increased from 3.56 mU/L in 20–29 year olds to 7.9 mU/L in persons >80 years of age. This shift has been confirmed in other studies as well e.g., [3, 4]. Therefore, the diagnosis of hypothyroidism in older individuals depends on a number of factors, and not just an elevated serum TSH: these include positive family history of thyroid dysfunction, the presence of a goiter or sonographic evidence of thyroid autoimmunity [5, 6], and the presence of circulating antithyroid antibodies. Other causes of elevated serum TSH levels without true thyroid disease must always be taken into account [6–8], including assay artifact [9, 10], and the possible presence of circulating macro TSH [11].

Replacement therapy with thyroid hormones in patients with primary and secondary hypothyroidism

The aim of replacement therapy in hypothyroid patients is to obtain (1) clinical euthyroidism with disappearance of specific symptoms and signs of thyroid hormone deficiency, (2) biochemical euthyroidism with normalization of serum TSH and FT4, (3) the improvement or reversibility of specific cardiovascular risk factors which can be associated with thyroid hormone deficiency (dyslipidemia, diastolic dysfunction and diastolic hypertension, endothelial dysfunction and insulin-resistance), and (4) avoidance of overtreatment with adverse effects of iatrogenic thyrotoxicosis.

Overt hypothyroidism represents severe thyroid hormone deficiency that requires mandatory treatment as soon as it is recognized [12, 13]. Treatment of severe subclinical hypothyroidism (serum TSH ≥ 10 mIU/L) is recommended in adults because of the high risk of progression to overt disease and the increased cardiovascular risk [12–15]. Two important meta-analyses, including individual participant data from large prospective studies have documented negative cardiovascular outcomes, with an increased risk of heart failure and coronary heart disease events and mortality in untreated patients with severe subclinical hypothyroidism [16, 17]. In contrast, there are continuing debates about whether mild subclinical hypothyroidism should be treated due to lack of evidence of treatment benefit through RCTs [18–20]. Treatment of mild disease is not recommended in elderly and asymptomatic patients [12–15], but it is recommended in pregnant women, [21, 22]. The onset of central hypothyroidism should be assessed by following FT4 levels over time and starting treatment when FT4 levels decrease by 20% or more or in symptomatic patients with evidence of pituitary disease [23].

Thyroid hormone formulations

Different thyroid hormone formulations are available for treatment of hypothyroidism. They are either synthetic or natural desiccated preparations from the thyroid glands of animals (usually porcine or bovine origin) [24]. However, only synthetic L-T4 is strongly recommended by international guidelines as the treatment of choice to replace hypothyroid patients for its proven efficacy in normalizing thyroid function and resolving hypothyroid symptoms [12, 13, 24]. Thyroid extracts were frequently used in the past, before the availability of synthetic L-T4 preparations [24]. Nevertheless, they are still used in some countries because they can facilitate weight loss in hypothyroid patients [25]. This effect may be related to the variable

amount of L-T4, L-T3, and other iodinated compounds (e.g., diiodotyrosine and monoiodotyrosine), which are usually present in these extracts [24]. However, thyroid extracts are generally not recommended for the treatment of hypothyroidism because they may contain an excessive amount of L-T3 and, therefore, could induce symptoms of thyrotoxicosis and adverse events such as atrial fibrillation [12, 24, 26]. Furthermore, they can also be antigenic [24]. Of course, thyroid hormones, nutraceuticals, and dietary supplements should not be used to attempt to improve symptoms or body weight in euthyroid subjects [12, 24, 27].

L-T4 has a long half-life that ensures stable and relatively constant blood levels of T4 and T3 [24]. The peripheral T4 deiodination by type 2 deiodinase (DIO2) activity yields T3 at normal serum levels in most patients L-T4 administration [28]. Therefore, L-T4 is easily and safely administered and well tolerated; it also has a low cost and good patient compliance [12, 24].

Several different branded and generic formulations of L-T4 are commercially available, including tablets, liquid formulations, or softgel capsules. Liquid and softgel formulations of L-T4 have a different dissolution and absorption profile compared with the solid tablets [29], and are better absorbed in patients with impairment of gastric acid secretion from atrophic gastritis or the use of proton pump inhibitors [29, 30].

The availability of the various L-T4 formulations in different dosages allows clinicians to personalize the treatment of hypothyroidism according to the severity of hypothyroidism, age, and comorbidities. Although all of commercially available formulations of L-T4 meet the bioequivalency standards established by the FDA, small changes in their dosages or absorption can be potentially clinically significant [31, 32]. In fact, L-T4 has a narrow therapeutic index, meaning that over or undertreatment can easily occur. Thus, switching among branded L-thyroxine products or among various generic preparations should be avoided if possible, especially in vulnerable populations such as children, patients with thyroid cancer, pregnant women, elderly patients, and those with heart disease [12, 24, 26].

L-triiodothyronine (L-T3) tablets and drops are also commercially available in some parts of the world. L-T3 is the active thyroid hormone and in a randomized double-blind crossover trial in hypothyroid patients showed important metabolic effects (improved body weight and lipid profile) when compared with L-T4 [33]. However, L-T3 monotherapy is not recommended because of its short one day serum half-life leading to wide and sometimes supraphysiological fluctuations in serum T3 levels, with the potential for adverse effects. [24, 26]. Moreover, the steady-state pharmacodynamic equivalence of L-T3 with L-T4 can be only obtained by using a thrice-daily regimen of L-T3 [33], which could be associated with poor patient compliance. Currently, the clinical use of L-T3 monotherapy is limited to severe hypothyroidism, inducing myxedema coma [24]. Short-term treatment with L-T3 is also useful in patients with differentiated thyroid cancer who are being withdrawn from L-T4 before radioiodine therapy to avoid symptomatic hypothyroidism.

Some commercially available preparations contain a mixture of variable amounts of synthetic L-T3 and L-T4. They are not recommended by the European guidelines on the use of L-T4 + L-T3 in the treatment of hypothyroidism because they do not allow clinicians to prescribe a physiological L-T4 + L-T3 dose ratio (between 13:1 and 20:1 by weight) during combination treatment with L-T4 and L-T3 [34].

Factors that determine L-thyroxine requirements (see Table)

The etiology and severity of hypothyroidism, sex, age, gender, body weight, and lean body mass are the main-determining factors of the L-T4 requirement.

Higher doses of L-T4 are necessary in thyroidectomized patients compared with patients with residual functional thyroid tissue (i.e., autoimmune hypothyroidism or hypothyroidism induced by radioiodine ablation) [24, 35]. Similarly, lower doses of L-T4 are needed in patients with subclinical hypothyroidism compared with patients with overt disease [14, 15, 24]. Moreover, the estimated starting dosage of L-T4 is lower (about 1.3 µg/kg/day) in patients with central hypothyroidism [36].

A decrease in L-T4 requirement is observed with advanced age, and higher doses of L-T4 are necessary in children with congenital or acquired hypothyroidism and in adolescents compared with adults [24]. The L-T4 dosage may also be associated with the patient's hormonal status, because lower doses are required in postmenopausal women compared with premenopausal women and men [37]. The L-T4 dose also correlates with body weight and body composition [38]. Lean body mass is the best parameter to predict L-T4 requirements because the adipose tissue is less metabolically responsive to L-T4 than the muscle compartment [38]. Therefore, lower doses of L-T4 per kg/body weight are necessary in obese patients. The age and sex-related changes in the requirements for L-T4 are probably mediated by differences body composition [39].

Higher doses of L-T4 are needed in pregnant women, with a reduction in the dose to prepregnancy values after delivery [22]. Patients with nephrotic syndrome may have increased L-T4 requirements due to the urinary losses of free and protein-bound thyroid hormones [40, 41]. Rare tumors which express deiodinase type 3, such as hemangiomas and

vascular tumors may increase the L-T4 requirement due to increased thyroid hormone catabolism [42, 43]. The use of drugs that increase thyroid hormone catabolism in the liver, such as tyrosine kinase inhibitors, phenytoin, carbamazepine, phenobarbital, ritonavir, and possibly sertraline is also associated with increased L-T4 dosage [44].

Normal gastric acid secretion is required for maximal L-T4 tablet dissolution, and L-thyroxine is incompletely absorbed (about 70–80% of the administered dose) by the intestinal mucosa [45]. The variability of gastric acid production can contribute to the individual variability in the requirement for L-T4. L-T4 absorption is increased by fasting (usually 30–60 min before breakfast or 3 h after dinner) [45–49]. A reduction of L-T4 absorption as much as 40–80% may be observed during the contemporaneous administration of food and drink [45–49]. Malabsorption syndromes (table) can decrease L-T4 absorption [50–57]. Thus, high doses of L-T4 are needed in patients with poor or inconstant compliance, incorrect administration of L-T4 with meals, and in patients with malabsorption syndromes.

Some medications can decrease the intestinal absorption of L-T4 by increasing gastric pH or by sequestrating L-T4 into insoluble complexes. [58, 59]. Therefore, these drugs or supplements should be taken 3–4 h before or after L-T4. Alternatively, the L-T4 dose should be increased by 20–30% [13]. Some studies have suggested the potential use of liquid and softgel formulations of L-T4 in malabsorption states, or in patients taking drugs that reduce L-T4 absorption [60–62]. These preparations can be given 30 min before breakfast due to its rapid absorption [63, 64].

A reduction of L-T4 dosage is necessary after weight loss (especially for malignancies, malnutrition, and often after bariatric surgery) [65, 66] and after the improvement of transient conditions of malabsorption (gastritis, Helicobacter pylori infection, bacterial overgrowth, or a gluten-free diet in patients with celiac disease) or after the withdrawal of drugs that interfere with L-T4 administration.

A persistent TSH increase can be observed during L-T4 therapy in patients with untreated adrenal insufficiency coexist with hypothyroidism [24].

"Pseudomalabsorption" should be investigated in some patients with persistent TSH elevation after the exclusion of the most common causes of malabsorption [67–69]. Non-compliant patients without underlying heart disease may take the entire L-T4 dose once weekly or half the dose twice weekly [70].

In patients with central hypothyroidism, it is important to consider the use of other replacement hormones, which may require adjustment of the L-T4 dosage. Higher doses of L-T4 may be necessary in patients receiving estrogens and growth hormone (rhGH) therapy [23, 36]

The starting dose of L-T4 and target serum TSH in patients with primary hypothyroidism

A full dose of L-T4 can be started in adult patients with hypothyroidism in absence of significant comorbidities, to obtain rapid improvement in symptoms and biochemical euthyroidism [24]. A dose window of 1.6–1.8 µg/kg/day can be used for replacement therapy in adults with primary hypothyroidism; higher doses (2.0–2.5 µg/kg/day) are necessary to suppress serum TSH in patients with metastatic thyroid cancer [15, 24]. A different approach, with a gradual increase in L-T4 dosage, should be undertaken in elderly patients and in those with coronary heart disease (25–50 µg/day) [12, 24]. Lower doses (12.5 µg/day) of L-T4 should be started in patients with severe ischemic heart disease and in very elderly patients with severe hypothyroidism [12, 24]. Coronary revascularization should be considered in patients who cannot tolerate low doses of L-T4 without developing angina [24]. Pericardial-pleural effusion and arrhythmias should be monitored by Holter ECG and Doppler echocardiography in patients with severe hypothyroidism [24]. Adrenal insufficiency should be excluded before starting L-T4 in symptomatic patients with autoimmune hypothyroidism and in those with central hypothyroidism [24].

With regard to the adequacy of treatment, serum TSH measurement is the most appropriate and sensitive marker to monitor during L-T4 treatment of primary hypothyroidism. Adjustments in the L-T4 dosage are guided by serum TSH levels assessed 4–8 weeks after starting L-T4 therapy. Serum TSH during L-T4 replacement therapy should be targeted considering the age of the patient, the cause of hypothyroidism, and any underlying physiological or pathological conditions. Changes of about 12.5–25 µg/day should be performed to normalize small deviations of the serum TSH from the target level, which has been proposed to be 0.5–2.5 in young and healthy patients, 1.5–3 in middle-aged patients, and 4–6 mU/L in the elderly [24].

Serum TSH cannot be a marker of euthyroidism in central hypothyroidism: FT4 levels in the upper half of the normal range is an appropriate treatment target in adults with central hypothyroidism, whereas it may be more judicious to maintain FT4 levels in the lower end of the reference range in older patients [24, 36].

Over- and undertreatment with levothyroxine

It may be a difficult statistic for clinicians to accept, but a large minority (30–40%) of patients who take levothyroxine have abnormal thyroid function tests (reviewed in [71]). In the very young or in the elderly, one might think that

undertreatment may be particularly common due to increasing rates of nonadherence, but this is not the case [72]. While rates of poor adherence for levothyroxine are in the 20–30% range across all age groups, this rate is similar or better than that observed for other commonly prescribed drug classes, e.g., proton pump inhibitors, etc. [72].

In fact, the elderly may be more likely to have low serum TSH values rather than elevated values, consistent with overtreatment [73]. The replacement dose of levothyroxine normally decreases with age [74], likely due to a decrease in thyroid hormone metabolism related to decreased lean body mass [75]. On the other hand, gastrointestinal absorption of levothyroxine may be lower in elderly persons [76], possibly related to a higher frequency of atrophic gastritis in older persons with concomitant autoimmune thyroiditis [77, 78]. In a more recent study, patients taking higher than predicted levothyroxine doses were surveyed to ascertain potential reasons [79]. Explanations included concomitant ingestion of medication(s) known to interfere with levothyroxine absorption in 21%, and suboptimal medication adherence in 17%. A small group (0.6%) had celiac disease, and 22% were noted to have antiparietal cell antibodies and potential achlorhydria. On the other hand, for unclear reasons, underlying comorbidities (e.g. diabetes, cirrhosis, COPD, hypertension, coronary artery disease, and malignancy), have an effect to lower the levothyroxine dose required to normalize serum TSH levels, independent of lean body mass [80]. The complexity of the situation makes it difficult to precisely predict the correct replacement dose a priori, especially in the older age group or in patients with chronic illnesses.

American Thyroid Association guidelines [13] recommend that "Patients being treated for established hypothyroidism should have serum TSH measurements done at 4–8 weeks after initiating treatment or after a change in dose. Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months and then at 12-month intervals, or more frequently if the clinical situation dictates otherwise". Interestingly, a recent study found that thyroid function testing often occurs sooner than it is recommended in levothyroxine treated patients who have been shown to have normal serum thyroid function tests, but at a greater time interval than is advised in patients whose thyroid function tests indicate over or undertreatment [80]. This suggests that physicians are not monitoring levothyroxine therapy appropriately in a large portion of patients.

Underreplacement with levothyroxine

Chronic underreplacement is, by definition, iatrogenic hypothyroidism characterized by elevated serum TSH values and free T4 values that can be low, normal, or rarely even elevated. In patients of all ages, ongoing hypothyroidism can have effects on mood, mentation, and well-being. In addition to poor medication adherence, other well-known causes of underreplacement, detailed above, include failure to take the medication on an empty stomach, taking the medication concomitantly with other medications or substances that interfere with absorption, malabsorption syndromes, abnormal tablet potency, or pharmacy error. In women of childbearing age, iatrogenic hypothyroidism can have negative effects on fertility and pregnancy outcomes. In one population-based study, 21.7% of levothyroxine treated pregnant women had first trimester serum TSH levels between 4–10 mU/L, and 7.4% had serum TSH levels >10 mU/L, with proportional increases in miscarriage rates compared with levothyroxine treated women with normal serum TSH values [81]. In another population-based study of middle-aged and older levothyroxine-treated persons (mean age ~60 years), those persons with high serum TSH levels had increased cardiovascular risk, and also had, surprisingly, an increased risk of osteoporotic fracture [82]. The latter was attributed to potential nonadherence to other medications used to treat or prevent osteoporosis.

Overreplacement with levothyroxine

Overreplacement, or iatrogenic thyrotoxicosis, is also associated with an increased cardiovascular and fracture risk. In the study cited above by Flynn et al. [82], a suppressed serum TSH level (serum TSH <0.04 mU/L) was associated with an increased risk of cardiovascular hospital admissions or death, "dysrhythmias" (most likely atrial fibrillation), as well as osteoporotic fractures. However, these adverse events were not observed in patients with a "low" serum TSH (0.04–0.4 mU/L). Similar data on cardiovascular outcomes have been reported among older patients with thyroid cancer treated with suppressive doses of levothyroxine [83]. On the other hand, in a large individual patient data meta-analysis, levothyroxine use per se was not associated with increase fracture risk [84].

Patients taking levothyroxine with persistent symptoms of hypothyroidism

Despite what would appear to be adequate replacement therapy reflected by serum TSH and free T4 values that are entirely normal, a significant number of patients have persistent symptoms of hypothyroidism [24, 85–87]. In a recent electronic survey conducted by the American Thyroid Association of over 11,000 hypothyroid patients, 95% of whom were women, the mean treatment satisfaction score was 5 on a visual analog scale of 1–10 [87]. Interestingly, satisfaction scores were significantly higher in

patients who were taking T4/T3 combination therapy or desiccated thyroid [87]. The most common symptoms were fatigue, body weight concerns, and issues with memory and mood.

Potential causes for persistent symptoms should be ruled out before considering alternate treatment strategies. Besides inadequate levothyroxine dosing, other issues to consider include suboptimal lifestyle measures (e.g., diet, sleep, and stress), coexisting disease (e.g., chronic fatigue syndrome, depression, sleep apnea, and other autoimmune diseases, psychiatric illness, and substance abuse. When other potential causes for persistent symptoms have been ruled out, combination therapy with L-T4 and L-T3 is a consideration that is gaining support among physicians [88, 89]. Professional clinical practice guidelines recognize the existence of patient dissatisfaction with levothyroxine monotherapy, but only support combination therapy if all other options are exhausted, and then only if done cautiously and with strict monitoring of thyroid function tests [89, 90]. This trend has been fueled by the recognition that serum T3 levels are often lower in L-T4-treated thyroidectomized patients than they are in persons with normal thyroid function [91, 92], as well as blinded studies showing that patients often prefer combination therapy despite no clear difference in measured outcomes such as mood, memory, or quality of life (reviewed in [93]). In athyreotic patients, lower serum T3 levels may be due to inadequate peripheral deiodination of T4 to T3, which may be related to polymorphisms in the DIO2) gene in about 16% of the population [94, 95]. However, this hypothesis is controversial [96]. A recent study found that patients with specific polymorphisms in genes for *both* DIO2 (*DIO2*, rs225014) and the thyroid hormone transporter MCT10 (*MCT10*, rs17606253) preferred combination T4/T3 therapy over L-T4 monotherapy [97]. Currently, consideration of combination therapy is a much more widely accepted strategy, with the proviso that normal thyroid function (i.e., a normal serum TSH level) is maintained.

Towards an optimized treatment strategy

L-T4 represents a safe and generally successful therapy for hypothyroidism when the treatment is personalized. The majority of hypothyroid patients are satisfied during long-term L-T4 monotherapy. The risk of potential adverse effects is only present when this treatment is inappropriately prescribed or monitored. The most appropriate management of patients who are dissatisfied and complain of persistent symptoms during L-T4 monotherapy remains an unanswered question and requires large randomized trials that focus on symptomatic patients who have low or low normal serum T3 levels [98].

The availability of a long-acting, slow-release form of T3 could help clinicians in obtaining physiological and stable T3 levels, improve compliance during combination treatment, and avoid the possibility of adverse events. In the future, the treatment of hypothyroidism will truly be personalized [99, 100], and will likely include the analysis of genes relevant to thyroid hormone transport and metabolism, to enable replacement therapy to mimic normal physiology in a way that is not currently possible.

Compliance with ethical standards

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

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. A. Gruters, H. Krude, Detection and treatment of congenital hypothyroidism. Nat. Rev. Endocrinol. **18**, 104–113 (2012)
2. W.M. Tunbridge, D.C. Evered, R. Hall et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin. Endocrinol. **7**, 481–493 (1977)
3. J.G. Hollowell, N.W. Staehling, W.D. Flanders et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J. Clin. Endocrinol. Metab. **87**, 489–499 (2002)
4. G.J. Canaris, N.R. Manowitz, G. Mayor, E.C. Ridgway, The Colorado thyroid disease prevalence study. Arch. Intern. Med. **160**, 526–534 (2000)
5. J. Doucet, C. Trivalle, P. Chassagne et al. Does age play a role in clinical presentation of hypothyroidism? J. Am. Geriatr. Soc. **42**, 984–986 (1994)
6. B. Biondi, A.R. Cappola, D.S. Cooper, Subclinical Hypothyroidism: A Review. JAMA **322**, 153–160 (2019).
7. A.P. Bremner, P. Feddema, P.J. Leedman et al. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J. Clin. Endocrinol. Metab. **97**, 1554–62 (2012)
8. T. Vadiveloo, P.T. Donnan, M.J. Murphy, G.P. Leese, Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the thyroid epidemiology, audit, and research study (TEARS). J. Clin. Endocrinol. Metab. **98**, 1147–1153 (2013)
9. H.S. Ahn, D.W. Kim, Y.J. Lee, H.J. Baek, J.H. Ryu, Diagnostic accuracy of real-time sonography in differentiating diffuse thyroid disease from normal thyroid parenchyma: a multicenter study. AJR Am. J. Roentgenol. **211**, 649–654 (2018)
10. O. Koulouri, C. Moran, D. Halsall, K. Chatterjee, M. Gurnell, Pitfalls in the measurement and interpretation of thyroid function tests. Best. Pract. Res. Clin. Endocrinol. Metab. **27**, 745–762 (2013)
11. N. Hattori, T. Ishihara, K. Yamagami, A. Shimatsu, Macro TSH in patients with subclinical hypothyroidism. Clin. Endocrinol. **83**, 923–930 (2015)
12. J.R. Garber, R.H. Cobin, H. Gharib, American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults et al., Clinical practice

guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid **22**, 1200–1235 (2012).
13. J. Jonklaas, A.C. Bianco, A.J. Bauer, American Thyroid Association Task Force on Thyroid Hormone Replacement et al., Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. Thyroid **24**, 1670–751 (2014).
14. B. Biondi, D.S. Cooper, The clinical significance of subclinical thyroid dysfunction. Endocr. Rev. **29**, 76–131 (2008)
15. D.S. Cooper, B. Biondi, Subclinical thyroid disease. Lancet **379** (9821), 1142–1154 (2012)
16. N. Rodondi, W.P. den Elzen, D.C. Bauer, Thyroid Studies Collaboration et al., Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA **304**, 1365–1374 (2010).
17. B. Gencer, T.H. Collet, V. Virgini, Thyroid Studies Collaboration et al., Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation **126**, 1040–1049 (2012).
18. S.H. Pearce, G. Brabant, L.H. Duntas et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur. Thyroid J. **2**, 215–218 (2013)
19. G. Brenta, M. Vaisman, J.A. Sgarbi et al. Task Force on Hypothyroidism of the Latin American Thyroid Society (LATS). Clinical practice guidelines for the management of hypothyroidism. Arq. Bras. Endocrinol. Metabol. 57, 265–291 (2013)
20. G.E. Bekkering, T. Agoritsas, L. Lytvyn et al. Thyroid hormones treatment for subclinical hypothyroidism : a clinical practice guideline. BMJ **14**(365), l2006 (2019)
21. J. Lazarus, R.S. Brown, C. Daumerie, A. Hubalewska-Dydejczyk, R. Negro, B. Vaidya,European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur. Thyroid J. **3**, 76–94 (2014)
22. E.K. Alexander, E.N. Pearce, G.A. Brent et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid **27**, 315–389 (2017)
23. M. Fleseriu, J.A. Hashim, N. Karavitaki et al. Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **101**, 3888–3921 (2016)
24. B. Biondi, L. Wartofsky, Treatment with thyroid hormone. Endocr. Rev. **35**, 433–512 (2014)
25. T.D. Hoang, C.H. Olsen, V.Q. Mai, P.W. Clyde, M.K. Shakir, Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism:a randomized, double-blind, crossover study. J. Clin. Endocrinol. Metab. **98**, 1982–1990 (2013)
26. B. Biondi, L. Bartalena, L. Chiovato et al. "Recommendations for treatment of hypothyroidism with levothyroxine and levotriiodothyronine: a 2016 position statement of the Italian Society of Endocrinology and the Italian Thyroid Association". J. Endocrinol. Investig. **39**, 1465–1474 (2016)
27. J.I. Mechanick, E.M. Brett, A.B. Chausmer, R.A. Dickey, S. Wallach, American Association of Clinical Endocrinologists, American Association of Clinical Endocrinologists medical guidelines for the clinical use of dietary supplements and nutraceuticals. Endocr. Pract. **9**, 417–470 (2003).
28. L.E. Braverman, S.H. Ingbar, K. Sterling, Conversion of thyroxine (T4) to triiodothyronine (T3) in athyreotic human subjects. J. Clin. Investig. **49**, 855–864 (1970)
29. R. Vita, S. Benvenga, Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. Endocr. Pract. **20**, e38–41 (2014)
30. C. Virili, P. Trimboli, F. Romanelli, M. Centanni, Liquid and softgel levothyroxine use in clinical practice: state of the art. Endocrine **54**, 3–14 (2016)
31. J.V. Hennessey, A.O. Malabanan, B.R. Haugen, E.G. Levy, Adverse event reporting in patients treated with levothyroxine: results of the pharmacovigilance task force survey of the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society. Endocr. Pract. **16**, 357–370 (2010)
32. L. Wartofsky, Levothyroxine: therapeutic use and regulatory issues related to bioequivalence. Expert Opin. Pharmacother. **3**, 727–732 (2002)
33. F.S. Celi, M. Zemskova, J.D. Linderman et al. Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. J. Clin. Endocrinol. Metab. **96**, 3466–3474 (2011)
34. W.M. Wiersinga, L. Duntas, V. Fadeyev, B. Nygaard, M.P. Vanderpump, ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur. Thyroid J. **1**, 55–71 (2014)
35. L. Bartalena, E. Martino, A. Pacchiarotti et al. Factors affecting suppression of endogenous thyrotropin secretion by thyroxine treatment: retrospective analysis in athyreotic and goitrous patients. J. Clin. Endocrinol. Metab. **64**, 849–855 (1987)
36. L. Persani, Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J. Clin. Endocrinol. Metab. **97**, 3068–3078 (2012)
37. J. Jonklaas, Sex and age differences in levothyroxine dosage requirement. Endocr. Pract. **16**, 71–79 (2010)
38. F. Santini, A. Pinchera, A. Marsili et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J. Clin. Endocrinol. Metab. **90**, 124–127 (2005)
39. M. Devdhar, R. Drooger, M. Pehlivanova, G. Singh, J. Jonklaas, Levothyroxine replacement doses are affected by gender and weight, but not age. Thyroid **21**, 821–827 (2011)
40. V. Fonseca, M. Thomas, A. Katrak, P. Sweny, J.F. Moorhead, Can urinary thyroid hormone loss cause hypothyroidism? Lancet **24**(8765), 475–476 (1991). 338
41. N.A. Junglee, M.F. Scanlon, D.A. Rees, Increasing thyroxine requirements in primary hypothyroidism: don't forget the urinalysis! J. Postgrad. Med. **52**, 201–203 (2006)
42. N. Jassam, T.J. Visser, T. Brisco et al. Consumptive hypothyroidism: a case report and review of the literature. Ann. Clin. Biochem. **48**, 186–189 (2011)
43. J.W. De Groot, T.P. Links, W.T. van der Graaf, Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine. Ann. Oncol. **17**, 1719–1720 (2006)
44. P. Kundra, K.D. Burman, The effect of medications on thyroid function tests. Med. Clin. North Am. **96**, 283–295 (2012)
45. M. Skelin, T. Lucijanić, D. Amidžić Klarić et al. Factors affecting gastrointestinal absorption of levothyroxine: a review. Clin. Ther. **39**, 378–403 (2017)
46. L. Liwanpo, J.M. Hershman, Conditions and drugs interfering with thyroxine absorption. Best. Pract. Res Clin. Endocrinol. Metab. **23**, 781–792 (2009)
47. J.C. Morris, How do you approach the problem of TSH elevation in a patient on highdose thyroid hormone replacement? Clin. Endocrinol. **70**, 671–673 (2009)
48. T.G. Bach-Huynh, B. Nayak, J. Loh, S. Soldin, J. Jonklaas, Timing of levothyroxine adminis-tration affects serum thyrotropin concentration. J. Clin. Endocrinol. Metab. **94**, 3905–3912 (2009)
49. N. Bolk, T.J. Visser, J. Nijman et al. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch. Intern. Med. **170**, 1996–2003 (2010)
50. H.M. Robertson, A.K. Narayanaswamy et al. Factors contributing to high levothyroxine doses in primary hypothyroidism: an

interventional audit of a large community database. Thyroid **24**, 1765–1771 (2014)
51. M. Centanni, L. Gargano, G. Canettieri et al. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. N. Engl. J. Med. **354**, 1787–1795 (2006)
52. S. Benvenga, L. Bartolone, M.A. Pappalardo et al. Altered intestinal absorption of L-thyroxine caused by coffee. Thyroid **18**, 293–301 (2008)
53. P. Gargiulo, L. Gargano, M. Centanni, Atypical celiac disease as cause of increased need for thyroxine: a systematic study. J. Clin. Endocrinol. Metab. **97**, E419–422 (2012)
54. M. Cellini, M.G. Santaguida, I. Gatto et al. Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. J. Clin. Endocrinol. Metab. **99**(8), E1454–1458 (2014)
55. S.K. Grebe, R.R. Cooke, H.C. Ford, J.N. Fagerström, D.P. Cordwell, N.A. Lever, G.L. Purdie, C.M. Feek, Treatment of hypothyroidism with once weekly thyroxine. J. Clin. Endocrinol. Metab. **82**, 870–875 (1997)
56. C. Virili, M. Centanni, Does microbiota composition affect thyroid homeostasis? Endocrine **49**, 583–587 (2015)
57. A. Lobasso, L. Nappi, L. Barbieri et al. Severe hypothyroidism due to the loss of therapeutic efficacy of L-thyroxine in a patient with esophageal complication associated with systemic sclerosis. Front. Endocrinol. (Lausanne) **8**, 241 (2017)
58. M. McMillan, K.S. Rotenberg, K. Vora et al. Comorbidities, concomitant medications, and diet as factors affecting. Levothyroxine therapy: results of the CONTROL surveillance project. Drugs R D **16**, 53–68 (2016)
59. S.A. Irving, T. Vadiveloo, G.P. Leese, Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). Clin. Endocrinol **82**, 136–141 (2015)
60. M.G. Santaguida, C. Virili, S.C. Del Duca et al. Thyroxine softgel capsule in patients with gastric-related T4 malabsorption. Endocrine **49**, 51–57 (2015)
61. C. Virili, L. Giovanella, P. Fallahi et al. Levothyroxine therapy: changes of TSH levels by switching patients from tablet to liquid formulation. a systematic review and meta-analysis. Front. Endocrinol. **9**, 10 (2018)
62. R. Vita, G. Saraceno, F. Trimarchi, S. Benvenga, Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J. Clin. Endocrinol. Metab. **99**, 4481–4486 (2014)
63. R. Vita, G. Saraceno, F. Trimarchi, S. Benvenga, A novel formulation of L-thyroxine (T4) reduces the problem of T4 malabsorption by coffee observed with traditional tablet formulations. Endocrine **43**, 154–160 (2013)
64. C. Cappelli, I. Pirola, L. Daffini et al. A double-blind placebo-controlled trial of liquid thyroxine ingested at breakfast: results of the TICO study. Thyroid **26**, 197–202 (2016)
65. P. Fierabracci, S. Martinelli, A. Tamberi et al. Weight loss and variation of levothyroxine requirements in hypothyroid obese patients after bariatric surgery. Thyroid **26**, 499–503 (2016)
66. S. Gadiraju, C.J. Lee, D.S. Cooper, Levothyroxine dosing following bariatric surgery. Obes. Surg. **26**, 2538–2542 (2016)
67. K.B. Ain, S. Refetoff, H.G. Fein, B.D. Weintraub, Pseudomalabsorption of levothyroxine. JAMA **266**, 2118–1220 (1991)
68. D.J. Lips, M.T. van Reisen, V. Voigt, W. Venekamp, Diagnosis and treatment of pseudomalabsorption. Neth. J. Med. **62**, 114–118 (2004)
69. J.N. Walker, P. Shillo, V. Ibbotson et al. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur. J. Endocrinol. **168**, 913–917 (2013)
70. S. Rangan, A.A. Tahrani, A.F. Macleod, P.K. Moulik, Once weekly thyroxine treatment as a strategy to treat non-compliance. Postgrad. Med J. **83**(984), e3 (2007)
71. V. Eligar, P.N. Taylor, O.E. Okosieme, G.P. Leese, C.M. Dayan, Thyroxine replacement: a clinical endocrinologist's viewpoint. Ann. Clin. Biochem. **53**(Pt 4), 421–433 (2016)
72. K. Andersson, A. Melander, C. Svensson, O. Lind, J.L. Nilsson, Repeat prescriptions: refill adherence in relation to patient and prescriber characteristics, reimbursement level and type of medication. Eur. J. Public Health **15**, 621–626 (2005)
73. L.L. Somwaru, A.M. Arnold, N. Joshi, L.P. Fried, A.R. Cappola, High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. J. Clin. Endocrinol. Metab. **94**, 1342–1345 (2009)
74. C.T. Sawin, T. Herman, M.E. Molitch, M.H. London, S.M. Kramer, Aging and the thyroid. Decreased requirement for thyroid hormone in older hypothyroid patients. Am. J. Med. **75**, 206–209 (1983)
75. T.O. Obisesan, M.H. Aliyu, V. Bond, R.G. Adams, A. Akomolafe, C.N. Rotimi, Ethnic and age-related fat free mass loss in older Americans: the Third National Health and Nutrition Examination Survey (NHANES III). BMC Public Health **5**, 41 (2005)
76. M.T. Hays, K.R. Nielsen, Human thyroxine absorption: age effects and methodological analyses. Thyroid **4**, 55–64 (1994)
77. M. Centanni, M. Marignani, L. Gargano et al. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. Arch. Intern Med. **159**, 1726–1730 (1999)
78. S. Checchi, A. Montanaro, L. Pasqui et al. L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. J. Clin. Endocrinol. Metab. **93**, 465–469 (2008)
79. J.J. Scargill, M. Livingston, D. Holland, C.J. Duff, A.A. Fryer, A.H. Heald, Monitoring thyroid function in patients on levothyroxine. Assessment of Conformity to National Guidance and Variability in Practice. Exp. Clin. Endocrinol. Diabetes **125**, 625–633 (2017)
80. U.M. Kabadi, Variability of L-thyroxine replacement dose in elderly patients with primary hypothyroidism. J. Fam. Pract. **24**, 473–477 (1987)
81. P.N. Taylor, C. Minassian, R.A. Rehman et al. TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. J. Clin. Endocrinol. Metab. **99**, 3895–902 (2014)
82. R.W. Flynn, S.R. Bonellie, R.T. Jung, T.M. MacDonald, A.D. Morris, G.P. Leese, Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J. Clin. Endocrinol. Metab. **95**, 186–193 (2010)
83. E.N. Klein Hesselink, M.S. Klein Hesselink, G.H. de Bock et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. J. Clin. Oncol. **31**, 4046–4053 (2013)
84. M.R. Blum, D.C. Bauer, T.H. Collet, H.A. Fink,Thyroid Studies Collaboration et al., Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA **313**, 2055–2065 (2015).
85. K.H. Winther, P. Cramon, T. Watt et al. Disease-specific as well as generic quality of life is widely impacted in autoimmune hypothyroidism and improves during the first six months of levothyroxine therapy. PLoS ONE **11**, e0156925 (2016)
86. E.A. McAninch, A.C. Bianco, The history and future treatment of hypothyroidism. Ann. Intern. Med. **164**, 50–56 (2016)
87. S.J. Peterson, A.R. Cappola, M.R. Castro et al. Degrees of satisfaction and coexistent diseases in those responding to a survey exploring perceptions about treatment of hypothyroidism. Thyroid **28**, 707–721 (2018)
88. L.F. Michaelsson, B.B. Medici, J.L. la Cour et al. Treating hypothyroidism with thyroxine/triiodothyronine combination

therapy in Denmark: following guidelines or following trends?. Eur. Thyroid J. **4**, 174–180 (2015)
89. J. Jonklaas, E. Tefera, N. Shara, Physician choice of hypothyroidism therapy: influence of patient characteristics. Thyroid **28**, 1416–1424 (2018)
90. O. Okosieme, J. Gilbert, P. Abraham et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin. Endocrinol. **84**, 799–808 (2016)
91. J. Jonklaas, B. Davidson, S. Bhagat, S.J. Soldin, Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA **299**, 769–777 (2008)
92. M. Ito, A. Miyauchi, S. Morita T et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. Eur. J. Endocrinol. **167**, 373–378 (2012)
93. J. Jonklaas, Persistent hypothyroid symptoms in a patient with a normal thyroid stimulating hormone level. Curr. Opin. Endocrinol. Diabetes Obes. **24**, 356–363 (2017)
94. A.C. Biancom, B.W. Kim, Deiodinases: implications of the local control of thyroid hormone action. J. Clin. Investig. **116**, 2571–2579 (2006)
95. A.C. Bianco, Pathophysiological relevance of deiodinase polymorphism. Curr. Opin. Endocrinol. Diabetes Obes. **25**, 341–346 (2018). BW
96. B.C. Appelhof, R.P. Peeters, W.M. Wiersinga et al. Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3'-triiodothyronine therapy. J. Clin. Endocrinol. Metab. **90**, 6296–6299 (2005)
97. A. Carle, J. Faber, R. Steffensen, P. Laurberg, B. Nygaard, Hypothyroid patients encoding combined MCT10 and DIO2 gene polymorphisms may prefer L-T3 + L-T4 combination treatment—data using a blind, randomized clinical study. Eur. Thyroid J. **6**, 143–151 (2017)
98. W.M. Wiersinga, Therapy of endocrine disease: T4 + T3 combination therapy: is there a true effect? Eur. J. Endocrinol. **177**, R287–R296 (2017)
99. J.C. Galofré, J.J. Díez, D.S. Cooper, Thyroid dysfunction in the era of precision medicine. Endocrinol. Nutr. **63**(7), 354–363 (2016)
100. P.W. Ladenson, Precision medicine comes to thyroidology. J. Clin. Endocrinol. Metab. **101**, 799–803 (2016)