

MANAGEMENT OF ENDOCRINE DISEASE

Pitfalls on the replacement therapy for primary and central hypothyroidism in adults

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Abstract

Hypothyroidism is one of the most common hormone deficiencies in adults. Most of the cases, particularly those of overt hypothyroidism, are easily diagnosed and managed, with excellent outcomes if treated adequately. However, minor alterations of thyroid function determine nonspecific manifestations. Primary hypothyroidism due to chronic autoimmune thyroiditis is largely the most common cause of thyroid hormone deficiency. Central hypothyroidism is a rare and heterogeneous disorder characterized by decreased thyroid hormone secretion by an otherwise normal thyroid gland, due to lack of TSH. The standard treatment of primary and central hypothyroidism is hormone replacement therapy with levothyroxine sodium (LT4). Treatment guidelines of hypothyroidism recommend monotherapy with LT4 due to its efficacy, long-term experience, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life and low cost. Despite being easily treatable with a daily dose of LT4, many patients remain hypothyroid due to malabsorption syndromes, autoimmune gastritis, pancreatic and liver disorders, drug interactions, polymorphisms in DIO2 (iodothyronine deiodinase 2), high fiber diet, and more frequently, non-compliance to LT4 therapy. Compliance to levothyroxine treatment in hypothyroidism is compromised by daily and fasting schedule. Many adult patients remain hypothyroid due to all the above mentioned and many attempts to improve levothyroxine therapy compliance and absorption have been made.

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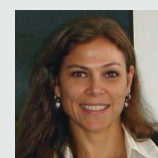
Introduction

Hypothyroidism is the most common thyroid disorder in adults, affecting women more frequently, and incidence of which increases with age. Its clinical presentation ranges from asymptomatic to severe, with myxedema

coma presenting as the most severe complication (1, 2). The severity of the clinical manifestations and health outcomes rely on the duration and degree of thyroid hormone deficiency (3). If untreated, patients with

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Review	G A de Carvalho and others	Pitfalls in hypothyroidism therapy	178:6	R232
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hypothyroidism can be affected by chronic comorbidities such as mood and cognitive disorders, dyslipidemia, infertility and higher risk of delivering children with birth defects (4).

The synthetic thyroid hormone levothyroxine (LT4) is a cost-effective treatment of hypothyroidism, with few side effects (5). The recommended daily dose of LT4 is 1.6–1.7 µg/kg body weight for most patients, which should be taken on an empty stomach, in the morning, 30–60 min prior to breakfast. Besides actual body weight, the LT4 dose depends on other factors, such as TSH goal (normal vs subnormal), ideal body weight, etiology of hypothyroidism, degree of serum TSH elevation, pregnancy and age. For example, athyreotic patients often require a higher LT4 dose than patients with chronic autoimmune thyroiditis. Thyroid hormone therapy can be initiated at full dose in most cases or as partial replacement with gradual increments (starting with 12.5–25 µg/day), in elderly, in those with mild or subclinical hypothyroidism, and in those with comorbidities, such as cardiovascular disease. Serum TSH represents the best marker for assessing the proper LT4 dose. The therapeutic target should be individually tailored, based on the patient's diagnosis, age and coexistent diseases (6, 7). The bioequivalence between different branded and generic formulations of levothyroxine is an important clinical issue that affects therapy. However, in the absence of prospective trials assessing bioequivalence and effectiveness, it is not possible to affirm that one formulation is superior to another. It is, however, recommended that the same formulation is used throughout therapy, to avoid variations in clinical effectiveness.

The management of hypothyroidism may vary in special populations. In pregnant women with overt hypothyroidism already under treatment, two extra doses per week may be started as soon as pregnancy is confirmed; dose should be titrated to achieve a thyrotropin concentration within the trimester-specific reference range. In patients with myxedema coma, LT4 should be given intravenously, with a loading dose of 200–400 µg (less for smaller, older patients or those with heart disease). Until oral therapy can be instituted, the intravenous dose is reduced to 75% of the usual replacement dose of 1.6 µg/kg, and liothyronine may be given in addition to levothyroxine (5–20 µg loading dose and maintenance dose of 2.5–10 µg every 8 h). In patients with heart disease, low doses of LT4 should be started, with slow increases in the absence of angina or other cardiac symptoms such as tachyarrhythmias.

Many patients fail to show clinical and biochemical response to the expected dose of LT4, which is most

frequently attributed to poor compliance (8). In addition, several studies have shown resistance to conventional doses of treatment with oral LT4 in patients with inflammatory bowel disease (9), celiac disease (10), lactose intolerance (11), atrophic gastritis (12) and *Helicobacter pylori* infection (13, 14). Food intake also can interfere with LT4 absorption, with studies showing that fiber supplements, soy protein, coffee and grape fruit can reduce LT4 absorption (15, 16). Also, some drugs coadministered with LT4 interfere with its absorption, such as calcium carbonate (17), ferrous sulfate (18), aluminum hydroxide (19), chromium picolinate (20), bile acids resins (21), sucralfate (22), raloxifene (19) and sevelamer (23).

Even after careful consideration of all these factors, discrimination between an unidentified cause of true thyroxine malabsorption and poor LT4 compliance can prove difficult. Thyroxine absorption test, with 1 mg of levothyroxine given in one dose, or weekly administration of LT4 for 4 weeks, may help identify the underlying cause of thyroid hormone deficiency despite proper therapy (24, 25).

It has been shown that as many as 40% of patients on LT4 replacement have TSH serum levels out of the reference range (26), which may lead to clinical signs and symptoms of hypothyroidism and its related comorbidities and determine a negative impact on health-related quality of life (HRQoL) (27). Therefore, adequate LT4 therapy should be given in primary hypothyroidism with the objective to maintain serum TSH within the reference range.

This review will address the pitfalls encountered when treating patients with primary and central hypothyroidism and describe the many strategies to improve levothyroxine therapy compliance and absorption, including new therapeutic alternatives.

Primary hypothyroidism

Therapeutic alternatives to treat hypothyroidism

Many studies have shown that up to 40% of patients with primary hypothyroidism are undertreated and that up to another 40% may be overtreated – particularly elderly patients (28, 29). A study evaluating 339 hypothyroid patients aged 65 years and over showed that more than 40% had low and 16% had high TSH levels (28). A study performed in Brazil with 2057 hypothyroid patients showed that more than 80% of the subjects said they did not follow physician instructions due to prescription misunderstanding or forgetfulness. The prevalences of

undertreated and overtreated patients in that study were 25.9% and 14.4%, respectively (30).

Non-compliance is attributed to the limitations and inconveniences imposed by therapy: the needs to take the medication while fasting, to wait approximately 30 min for the next meal, to take the medication on a daily basis and to avoid medications that may interfere with LT4 absorption (20). Many attempts to improve LT4 therapy compliance have been made, and new therapeutic alternatives have been suggested; weekly administration of LT4 is one of them.

The influence of food intake on LT4 absorption was first reported by Wenzel *et al.* The absorption of oral LT4 was significantly better if taken while fasting than if taken with simultaneous food intake, 79.3% and 63.9%, respectively (31). Bevenga and coworkers examined five patients in whom LT4 therapy failed to achieve the target serum TSH through ingestion of LT4 15 min before breakfast. After a month of postponing breakfast for at least 60 min after LT4 ingestion, patients obtained a normal TSH level (32). Bolk and coworkers studied the effects of changing LT4 intake to bedtime. Compared to morning intake, there was a mean decrease in TSH by 1.25 mIU/L, a mean increase in FT4 by 0.07 ng/dL and an increase in T3 by 6.5 ng/dL when LT4 was taken at bedtime (33). Bach-Huynh *et al.* evaluated the effect of the timing of LT4 administration in relation to food on serum TSH (30). They studied 65 patients receiving LT4, and randomized them to different treatment regimens, with intake of LT4 while fasting, with breakfast and at bedtime. Nonfasting regimens of LT4 administration were associated with higher TSH concentrations. The mean TSH was 2.93 mIU/L when taken with breakfast, 2.19 mIU/L when taken at bedtime and 1.06 mIU/L when LT4 was administered while fasting. Considering that LT4 administration at breakfast could be a more convenient treatment scheme, a study was conducted with 45 hypothyroid patients to compare LT4 administration while in a fasting state with administration during breakfast. The TSH level was higher for LT4 administration with breakfast than while fasting, 2.9 mIU/L and 1.9 mIU/L, respectively (15). These studies showed that despite a mild TSH elevation, TSH levels remained in an acceptable therapeutic range when LT4 was administered with breakfast or at bedtime.

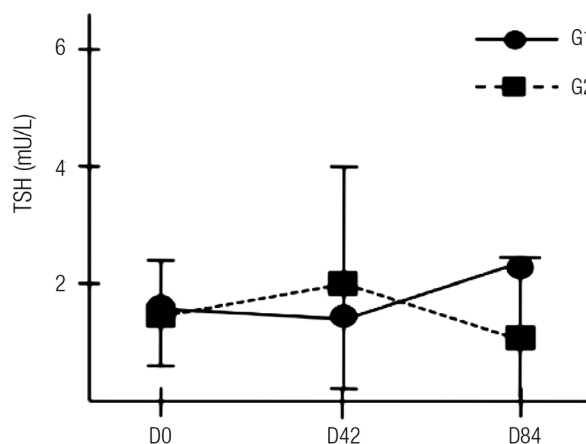
A randomized, crossover study assigned 14 patients to daily or weekly doses of LT4. The weekly treatment led to a transient increase in mean FT4 levels when compared with daily treatment (1.91 vs 1.16 ng/dL for daily vs weekly doses of LT4), without thyrotoxicosis or cardiac symptoms on an echocardiographic evaluation. After

6 weeks, no statistically significant difference was found in mean TSH levels (3.45 vs 1.87 mIU/L for daily vs weekly doses of LT4) (29) (Fig. 1). Weekly administration of LT4 was safe, well tolerated and without evidence of treatment toxicity, including cardiac effects (29, 34).

Those alternative therapeutic regimens for patients who have adherence difficulties due to the need for delaying food intake in the morning could be a good option. For patients in whom a specific serum TSH goal is important, taking levothyroxine while fasting is still the most recommended approach.

Malabsorption syndromes

Levothyroxine (LT4) is largely absorbed (62–82%) in small intestine (jejunum and ileum) during the first 3 h after its ingestion (32). Gastric acidity with an empty stomach enhances LT4 absorption. Euthyroid persons absorb 70–80% of ingested L-T4 but in hypothyroid patients LT4 absorption is lower (35). Gastrointestinal disorders can interfere with L-T4 absorption in hypothyroid patients. The coexistence of other diseases, which can interfere with levothyroxine absorption should be suspected whenever



$p > 0.05$ for all comparisons between groups and within the same group; Bars: means \pm SD.

Figure 1

Changes in TSH serum levels with daily and weekly regimens of LT4. G1: D0–D42 of daily regimen of LT4 (TSH 2.03 ± 1.40 mIU/L) and weekly regimen of LT4 (TSH 2.39 ± 1.19 mIU/L). G2: D0–D42 of weekly regimen of LT4 (TSH 3.32 ± 3.10 mIU/L) and daily regimen of LT4 (TSH 2.38 ± 1.37 mIU/L). $P > 0.05$ for all comparisons between groups and within the same group; bars show means \pm s.d. Adapted from Bornschein A *et al.* Arq Bras Endocrinol Metab 2012; 56:250–258, with permission.

high LT4 doses ($>2\mu\text{g/kg}$ of body weight) do not achieve biochemical control in adherent patients (Table 1).

Conditions affecting gastric acidity

Atrophic gastritis interferes with gastric acidity due to the presence of parietal cell antibodies (PCA) and is often associated with Hashimoto's thyroiditis. Up to 30% of patients with autoimmune thyroid disease present circulating PCA (2), which target antigen is the pump H⁺/K⁺/ATPase located on the apical membrane and in the intracellular space of gastric parietal cells (37, 38). The autoimmune attack leads to the disappearance of the oxyntic glands and to gastric atrophy, which ultimately results in chronic gastritis (39). The consequent achlorhydria and decreased intrinsic factor production causes inadequate vitamin B12 absorption (40). The thyroxine molecule changes its conformation due to the reduced gastric acidity with consequent less LT4 absorption in the small intestine (41). In a study involving 391 patients receiving LT4 due to autoimmune thyroid disease, it was shown that 40% of them had positive PCA and higher LT4 requirement compared to PCA-negative patients ($1.24\pm 0.40\mu\text{g/kg}$ vs $1.06\pm 0.36\mu\text{g/kg}$). LT4 requirement was even higher in patients with gastritis evident on histology (12).

Helicobacter pylori infection is associated with atrophic gastritis, hypochloridria and increased production of ammonia, reducing the efficiency of intestinal absorption of LT4 (13, 14). One study evaluating patients with atrophic gastritis and *Helicobacter pylori* infection showed that those patients required an increase of 34% in the LT4 dose. Eleven patients were treated for *Helicobacter pylori* infection and had their TSH levels were measured before and after treatment; their TSH levels were reduced after eradication of infection (13).

Table 1 Main gastrointestinal disorders that interfere with LT4 absorption.

Gastrointestinal disorder	Mechanism
Atrophic gastritis <i>Helicobacter pylori</i> infection	Hypochlorhydria Ammonia production; Increased gastric pH;
Celiac disease	Inflammation; Intestinal villous atrophy
Lactose intolerance Bowel resection	Inflammation Short bowel syndrome

Adapted from (36).

Bowel disorders

Celiac disease (CD) is an immune-mediated enteropathy that develops in genetically susceptible individuals in response to the ingestion of wheat gluten and related proteins found in barley and rye. Inflammation, hyperplasia of crypts and villous atrophy are some of the histological findings, which may regress or disappear with the removal of gluten from the diet (42). The prevalence of CD in the population is approximately 1%, and the prevalence of CD in patients with thyroid autoimmune disease is increased – approximately 1.5–5% (43, 44).

Autoimmune thyroid disease and CD coexistence is associated with genetic predisposition demonstrated by HLA-DQ2 and HLA-DQ8 haplotypes (45). Both diseases are related to cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), associated with susceptibility to autoimmune thyroid disease (46). Adequate CD treatment reduces inadequate absorption as well as other complications, such as malnutrition, infertility, osteoporosis and lymphoma (47, 48). Hypothyroid patients with treated CD present an improvement in LT4 absorption (49). In patients with inadequate control of hypothyroidism even with the use of high doses of levothyroxine, CD must be evaluated (50). However, the impact of the treatment and control of CD on the risk of developing autoimmune thyroid diseases remains controversial (51).

Lactose intolerance (LI) represents an intestinal disorder due to reduced lactase enzymatic activity that breaks down lactose into glucose and galactose (52). Very active in humans at birth, lactase function declines and persists only in about 30% throughout adulthood (53). LI may interfere with the absorption of LT4; severe malabsorption of oral LT4 has been described in a patient with LI, primary hypothyroidism and persistently elevated TSH levels, despite treatment with high doses of LT4 ($>900\mu\text{g/day}$). After 3 months of the institution of a lactose-free diet, thyroid function tests were normal (54). Cellini and coworkers analyzed hypothyroid patients due to chronic autoimmune thyroiditis with or without concomitant LI. In all patients with isolated chronic autoimmune thyroiditis, target TSH was obtained at a median LT4 dose of $1.31\mu\text{g/kg/day}$. In patients with LI who were noncompliant with a lactose-free diet, only 14% reached the desired TSH with a similar LT4 dose. In those patients with isolated LI, a median LT4 dose of $1.72\mu\text{g/kg/day}$ was required to attain pharmacological homeostasis (55), demonstrating that LI increases the need of oral LT4 in hypothyroid patients.

Intestinal resection

In recent years, bariatric surgery has been sought by many obese patients. Based on the mechanisms of drug absorption, increased LT4 requirements are expected after bariatric surgery. Some studies have shown that bariatric procedures may modify the absorption of LT4; however, available data are still controversial (11).

A review evaluated the effects of bariatric surgery on levothyroxine dosing. Six of ten studies demonstrated decreased postoperative requirements. Most studies demonstrated inverse correlations between weight loss and dose of LT4; 3 case reports and 1 case series demonstrated increased LT4 requirements, which were attributed to malabsorption.

Loss of fat and lean body mass may counteract malabsorptive effects from surgery, resulting in decreased postoperative levothyroxine requirements (56). The most appropriate approach to date is individual LT4 dose adjustment after bariatric surgery. There are few data concerning the benefits of liquid LT4 in case of impaired absorption determined by bariatric surgery, with one case report demonstrating faster and more efficient absorption of liquid LT4 formulation (57).

Parasitic infestations

Intestinal parasitosis is a less reported condition involved with LT4 malabsorption (58, 59). In a clinical case description, a well-controlled hypothyroid patient started to present symptoms of fatigue, myalgia, cramps, dyspepsia and diarrhea. Laboratory evaluation disclosed a serum TSH >100 mIU/L, despite an apparent good treatment adherence. Parasitological stool examination showed the presence of *Giardia Lamblia* and after adequate anti-parasitic treatment, normal thyroid function tests were achieved (58).

In conclusion, different disorders of the digestive tract may potentially interfere in normal LT4 absorption, leading to the requirement of higher LTA doses to control hypothyroidism. Sometimes a picture of uncontrolled hypothyroidism is the first indication of a malabsorption syndrome. The main cause of uncontrolled hypothyroidism is poor patient adherence, but once this is excluded, gastrointestinal disorders, including atrophic gastritis, *Helicobacter pylori* infection, CD, lactose intolerance, short bowel syndrome and parasitic infestations should be considered as differential diagnoses. Treatment of these disorders should improve the hypothyroidism control.

Combination treatment with LT4 and LT3

Although the normal thyroid gland secretes both T4 and T3, currently LT4 is the drug of choice for treatment of patients with hypothyroidism. Available LT4 formulations have a half-life of seven days and provide stable blood levels of thyroid hormones after ingestion of oral daily doses (60). Normal TSH and thyroid hormone blood levels are achieved in most patients, with improvements in hypothyroid signs and symptoms. Thus, guidelines from all professional societies recommend LT4 monotherapy as the treatment of choice for all hypothyroid patients (60).

However, approximately 5–10% of patients given monotherapy complain of symptoms of hypothyroidism, despite their TSH levels being within the normal reference range (61). Mounting evidence suggests that LT4 without the concomitant administration of T3 cannot assure a euthyroid state in the blood and in all tissues simultaneously and that normal serum TSH levels in patients receiving LT4 monotherapy reflect only pituitary euthyroidism (62). This could be explained by the fact that the peripheral conversion from T4 to T3 is not sufficient to restore normal T3 levels. In humans, about 20% of circulating T3 is secreted by the thyroid gland, and 80% of T3 arises from the 5'-deiodination of T4 in peripheral tissues.

T3 is the most active hormone, and its affinity for the nuclear receptors is much stronger than T4. T3 has a half-life of 1 day, and, ideally, three daily doses of T3 are necessary to determine stable circulating levels (63). Studies of hypothyroid rats failed to show normalization in tissue concentration of T4 and T3 with LT4 monotherapy; only the combination LT4/LT3 (levothyroxine/liothyronine) ensured euthyroidism in all tissues of thyroidectomized rats. In humans, this issue remains controversial and several clinical trials have evaluated the potential role and the efficacy of LT4/LT3 combination therapy (64). The first trial reported in 1970 showed no positive results regarding patient preference toward LT4/LT3 therapy and revealed a high incidence of hyperthyroid symptoms (65). Bunevicius *et al.* described an increase in well-being, mood and psychometric functionality in patients treated with LT4/LT3 treatment (66), and two other studies also showed similar beneficial effect (67, 68). Those findings could not be further replicated by other studies (69, 70, 71, 72, 73). The study with the largest sample size, 697 patients, and longest follow-up was conducted by Saravanan and coworkers. That study reported a slight improvement in mood, QoL and anxiety after 3 months of the LT4/LT3 therapy, which was not confirmed subsequently after

Review	G A de Carvalho and others	Pitfalls in hypothyroidism therapy	178:6	R236
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Table 2 Studies evaluating the effects of the treatment with T4 alone vs LT4/LT3 in hypothyroid patients.

Author	Study design	Duration* (weeks)	n	Main outcomes	Benefits T3+T4 > T4	Side effect	Preference
Smith <i>et al.</i> (65)	C	8	87	TFT; QoL	No	Hyper	LT4
Bunevicius <i>et al.</i> (66)	C	5	33	TFT; QoL	Yes	No	LT4/LT3
Nygaard <i>et al.</i> (67)	C	12	59	TFT; QoL	Yes	Hyper	LT4/LT3
Fadeyev <i>et al.</i> (68)	P	24	36	TFT; QoL	Yes	No	LT4/LT3
Kaminski <i>et al.</i> (69)	C	8	32	TFT; QoL	No	No	No
Walsh <i>et al.</i> (70)	C	10	101	TFT; QoL	No	NR	No
Appelhof <i>et al.</i> (71)	P	15	130	TFT; QoL	No	NR	LT4/LT3
Rodriguez <i>et al.</i> (72)	C	13	26	TFT; QoL	No	Hyper	NA
Escobar-Morreale <i>et al.</i> (73)	C	8	28	TFT; QoL	Yes	Low TSH	LT4/LT3
Saravanan <i>et al.</i> (74)	P	52	697	TFT; QoL	No	Hyper Hypo	NA

*, Treatment duration; C, crossover; Hyper, hyperthyroidism; NA, not evaluated; NR, not reported; P, parallel; QoL, quality of life; TFT, thyroid function tests.

1 year (74). Based on these studies, some meta-analyses on LT4/LT3 therapy did not show any evidence supporting a superior effect of the combination treatment (75, 76) (Table 2).

Patients receiving LT4 monotherapy generally have higher T4/T3 ratios than euthyroid individuals, and some of them have normal TSH levels and serum T3 levels at the lower end or below the reference range. Therefore, decreased D2 expression or function could explain the residual complaints in treated hypothyroid patients. Numerous studies have investigated the effects of common genetic variation in the *DIO2* gene on thyroid function tests, thyroid-related outcomes, D2 expression and function (77, 78, 79, 80, 81, 82). The D2 Thr92Ala polymorphism, the most frequently studied variant, has been associated with insulin resistance, obesity, hypertension, altered bone turnover, cognition and alterations in the HPT axis and in response to thyroid hormone replacement therapy (60). Several studies failed to demonstrate the associations of the D2 polymorphism Thr92Ala with thyroid function tests, suggesting that this variant does not have an effect on serum thyroid parameters in the general population (77).

Recently, Castagna *et al.* demonstrated an association between low free T3 values and the Thr92Ala polymorphism in 140 thyroidectomized patients; they also demonstrated that the polymorphism reduced D2-mediated thyroxine-to-T3 conversion (83). This discrepancy in findings can be explained by differences in the study design and sample size, among other factors. Most of the studies included predominantly euthyroid individuals (79, 80, 81). The effects of the Thr92Ala variant become only apparent in athyreotic patients receiving only LT4 and are masked by thyroidal T3 production in euthyroid individuals (77). A large, well-powered study is needed to replicate the effects

of the D2 Thr92Ala polymorphism on thyroid function tests in athyreotic patients receiving LT4 to clarify whether these patients are indeed more vulnerable to the effects of this polymorphism. These studies should also investigate whether these effects contribute to the residual complaints that impair the quality of life of 10–20% of the hypothyroid patients, thus providing evidence in favor of customized treatment of hypothyroidism mainly in athyreotic patients.

Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) is defined as normal free T4 and free T3 levels in the presence of abnormal elevation of TSH. This condition has been diagnosed more frequently in clinical practice; however, its clinical significance is still much debated (84). Although the term subclinical hypothyroidism suggests an asymptomatic condition, a substantial proportion of patients presents nonspecific symptoms of hypothyroidism (85, 86). The prevalence of SCH is relatively high and varies from 4% to 20%. Its incidence depends on age and sex and is usually more frequent in patients older than 60 years, with a prevalence of about 15% in women and 8% in men (87).

SCH has important clinical implications in overall health and may increase cardiovascular risk due to its association with arterial hypertension, dyslipidemia, endothelial dysfunction, insulin resistance, inflammation and oxidative stress (84, 88, 89, 90, 91, 92, 93, 94). There are different questions to ask regarding SCH: are we hyper-diagnosing SCH? Are we perhaps hyper-treating SCH? Are there different SCH presentations? When evaluating SCH patients, it is very important to distinguish between temporary elevations of TSH from persistent and

progressive TSH elevations, the latter usually associated with chronic autoimmune thyroiditis. According to the Brazilian Society of Endocrinology Guidelines on SCH, TSH levels should be reevaluated after three months to confirm persistent SCH (95). Spontaneous TSH normalization can occur, especially when TSH elevations are mild. This can occur in the presence or absence of antithyroid antibodies, which is frequently with the latter presentation (96).

Chronic autoimmune thyroiditis, the main cause of primary hypothyroidism in children and adults, is a chronic and progressive disease. In individuals with a genetic predisposition, the immune process can be triggered by environmental factors. Very precocious thyroid alterations are detected through ultrasonography, which reveals a heterogeneous and hypoechoic gland, characteristic of an inflammatory process, with the appearance of antithyroid antibodies subsequently. As the process progresses, T4 levels can decrease with an elevation of TSH. This combination of still normal T4 levels and TSH elevation is indicative of minimal thyroid insufficiency (96, 97). In the presence of positive antithyroid antibodies, the progression from SCH to overt hypothyroidism in women occurs in 4.3% per year (98).

Many drugs can induce SCH, particularly in patients with subjacent autoimmune thyroiditis. Among them, amiodarone, a widely used antiarrhythmic drug, frequently interferes with thyroid hormone production. Beside this, the chronically high iodine levels seen in patients using the drug can enhance the prevalence of chronic autoimmune thyroiditis in genetically susceptible individuals (99). Other drugs that contain iodine, lithium carbonate, cytokines or interferon can also induce SCH (100).

The term subclinical hypothyroidism suggests the absence of symptoms in these patients. However, a high prevalence of patients with SCH presents signs and symptoms of hormonal deficiency, although less exuberant than in patients with overt hypothyroidism (84). The early diagnosis of SCH is accompanied by unspecific symptoms, which are reversible with thyroxine replacement. The development of symptoms is related to the disease duration and to the individual sensitivity to thyroid hormone deficiency, which in turn depends on the sensitivity of peripheral target organs (84). Overt hypothyroidism is associated with a higher cardiovascular risk (101). During the last years, with the increasing prevalence of SCH and the potential progression to overt thyroid disease, cardiovascular dysfunctions have been studied more intensively in SCH (102). Potential cardiovascular risk in SCH is an important aspect in

screening and treatment programs (103). The degree of hemodynamic changes depends on the severity of thyroid hormone deficiency, the increase in systemic vascular resistance (SVR) being one of the most frequently studied dysfunction, together with systolic and diastolic dysfunction (104, 105). Those are alterations frequently reversed with thyroid hormone replacement (84).

Epidemiologic and autopsy studies support the higher risk of arteriosclerosis in patients with SCH (84), which are related to hypercholesterolemia and LDL elevations. Furthermore, diastolic hypertension due to elevated SVR, arterial stiffness, endothelial dysfunction, altered coagulability state and elevated PCR levels all can contribute for the higher cardiovascular risk associated with SCH (89, 105, 106). The most reported cardiac abnormality is left ventricular diastolic dysfunction, characterized by a diminished muscle relaxation time and decreased left ventricular filling (107, 108, 109). Neuromuscular alterations are not uncommon in SCH, probably due to altered glycogenolysis (110), altered expression of myosin heavy chain (111) and a reduction in mitochondrial activity (112, 113).

Prospective, randomized, placebo-controlled studies evaluating symptoms improvement with LT4 in patients with SCH are scarce, with conflicting results probably due to differences in patient recruitment regarding etiology, age and TSH levels at the treatment beginning (84). In a recent randomized study controlled with placebo in elderly patients, there was no difference in the score of hypothyroidism symptoms and of quality of life after 12 months of LT4 treatment (114). Issues regarding this study include mean patient age (74.4 years), mild TSH elevation (6.4 ± 2.01 mU/L) and the absence of evident hypothyroid symptoms at the beginning of treatment (115).

What are the consequences of LT4 replacement on cardiovascular risks such as dyslipidemia, insulin resistance, arterial hypertension, inflammation, oxidative stress, endothelial dysfunction and the altered coagulation pattern? Regarding the lipid profile, a recent systematic review and meta-analysis of randomized treatments with LT4 and controlled with placebo demonstrated a significant reduction in LDL cholesterol levels, with compelling evidence in favor of benefits with LT4 treatment (87). Arterial stiffness changes are normalized with LT4 replacement (116). The characteristic left ventricular diastolic dysfunction seen in SCH is normalized with LT4, as reported in many studies (107, 109, 117). In a double-blind study controlled with placebo, a decrease in the isovolumetric relaxation time was observed with T4 (26).

Review	G A de Carvalho and others	Pitfalls in hypothyroidism therapy	178:6	R238
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In other clinical trials controlled with placebo, a positive effect in systolic function was also observed with T4 (109, 117, 118).

Thyroid hormones act on the endothelium and smooth muscle cells, with a key role in vascular tonus modulation (119). There is an inverse correlation between TSH and endothelium-dependent vasodilatation (120, 121). Thyroxine replacement in SCH induces a significant reduction in SVR, median arterial pressure and central arterial stiffness (122, 123, 124). An evaluation of SCH treatment after six months of stable euthyroidism showed a significant improvement of endothelial function, evidenced by acetylcholine-induced vasodilatation, due to the reestablishment of nitric oxide availability (121). In a double-blind study, brachial arterial flow improved significantly after hormone replacement, independent of other cardiovascular risks (125). Finally, an improvement was observed in treated SCH patients with coronary microvascular dysfunction (126).

Progressive decrease in thyroid function in patients with autoimmune gland disease is associated with a wide spectrum of manifestations, from early alterations with mild TSH elevation and normal thyroid hormone levels, to overt clinical hypothyroidism. The treatment of SCH patients should be individualized, taking into account factors as age, sex, presence of other comorbidities and treatment adherence. In general, adequate thyroid hormone replacement with thyroxine in SCH patients is associated with clinical benefits. According to the European Consensus on Subclinical Hypothyroidism, age is an important determinant of the therapeutic approach in patients with SCH. Younger patients (<65–70 years) with serum TSH >10mU/L should be treated, even in the absence of symptoms. In those younger patients with serum TSH <10mU/L and with symptoms suggestive of hypothyroidism, a trial of LT4 replacement can be considered. In patients over age 70 years and serum TSH <10mU/L, clinical observation is recommended, and thyroid function tests repeated in 6 months; if TSH is equal or higher than 10mU/L, LT4 therapy can be considered if clear symptoms of hypothyroidism or high cardiovascular risk. Patients over >80–85 years with serum TSH ≤10mU/L should be followed closely, and LT4 therapy less often used (127).

Central hypothyroidism

Central hypothyroidism (CH) is defined as insufficient thyroid hormone production due to quantitative or

qualitative alterations in TSH. CH can be isolated or combined with other pituitary hormone deficiencies. Congenital or acquired defects causing functional or anatomic disorders of the pituitary gland and/or hypothalamus can lead to CH (128, 129). It is a rare cause of hypothyroidism, affecting 1 of 1000 patients with hypothyroidism (130). The diagnosis is suspected when a low level of free T4 (FT4) is associated with inappropriately normal or low level of TSH (131, 132). TSH is normal in most of cases, but it can be low or even slightly elevated in few patients. Total T3 and total T4, as well as free T3, are within the reference range in a significant subset of patients, and FT4 is usually reduced or in the low normal range particularly in the congenital cases (131, 132).

In primary hypothyroidism, all recommendations on the diagnosis and treatment are made based on TSH levels, and the definition of subclinical thyroid dysfunction is well established when TSH levels is high and FT4 is normal. In that form of hypothyroidism, FT4 is not an adequate marker of thyroid function (133). However, in CH, as TSH is not a reliable marker of thyroid function, the most important biochemical parameter for the diagnosis and monitoring of the treatment is FT4.

The aim of CH treatment is to restore euthyroidism (128, 129, 130, 131, 132). Levothyroxine is considered the standard treatment as it is inexpensive, worldwide available, has a long half-life of 7 days, lead to more stable serum levels comparing with LT3, enabling the administration of a single daily dose (134). The combination of LT4 and LT3 has not proven to be superior to isolated LT4 therapy and leads to FT3 levels above the reference range in a considerable number of patients (135). Treatment with TRH and TSH is not justifiable because of the prohibitive costs and lack of demonstrated superiority over thyroid hormone replacement (2). Comparing with primary hypothyroidism, CH patients achieve lower levels of FT4 under LT4 replacement, suggesting possible undertreatment (136). As matter of fact, FT4 levels are higher in patients with primary hypothyroidism adequately treated based on TSH levels, comparing with euthyroid controls, suggesting that the level of FT4 needs to be higher than that in the normal population to maintain an euthyroid state (136). Based on these data from primary hypothyroidism patients, the recommendation to keep FT4 levels in the middle upper level of the normal reference range as a target for CH patients receiving LT4 seems to be appropriate (128, 129, 131, 136). Because LT4 determines a peak concentration 2–4h after ingestion, it is recommended to perform blood tests before the ingestion of LT4 tablets, to avoid

Review	G A de Carvalho and others	Pitfalls in hypothyroidism therapy	178:6	R239
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the peak concentration (128, 129, 134). TSH levels are usually low (<0.5 mU/L) in more than 80% of patients receiving LT4 (137). Thus, insufficient replacement can be suspected when TSH is inappropriately elevated, above 1 mIU/L (137). Even though FT3 levels are not a good biochemical marker for the diagnosis in CH, they can be useful for monitoring treatment, as some patients on LT4 replacement can have high-normal FT4 and high FT3 levels, demonstrating overtreatment (137).

The mean average dose of LT4 replacement is around 1.6 µg/kg/day (131, 132), and elderly may need a smaller dose (1.3 µg/kg/day) (131, 132). It is recommended to start with low doses (25–50 µg/day) and adjust gradually every 2–3 weeks according with FT4 levels and symptoms (128, 129). Caution is necessary when hypothyroidism is associated with untreated corticotropin deficiency, as the restoration of thyroid hormones function can precipitate adrenal crisis in a patient with unrecognized central adrenal insufficiency (128, 129). Growth hormone (rhGH) replacement can unmask CH that was unapparent before rhGH treatment in patients with multiple pituitary deficiencies, but not in isolated GH deficiency (138). GH was found to increase T4 to T3 conversion through type 2 deiodinase activation (139), thus, usually FT4 levels drop in patients with CH taking LT4 following rhGH replacement therapy. Some experts recommend increased LT4 dose targeting the upper normal reference FT4 range (129). In contrary, other authors found that T3 levels increase after rhGH therapy, which increases the conversion of T4 into T3. In that case, targeting FT4 to the upper normal reference range can lead some patients to overtreatment; thus, it is recommended the monitoring of T3 levels in those patients (140). In addition, estrogen replacement can increase thyroid-binding globulin (TBG) concentrations, warranting increase LT4 dose, regardless of the route of estrogen administration, oral or transdermal (131).

Hypothyroidism induced by anti-cancer drugs

Special consideration should be given to tyrosine kinase inhibitors (TKIs) used in the treatment of many forms of cancer (including thyroid cancer), which can induce hypothyroidism and thyrotoxicosis. Many different mechanisms have been proposed to explain the TKIs effects on the hypothalamic–pituitary–thyroid axis, which include destructive processes in the thyroid gland

(due to inhibition of VEGF and capillary dysfunction), inhibition of thyroid hormone transporters such as MCT8, antithyroid peroxidase antibody production and decreased iodine uptake by the thyroid gland and increased inactivation of thyroid hormone by enhanced type 3 deiodinase activity (141, 142).

Thyroid function should be assessed before starting TKIs (such as sunitinib sorafenib, imatinib, dasatinib, nilotinib and axitinib), which should be monitored during and after the end of treatment. The medium time to hypothyroidism onset is variable, and treatment with levothyroxine may be considered during TKI therapy. After TKIs withdrawal, some patients remain hypothyroid and others recover a normal thyroid function, warranting discontinuation of levothyroxine replacement (143).

Other anti-cancer immunomodulatory targeted therapies may also be involved in the pathogenesis of thyroid dysfunction, such as cytokine-based therapies (e.g. interferons and interleukins) and monoclonal antibodies (such as ipilimumab and alemtuzumab). Similar approach is recommended in such cases (142).

Conclusions

The hypothyroid spectrum, from SCH to overt hypothyroidism, is a common disorder that is managed, in most cases, with daily oral administration of LT4. Physicians should be aware of the peculiarities regarding the diagnosis, treatment and monitoring of SCH and the forms of overt hypothyroidism, central and primary.

Most patients achieve euthyroidism with such approach, but some cases are refractory to therapy. Those cases warrant further investigation to identify the underlying cause of lack of response to LT4 therapy, and poor compliance is the most common factor. Other contributing causes include malabsorption syndromes, and concomitant use of drugs that interfere with the LT4 pharmacokinetic profile. In case of noncompliant patients, different strategies can be attempted, such as weekly administration of LT4 and change of the timing of LT4 administration.

Despite achieving biochemical euthyroidism, some patients sustain symptoms of hypothyroidism. Several animal studies have attributed this to low tissular levels of T3 despite proper LT4 therapy, but clinical trials have failed to consistently demonstrate a benefit of combination LT4/LT3 therapy. However, in selected patients, the use of combination therapy may be considered.

Declaration of interest

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Review	G A de Carvalho and others	Pitfalls in hypothyroidism therapy	178:6	R242
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