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Review Article

Are We Restoring Thyroid Hormone Signaling in Levothyroxine-Treated Patients With Residual Symptoms of Hypothyroidism?

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ABSTRACT

Introduction: Levothyroxine (LT4) at doses that maintain the serum thyroid-stimulating hormone levels within the normal range constitutes the standard of care for the treatment of hypothyroidism. After a few months, this eliminates the signs and symptoms of overt hypothyroidism in the majority of patients, owing to the endogenous activation of thyroxine to triiodothyronine, the biologically active thyroid hormone. Still, a small percentage of the patients (10%-20%) exhibit residual symptoms, despite having normal serum thyroid-stimulating hormone levels. These symptoms include cognitive, mood, and metabolic deficits, with a significant impairment in psychological well-being and quality of life.
Objective: To provide a summary of progress in the approach of patients with hypothyroidism that exhibit residual symptoms despite treatment.
Methods: We reviewed the current literature and here we focused on the mechanisms leading to a deficiency of T3 in some LT4-treated patients, the role of residual thyroid tissue and the rationale for combination therapy with LT4 + liothyronine (LT3).
Results: A score of clinical trials comparing therapy with LT4 versus LT4 + LT3 concluded that both are safe and equally effective (neither is superior); however, these trials failed to recruit a sufficiently large number of patients with residual symptoms. New clinical trials that considered LT4-treated symptomatic patients revealed that such patients benefit from and prefer therapy containing LT4 + LT3; desiccated thyroid extract has also been used with similar results. A practical approach to patients with residual symptoms and on initiation of combination therapy with LT4 + LT3 is provided.
Conclusion: A recent joint statement of the American, British, and European Thyroid Associations recommends that a trial with combination therapy be offered to patients with hypothyroidism that do not fully benefit from therapy with LT4.

Introduction

Hypothyroidism is a condition that occurs as a result of insufficient production of thyroid hormones (THs).[1] The thyroid gland produces ~100 mcg of thyroxine (T4) per day in a healthy adult. However, the active TH is 3,3′,5-triiodothyronine (T3), approximately 20% of which is secreted directly from the thyroid gland (~5 mcg/day in healthy adults), whereas the rest (approximately 25 mcg) comes from the extrathyroidal outer ring deiodination of T4.[2]

Chronic autoimmune thyroiditis is the most common cause of hypothyroidism in iodine-sufficient areas. The reduction in the TH levels observed in patients with hypothyroidism leads to insufficient TH signaling (and the subsequent modification in the expression of TH-responsive genes) in multiple body systems.[3,4] For example, T3 universally accelerates metabolic reactions, which leads to a faster rate of energy expenditure and heat production. Thus, when the T3 levels are low, the expression of the genes

Abbreviations: DTE, desiccated thyroid extract; D2, type 2 deiodinase; FT4, free thyroxine; FSH, follicle-stimulating hormone; HPT, hypothalamus-pituitary-thyroid; LT3, liothyronine; LT4, levothyroxine; MMA, methylmalonic acid; QoL, quality of life; T4, thyroxine; TH, thyroid hormone; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

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involved in these pathways is reduced, slowing down the overall metabolic rate and explaining typical signs and symptoms of hypothyroidism, namely, fatigue, hypometabolism, weight gain, and cold intolerance. Although T3 also regulates gene expression in the brain (and hypothyroidism is associated with major alterations in mood and cognitive function), the cellular pathways involved in the central nervous system are less clear. Nonetheless, hypothyroidism can be a debilitating disease, and if left untreated, it may lead to what is known as myxedema coma (however, this is rarely observed).

Patients with overt hypothyroidism may present with few or no symptoms at all, whereas others have clear-cut identifiable symptoms and/or signs of TH deficiency. Nonetheless, all exhibit increased thyroid-stimulating hormone (TSH) levels and decreased T4 levels in the circulation. A recent analysis of a large administrative claims data set from 2012 to 2019 and the 2009 to 2010 and 2011 to 2012 National Health and Nutrition Examination Survey cycles estimated that approximately 8.2% of the U.S. population exhibits overt hypothyroidism.[5] At the same time, patients may exhibit subclinical hypothyroidism, a condition characterized by an elevated plasma TSH level (<10 mU/L) in an otherwise asymptomatic (or minimally symptomatic) patient with normal free T4 (FT4) levels. It is estimated that the prevalence of both overt hypothyroidism and subclinical hypothyroidism has increased over time and has reached 11.7% of the adult population.[5]

The ideal treatment of hypothyroidism should restore the circulating TH levels and normalize their biologic effects throughout the body. Therapy with desiccated thyroid extract (DTE) contains both T4 and T3 (4:1). It was developed in the 1890s and remained the standard of care during the better part of the 20th century.[6] Since the early 1960s, therapy with synthetic LT4 + liothyronine (LT3) has also been used in the United Kingdom[7] and the United States,[8] and therapy with DTE was all but abandoned with the discovery that T4 is endogenously activated to T3 via the deiodinases.[9] Although there were signs that some patients preferred and benefited from therapy with DTE or LT4 + LT3,[10] clinical guidelines favored therapy with LT4 given the safety concerns with LT3 (the fast T3 kinetics in the plasma results in a peak and trough that may cause palpitations and fine tremor in patients taking a relatively large dose of LT3) and reports of potency inconsistencies among brands and of the same brand.[11]

The current standard of care for the treatment of patients with hypothyroidism is daily levothyroxine (LT4) tablets at doses that normalize the TSH levels.[11,12] It is expected (and generally assumed) that normalization of the TSH levels occurs alongside the resolution of symptoms of hypothyroidism. Indeed, this is the case after a few months of treatment for the majority of patients. Nonetheless, a consensus exists today that a poorly defined minority of LT4-treated patients exhibit persistent symptoms that are thyroid-related despite normalization of the serum TSH levels.[13] It is difficult to ascertain the exact number because it will depend on the intrinsic nature of the population served by each practice, for example, endocrinologists versus general internists. Two seminal studies indicate that this number varies between 10% and 20% of all LT4-treated patients.[14,15]

We have known that treatment with LT4 does not always resolve all symptoms of hypothyroidism since the early 1970s[16] and that some patients resisted being switched off DTE.[6] Others wrote letters alerting providers of how they felt,[17] which led to the development of thyroid-specific quality of life (QoL) questionnaires[14] that later were expanded and validated in different languages.[18] Although LT4 is safe and resolves the signs and symptoms of overt hypothyroidism, a seminal community-based study revealed that patients treated with LT4, even with a normal serum TSH level, exhibited a significant impairment in psychological well-being compared with controls matched for age, sex, and comorbidities.[14] In another study in which cognitive functioning tests were applied, LT4-treated patients showed poor performance in various domains, especially on complex attention tasks and verbal memory tests.[14] The QoL level also decreased in these patients compared with those of the general population, independently of the serum TSH levels.[16] Similar results were obtained in other centers,[19,20] except for the Rancho Bernardo study,[21] in which differences may have been masked by the natural cognitive decline exhibited by the much older population in that cohort (both LT4-treated and control populations included individuals aged ≤94 years). Sometimes referred to as brain fog, these cognitive-, mood-, and QoL-residual symptoms include mental fatigue, memory, and sleep problems, difficulty focusing and making decisions, anxiety, and mental confusion, which may be present during most of the day.[22]

Textual-data analysis of an open-ended survey of thousands of patients self-referred as having hypothyroidism and brain fog identified 2 major groups of responses, namely, symptom-centric (issues with language/memory and sleep/time) and medical-centric (issues with disease/diagnosis, patient/doctor, and medication).[22] As in other surveys,[23] concerns with the patient/doctor relationship came across extremely clearly. The textual analysis indicated that several patients have the perception that physicians do not regard their residual symptoms as thyroid-related and/or within their sphere of responsibility, logically leading to frustration and a feeling of neglect.

Adequately treated patients with hypothyroidism may also exhibit abnormal metabolic signs or symptoms, including difficulty managing body weight[23] (they weigh approximately 10 lbs more than a control-matched population[24]) and lower basal metabolic rate.[25-28] However, one should keep in mind that hypothyroidism is rarely an isolated cause of obesity, given that even in the control-matched population, the body mass index was above normal but within the overweight range (43). Furthermore, LT4-treated patients may have slightly elevated serum cholesterol levels[29-31] despite being more likely to be on statin medications.[24,32] Although these parameters have been studied in relatively smaller cohorts

Highlights

- LT4 resolves symptoms of overt hypothyroidism, owing to its activation to T3.
- Some patients (10%-20%) remain symptomatic, despite normalization of TSH.
- Residual symptoms could reflect a deficiency of T3, hence therapy with LT4 + LT3.
- Randomized clinical trials found that therapy with LT4 + LT3 is safe and effective.
- Symptomatic patients may benefit from LT4 + LT3 or desiccated thyroid extract.

Clinical Relevance

This review discusses the shortcomings of therapy with levothyroxine, provides a mechanistic explanation for the incomplete normalization of thyroid hormone signaling, and details how to approach patients with residual symptoms of hypothyroidism. This review also discusses the effectiveness and safety of combination therapy and offers a practical approach to initiate patients on therapy with levothyroxine + liothyronine.

and mostly in cross-sectional studies, the results are consistent and indicate that metabolic parameters should be incorporated into the main outcomes of future clinical trials investigating TH treatments.

This study aimed to review the relevant evidence indicating the incomplete effectiveness of treatment with LT4, along with potential factors that may explain such persistent symptoms. We advocate that, once thyroid-independent factors have been ruled out, an alternative treatment approach should be used for the subset of patients who remain symptomatic on LT4. The recognition of these 2 points (and the appropriate corrective actions) should improve the overall quality of treatment provided to patients with hypothyroidism. It should also assist physicians, particularly general endocrinologists, in the discussion of definitive treatment of thyroid diseases and in setting appropriate therapeutic expectations with their patients.

Does the Treatment of Patients With Hypothyroidism With LT4 Normalize TH Economy?

The residual symptoms experienced by LT4-treated patients are similar to those symptoms experienced by patients with overt hypothyroidism, albeit less intense.[33] This suggests that treatment with LT4 does not normalize TH signaling in all tissues. It is logical to conceive a scenario in which, once a nonthyroid-related condition has been ruled out (or adequately treated), residual symptoms result from the incomplete recovery of T3 signaling in specific organs, despite the normalization of the serum TSH levels. Most symptoms identified so far are cognitive and mood-related; hence, normalization of TH signaling in the brain seems to be particularly problematic in these patients.[34]

Iodine deficiency has been the major driving force that shaped how the hypothalamus-pituitary-thyroid (HPT) system evolved. In adult individuals with mild-moderate iodine deficiency, T4 secretion decreases, and TSH secretion is accelerated, increasing the T3/T4 ratio in thyroid secretion. The decrease in the serum T4 level also accelerates T4 to T3 conversion via the type 2 deiodinase (D2) in multiple tissues. As a result of these homeostatic adjustments, the serum T3 levels remain unaffected in adult individuals living in areas of mild-moderate iodine deficiency. Studies of mice carrying inactive genes for the deiodinases revealed that also in this case, the HPT adjusts to preserve the serum T3 levels, despite tolerating higher serum T4 and TSH levels.[35,36] Thus, it is tempting to conclude that the prime directive of the HPT axis is to adjust the T3/T4 ratio in thyroid secretion (via TSH secretion) to defend the normalcy of the serum T3 levels. Patients with hypothyroidism lack such an adaptive mechanism, which begs the question of whether the deiodinases alone can preserve the serum T3 levels without the contribution of the thyroid gland.[3,36] This is important because T3 is the biologically active TH. Its levels in the circulation are in equilibrium with and reflect the T3 content in most tissues (except for those tissues that express D2, such as the brain and pituitary gland).[34]

Rightly so, less focus has been placed on the T3 levels in the *diagnosis* of patients with hypothyroidism. Because the directive of the HPT system is to preserve the circulating T3 levels, these are highly regulated and, thus, have poor diagnostic value. In a patient with autoimmune thyroiditis, an increase in the serum TSH level and decrease in the FT4 level are the early signs of thyroid failure, and both contribute with T3 homeostasis (TSH accelerates the relative secretion of T3, and the low T4 levels accelerate the D2-mediated T4 to T3 conversion). Therefore, the changes in TSH and T4 are followed by a distant decrease in the serum T3 levels.[37]

A similar rationale was used to justify not monitoring the T3 levels in the *follow-up* of LT4-treated patients (not common in clinical practice or recommended in clinical guidelines). However, this rationale ignores that the prime directive of the HPT axis is to preserve the circulating T3 levels, despite abnormal TSH and T4 levels. We interpret this as a strong indication that we should have the same goal while treating patients with hypothyroidism, that is, restoring and preserving the circulating T3 levels.

This has not been highlighted in clinical guidelines, despite the early observation that LT4-treated patients (with normal serum TSH levels) maintain slightly lower serum T3 levels.[38] Some studies may not have been sufficiently powered to reproduce these findings, whereas the majority of the studies performed since the 1970s indicate that LT4-treated patients have relatively lower serum T3 and relatively higher serum T4 levels; approximately 15% of the patients have serum T3 levels below the normal reference range.[6] Although the available data do not allow us to conclude that the residual symptoms experienced by some of the LT4-treated patients are connected with the incomplete normalization of the serum T3 levels, the evidence is suggestive and deserves further investigation.

What could explain the relatively low T3 levels in LT4-treated patients? We know that the rate at which T4 is converted to T3 (in the tissues that provide T3 for the circulation) is inversely correlated with the T4 levels. Thus, at the beginning of the treatment of hypothyroidism, T4 is rapidly converted to T3, building up substantial amounts of T3 in the circulation, even before the serum T4 levels have been normalized. However, further increases in the serum T4 levels do not result in proportional increases in the serum T3 levels.[39] This is likely due to the downregulation of the T3 production via D2. The T3 levels will only increase substantially once the FT4 levels are above the normal reference range, at which point the participation of the D1 pathway becomes relatively more significant.[39] Notably, this homeostatic mechanism (ie, the decrease in D2 activity in response to T4) does not occur in the hypothalamus-pituitary unit, where T4 continues to be converted to T3 at high rates despite an increase in the serum T4 levels.[40] As a consequence, during treatment with LT4, the T3 levels are rapidly restored in the hypothalamus-pituitary unit, normalizing the serum TSH levels, even as the serum T3 levels remain relatively lower. A common DIO2 polymorphism reduces the D2 activity by approximately 20%[41,42] and has been used to explain the relatively lower serum T3 levels in LT4-treated patients who are carriers of the polymorphism[43]; however, these latter findings have not been universally reproduced.[44] Rare loss of function D1 alterations have also been described;[45] however, the extent to which they could disrupt TH homeostasis in LT4-treated patients remains unknown.

Residual Thyroid Tissue Participates in the T3 Economy During Therapy With LT4

The observations that the HPT system plays a critical role in maintaining the serum T3 levels and that this homeostatic mechanism is lost in patients with hypothyroidism[36] raise the question as to whether any residual thyroid tissue may play a role, even if less significant. Indeed, this could be important when planning definitive treatment for thyroid disease, such as total versus partial thyroidectomy. To address that question, approximately 400 consecutive LT4-treated patients with Hashimoto thyroiditis, with normal serum TSH levels (0.3-5.0 μIU/mL) were identified.[46] In this cohort, there was a positive correlation between the serum T3 levels (and the T3/FT4 ratio) and thyroid volume (based on neck ultrasonography); however, no correlation was found between the T3 levels and LT4 dose. Notably, the serum T3 levels were *lower* in patients with thyroid volumes of <5, 5 to 10, and 10 to 15 mL, *similar* in patients with thyroid volumes of 15 to 20, 20 to 50, and 50 to 80 mL, and *higher* in patients with thyroid volumes of ≥80 mL than in the matched controls.[46] Consistent findings were obtained

in LT4-treated patients who underwent hemithyroidectomy.[47] Thus, having residual thyroid tissue does seem to help maintain TH economy (and preserve the T3 levels) in patients treated with LT4. This has been mathematically modeled to predict the combination doses of LT4 and LT3 required to achieve the midnormal serum levels of T4 and T3.[48] Furthermore, modeling of the published trials of combination therapy suggested that achieving higher T3 levels would allow either improvement in QoL, mood, and neurocognitive benefits or patient preference.[48]

Can "Overtreatment" With LT4 Normalize TH Signaling and/or Improve QoL?

Overtreatment with LT4 (which suppresses serum TSH) is a common strategy to minimize residual symptoms of hypothyroidism.[6] The prevalence of iatrogenic subclinical hyperthyroidism in LT4-treated patients is surprisingly elevated[49] despite not being recommended by clinical guidelines.[11,12] The question remains whether treatment with higher LT4 doses can improve TH economy and possibly facilitate the resolution of residual symptoms.[50,51] A retrospective study of 250 LT4-treated athyreotic patients revealed that approximately 42% of those with normal serum TSH levels (0.5-5.0 μIU/mL) had FT4 levels above the reference range (0.9-1.7 ng/dL), whereas approximately 26% of those patients had FT3 levels below the reference range (2.3-4.0 pg/mL).[46] In contrast, in those patients with suppressed serum TSH levels (<0.5 μIU/mL), approximately 71% had FT4 levels above the reference range, and only 4.8% had FT3 levels below the reference range.[46] Thus, increasing the LT4 dose to the point that TSH becomes undetectable increases the serum T3 levels (presumably via D1) and substantially reduces the number of patients who remain with T3 below the reference range.

These findings were expanded in a prospective 5-year study that enrolled approximately 210 thyroidectomized patients, in whom TSH-suppressive doses of LT4 were more effective in improving QoL.[52] Patients were stratified among 3 groups according to the TSH levels, that is, complete suppression (undetectable), mild suppression (detectable but <0.50 μIU/mL), and normal (0.5-5.0 μIU/mL). Significant differences were found for anxiety, impaired social and daily life, and the overall impact of thyroid disease domains. Subjects with complete TSH suppression reported the best scores in almost all domain scales. Using multiple regression analyses, the FT3 levels were the best explanatory factor for the overall impact of thyroid disease on the patient's QoL.[52]

While maintaining a suppressed serum TSH level seems to offer some relief of residual symptoms of hypothyroidism, this strategy is not without concerns. In a recent retrospective cohort study that used data from approximately 705 300 adults on LT4, with a median follow-up of 4 years, patients with TSH levels of <0.10 μIU/mL had an increased risk of cardiovascular mortality (compared with euthyroid individuals) after adjusting for age, sex, and cardiovascular risk factors.[53] Additional longitudinal studies from large patient registries have found an association between the suppressed TSH levels (<0.1 μIU/mL) and excess mortality.[54,55] Complete suppression of the TSH levels (undetectable) has been associated with an increased risk of cardiovascular disease, dysrhythmias, and bone fractures but not in patients with a low unsuppressed TSH level (0.04-0.40 μIU/mL).[56] Therefore, at this time, given the available evidence for the risk of adverse cardiovascular outcomes, treatment with the TSH-suppressing levels of LT4 to treat residual symptoms should be performed cautiously, on a case-by-case basis.

What Is the Rationale for Combination Therapy?

In the last 50 years, a score of clinical trials comparing both forms of therapy for hypothyroidism, that is, LT4 versus LT4 + LT3 have been performed, and 2 meta-analyses have recently been published.[57,58] Although the details of each clinical trial varied, including the types of patients, ratios of LT4 and LT3, duration, and clinical outcomes, they all had in common the fact that the LT4 dose was reduced to accommodate the introduction of LT3 without leading to TSH suppression or thyrotoxicosis. A meta-analysis of these trials revealed that both forms of therapy performed similarly in terms of effectiveness and safety; however, patients preferred therapy with LT4 + LT3.[57,58]

A more critical analysis of these studies revealed that the trials comparing therapy with LT4 versus LT4 + LT3 did not specifically recruit participants with attention to patient dissatisfaction or persistent symptoms of hypothyroidism.[59] The American, British, and European Thyroid Associations in a joint statement concluded for the possibility that those individuals most likely to benefit from combination therapy may not yet have been included in trials in sufficient numbers to provide adequate power for detecting a response.[59] The inclusion in these trials of asymptomatic LT4-treated patients (the majority of patients with hypothyroidism) and of patients with nonthyroid-related symptoms diminished the statistical power and confused the results. Future trials should focus on triaging out these 2 groups and focusing on LT4-treated patients with thyroid-related symptoms.

With time, the safety record of LT3 was expanded. Mathematical modeling based on the T3 and T4 kinetics in a 70-kg individual indicates that LT3 can be used in combination with LT4 at doses not to exceed 10 mcg/day twice a day, resulting in 2 daily peaks of the serum T3 levels that remain within the normal reference range.[60] There were also 2 critical retrospective studies examining LT3 safety. The first included approximately 400 individuals taking LT3 for ≤17 years in the Scottish region of Tayside,[61] and the second was a Swedish registry study of approximately 575 000 individuals taking TH replacement during a median follow-up time of 8.1 years, of whom approximately 11 150 were using LT3.[62] Neither of these studies identified an excess risk of cardiovascular morbidity, cancer incidence, or excess mortality in LT3-treated patients. There are also 3 studies in which patients were treated with DTE that did not find an excess incidence of cardiovascular risk; however, the duration of these studies was relatively shorter.[63-65]

In contrast, a Korean study compared safety outcomes between approximately 1400 LT3 users and 3900 LT4 users with hypothyroidism and found that the risks of heart failure and stroke were higher in LT3 users; the length of the LT3 use (>52 weeks) was identified as an additional risk factor. Although these are important findings, the thyroid function tests (TSH, FT4, or T3) were not considered in the study, and the possibility of overtreatment with LT4 or LT4 + LT3 leading to TSH suppression could not be investigated.[66] Nonetheless, the study serves as a reminder that careful LT3 titration and follow-up are needed for patients on combination therapy (no safety data are available for children, pregnant women, or patients with significant cardiovascular disease; data on the LT4 and LT3 regimens and detailed safety recommendations are shown in the studies by Wiersinga et al[12] and Idrees et al[67]). Safety concerns with LT3 should decrease even further once slow-release T3 formulations currently under development become clinically available.[68,69]

A single-center study recently performed a prospective, randomized, double-blind, crossover study of 75 hypothyroid patients randomly allocated to LT4, LT4 + LT3, or DTE treatment arms for 22

weeks.[63] When focusing on the whole group of patients, there were no differences in the posttreatment scores of QoL questionnaires and cognitive and depression tests, except for a minor increase in the heart rate caused by DTE; the serum TSH level remained within the reference range across all treatment arms. Treatment preference was not different, and there were no interferences of secondary parameters in any of the outcomes. However, a subgroup analysis of the most symptomatic patients on LT4 (upper tertile) revealed a strong preference for either treatment arm that contained T3. These patients also had improved QoL, cognitive, and mood performance in response to therapy with T3. Overall, these results confirm the prediction put forward by the joint statement that, as a group, outcomes were similar among patients taking LT4, LT4 + LT3, or DTE. However, the subgroup of patients most symptomatic on LT4 exhibited strong preference and responded positively to therapy with LT4 + LT3 or DTE.[63]

Similar results were obtained in an open-labeled trial that included 31 consecutive patients with hypothyroidism who exhibited a lack of improvement in symptoms while on LT4.[70] We are aware that large multicentric studies comparing LT4 with LT4 + LT3 and DTE have been completed,[71-73] are in the recruiting phase (ClinicalTrials.gov identifier, NCT05412979), or are being planned; hence, more extensive data should be available in the near future.

Nonthyroid-Related Factors in LT4-Treated Patients With Residual Symptoms

Persistent symptoms in patients with hypothyroidism kept on "adequate" hormonal replacement with LT4 could be explained by nonthyroid-related factors (Table). Just the knowledge of carrying a chronic disease that requires treatment for life in itself can play a role in the development of mood and QoL symptoms. It has been the experience of several clinicians that finding and treating these factors lead to clinical improvement at least as often as trying combination therapy. The importance of recognizing and diagnosing these comorbidities cannot be overstated, especially with several patients feeling unheard and frequently being told by their endocrinologists that this investigation is outside of their scope of practice.

It is, therefore, important for physicians to conduct a comprehensive evaluation of each patient, with consideration for the presence of comorbidities with symptoms that may be indistinguishable from those of hypothyroidism. Contrasting the timing of the diagnosis of hypothyroidism with the start of symptoms may help establish a potential cause-effect relationship. Whether a patient has always experienced residual symptoms once placed on LT4 as opposed to symptoms that only developed after years of treatment with LT4 may also be informative.

In addition to the general approach to symptomatic LT4-treated patients, we should also consider that Hashimoto thyroiditis, one of the main causes of primary hypothyroidism, may have a clinical impact that goes beyond a reduction in the TH levels. Even when the thyroid function test results are within the normal range, positivity for thyroid peroxidase (TPO) antibodies has been associated with fertility issues in women, an increased risk of miscarriages,[74,75] and decrements of QoL.[76-79] In patients with Hashimoto thyroiditis and residual symptoms that were biochemically euthyroid on hormone replacement, total thyroidectomy reduced the level of anti-TPO antibodies and improved QoL when compared with those of a control group.[80] Although these studies have several limitations (the safety, effectiveness, and practicality of this approach should be further evaluated given the relatively higher difficulty and complications from thyroidectomy in the setting of severe lymphocytic thyroiditis), they highlight the potential role played by the autoimmune process per se in the genesis of residual symptoms.[81]

While we await a more approachable medical treatment to reduce TPO titers (rather than total thyroidectomy[82]) and further

Table
Initial Approach to Levothyroxine-Treated Patients With Residual Symptoms

Following a standard physical examination and biochemical evaluation, including electrolyte levels, renal function, calcium level, liver function tests, and complete blood count, we consider the following:		
Most common comorbidities to consider	**When to suspect it**	**Initial diagnostic tests**
Iron deficiency	All women especially during reproductive age Vegetarian diet Microcytic anemia History of celiac disease or atrophic gastritis or *Helicobacter pylori* infection History of bariatric surgery History of GI bleeding	Check the ferritin level. If low, the diagnosis is confirmed. If normal but the clinical evidence is strong, check iron and total iron binding capacity, and calculate TSAT; a low TSAT will confirm the diagnosis.
Vitamin B12, folate deficiency	In all patients who complain mainly of cognitive dysfunction Macrocytic anemia Vegetarian diet Metformin therapy History of bariatric surgery Peripheral neuropathy and abnormal gait Neuropsychiatric changes	Vitamin B12 and folate level. If extremely low, the diagnosis is confirmed. If borderline, check the MMA and homocysteine levels. If both levels (MMA and homocysteine) increase, vitamin B12 deficiency is confirmed. If only the homocysteine level increases, folate deficiency is confirmed.
Sleep apnea	History of excessive daytime sleepiness History of loud snoring and witnessed apnea	Refer patient to sleep study
Overweight/obesity	Clinical diagnosis	BMI
Perimenopause, menopause	Clinical diagnosis	Measurement of the FSH level to confirm the diagnosis may be needed
Celiac disease	In patients with Hashimoto thyroiditis (or other autoimmune diseases) First- and second-degree relatives with celiac diseases GI or extra-GI symptoms (eg, unexplained iron, folate, or vitamin B12 or D deficiencies)	Tissue transglutaminase IgA antibody and IgA levels

Abbreviations: BMI = body mass index; FSH = follicle-stimulating hormone; GI = gastrointestinal; IgA = immunoglobulin A; TSAT = transferrin saturation.

the investigation of their potential role in residual symptoms, some studies suggest that selenium supplementation (80-200 mcg daily for ≥3 months; the recommended dietary allowance for selenium is 55 mcg daily, and the upper tolerable dose is 400 mcg/day), with or without myo-inositol (600 mg daily), can attenuate the autoimmune process, reduce the levels of TPO and TG antibodies, and improve the thyroid functions test results in patients with Hashimoto disease.[83-86] However, these and other supplemental treatments remain investigational and not a part of the standards of care in clinical guidelines. In addition, more investigation is needed to both confirm the potential role of TPO antibodies in the genesis of residual symptoms in biochemically euthyroid patients and suggest monitoring the TPO levels in clinical practice.

How Should We Approach LT4-Treated Patients With Residual Symptoms of Hypothyroidism?

The complexity and multifaceted nature of the residual symptoms of hypothyroidism suggest that not a single approach can resolve all issues in all patients. In our practice, the following points have been identified as important:

1. Acknowledge to the patient that although LT4 is effective for most patients with hypothyroidism, a small number of patients may remain symptomatic despite having normal serum TSH levels. Many such patients have moved their care among multiple physicians and may be frustrated. Therefore, being attentive to their needs is particularly helpful.
2. Confirm that the patient has hypothyroidism from prior thyroid function tests, if available. Recent studies have identified an "epidemic" of LT4 prescriptions for individuals with normal serum TSH levels. Specifically, up to one third of LT4-treated patients remain euthyroid after LT4 discontinuation,[87] and approximately 25% of the new LT4 starts on a year-over-year basis have normal TSH and FT4 levels before LT4 start.[88] Thus, if needed, LT4 should be withdrawn so that an adequate increase in the serum TSH level can be documented.
3. Ensure the patient is on adequate LT4 dosage. A surprisingly large number of LT4-treated patients have been found to have off-target serum TSH levels in cross-sectional studies.[89-92]
4. Investigate other conditions and comorbidities (eg, psychological comorbidities) that can cause or contribute to residual symptoms. From a practical standpoint, we routinely ask for a complete metabolic panel and complete blood count, which screens for conditions such as anemia and renal and liver disease. We also check for the ferritin levels, especially in women during reproductive age, and we treat it if <50 ng/mL (iron deficiency has been associated with symptoms even in the absence of anemia).[93,94] It has been our experience that this approach oftentimes resolves some of the symptoms and improves overall stamina.

We treat patients will vitamin D deficiency (<20 mg/mL), and if no improvement is obtained, then we routinely screen for celiac disease with tissue transglutaminase immunoglobulin A, including patients with a history or clinic suggestive of iron deficiency. We routinely check for the vitamin B12 levels in patients who are on a vegetarian diet, on metformin therapy, or have a history of bariatric surgery, macrocytic anemia, peripheral neuropathy, or gait instability and in patients who have neuropsychiatric changes. Both vitamin B12 and folate deficiency can cause cognitive dysfunction; therefore, we screen for both in all LT4-treated patients who complain of "brain fog" and/or cognitive dysfunction.[95] If 1 or both (vitamin B12 and folate) are near the lower limit of normal, then we check the levels of methylmalonic acid and homocysteine. Increased levels of methylmalonic acid and homocysteine confirm vitamin B12 deficiency (if only the homocysteine levels are increased, then folate deficiency is confirmed) and the need for adequate treatment. The hemoglobin A1C levels are used as a screening tool whenever indicated. Given that being overweight (or sedentary) is one of the indications for screening, we would argue that almost all patients should be screened. Perimenopause and menopause are investigated clinically and may require measuring the follicle-stimulating hormone levels.[96] Estrogen replacement therapy should be considered and discussed with symptomatic patients if appropriate. Being overweight or obese is diagnosed clinically and should be addressed accordingly. We also refer patients for sleep studies if fatigue and/or brain fog is the main complaint and when the clinical history is suggestive (overweight/obesity, history of snoring, and falling asleep during the day).[97]

5. Attempt combination therapy with LT4 + LT3 if it is unequivocal that the patient has hypothyroidism or did not fully benefit from therapy with LT4 and no other explanation for the residual symptoms can be found.

In our practice, we follow the general guidance provided in 2 outstanding publications to place patients on therapy with LT4 + LT3.[12,98] The starting regimen requires a decrease in the LT4 dose and replacement with LT3. There are multiple methods to calculate the new doses.[12,98] A reasonable starting point is to aim at an LT4/LT3 dose ratio similar to what the thyroid gland physiologically produces, which ranges between 13 and 20:1. For example, if a patient is biochemically euthyroid on 100 mcg of LT4/day, then the LT3 dose is calculated as follows: 100/20 = 5 mcg (the dose is split into 2 daily doses, the second dose is approximately 8 hours after the first 1 or 1-2 hours before dinner). The new LT4 dose will be 100 mcg minus the dose of LT3 × 3 [100 − (5 × 3) = 85 mcg] (round off 88 mcg). Therefore, a patient on 100 mcg daily of LT4 can be switched to 88 mcg daily of LT4 plus 2.5 mcg of LT3 twice daily.

Most of the methods suggested take into account the initial LT4 dose even when it is extremely low (eg, 25-50 mcg/day). In such cases, however, especially in older patients, physicians should carefully consider the initial TH levels to confirm the indication of treatment. The amount of LT3 can be adjusted up depending on symptoms and the serum TSH (as long as the ratio is not >13:1).

Measure the levels of serum TSH, FT4, and T3 fasting and 2-4 hours after dose (expected peak of the serum T3 level). The serum TSH and T3 levels should be kept within the reference range; otherwise, an appropriate dose adjustment is necessary. Consider reducing the dose of LT4 if the peak of T3 is within the normal range but the serum TSH level is suppressed. If needed, adjustments in the LT4 and LT3 doses should be performed at 6-week intervals. Monitor the blood pressure, pulse rate, and heart rhythm every 3 to 6 months for the first year of therapy and then annually thereafter. An increased heart rate and/or palpitations may warrant additional testing, including electrocardiography and echocardiography. Assessment of benefit should be performed at 6 and 12 months after combination therapy has started. Although clinical guidelines do not recommend the use of DTE, it is notable that a substantial number of our patients with hypothyroidism already come for a new patient visit on a regular DTE regimen. DTE contains slightly more T3 than we would otherwise prescribe using synthetic TH. DTE is prescribed in grains: 1 grain is 65 mg of DTE and most commonly contains 38 mcg of T4 and 9 mcg of T3, with a margin of error of ±10%.[67]

6. To switch patients between LT4 and DTE, we use the conversion table defined previously[63] (eg, 100 mcg of LT4 is equivalent to 67.5 mg of DTE). The conversion chart proposed by the U.S. Pharmacopeia slightly overestimates the DTE potency, as it was recently found in the first clinical trial that tested the chart.[71]

Conclusion

Patients with hypothyroidism appropriately treated with LT4 (who have normal serum TSH levels) may remain symptomatic. This has been documented in several studies and should be discussed with patients starting therapy for hypothyroidism or those considering definitive treatment for thyroid disease. The mechanistic explanation for the residual symptoms is under current investigation; however, it could involve a relative deficiency of T3. New trials focusing on LT4-treated patients who remained symptomatic revealed preference and superiority of combination therapy containing LT4 + LT3. Given the new long-term safety data available for LT3, a recent joint statement of the American, British, and European Thyroid Associations recommends that a trial with combination therapy be offered to patients with hypothyroidism who did not fully benefit from therapy with LT4.

Disclosure

A.C.B. is a consultant for AbbVie, Acella, Synthonics, Thyron, and Madrigal. The other authors have no multiplicity of interest to disclose.

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References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism and hypertension: fact or myth? - Authors' reply. *Lancet*. 2018;391(10115):30.
2. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23(1):38–89.
3. Bianco AC, Dumitrescu A, Gereben B, et al. Paradigms of dynamic control of thyroid hormone signaling. *Endocr Rev*. 2019;40(4):1000–1047.
4. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev*. 2014;94(2):355–382.
5. Wyne KL, Nair L, Schneiderman CP, et al. Hypothyroidism prevalence in the United States: a retrospective study combining National Health and Nutrition Examination Survey and Claims Data, 2009-2019. *J Endocr Soc*. 2022;7(1):bvac172.
6. Bianco AC. *Rethinking Hypothyroidism*. Chicago: University of Chicago Press; 2022.
7. Taylor S. A new thyroid preparation. *Lancet*. 1961;277(7172):341.
8. Wool MS, Selenkow HA. Physiologic combinations of synthetic thyroid hormones in myxedema. *Clin Pharmacol Ther*. 1965;6(6):710–715.
9. Braverman LE, Ingbar SH, Sterling K. Conversion of thyroxine (T4) to triiodothyronine (T3) in athyreotic human subjects. *J Clin Invest*. 1970;49(5):855–864.
10. Taylor S, Kapur M, Adie R. Combined thyroxine and triiodothyronine for thyroid replacement therapy. *Br Med J*. 1970;2(5704):270–271.
11. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–1751.
12. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J*. 2012;1(2):55–71.
13. Jonklaas J. Optimal thyroid hormone replacement. *Endocr Rev*. 2022;43(2):366–404.
14. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol (Oxf)*. 2002;57(5):577–585.
15. Wekking EM, Appelhof BC, Fliers E, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. *Eur J Endocrinol*. 2005;153(6):747–753.
16. Smith RN, Taylor SA, Massey JC. Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. *Br Med J*. 1970;4(5728):145–148.
17. Roberts ND. *British Thyroid Foundation Newsletter*. 1996.
18. Uslar V, Becker C, Weyhe D, Tabriz N. Thyroid disease-specific quality of life questionnaires - a systematic review. *Endocrinol Diabetes Metab*. 2022;5(5):e357.
19. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. *Thyroid*. 2007;17(3):249–258.
20. Wouters HJ, van Loon HC, van der Klauw MM, et al. No Effect of the Thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. *Thyroid*. 2017;27(2):147–155.
21. Kramer CK, von Muhlen D, Kritz-Silverstein D, Barrett-Connor E. Treated hypothyroidism, cognitive function, and depressed mood in old age: the Rancho Bernardo Study. *Eur J Endocrinol*. 2009;161(6):917–921.
22. Ettleson MD, Raine A, Batistuzzo A, et al. Brain fog in hypothyroidism: understanding the patient's perspective. *Endocr Pract*. 2022;28(3):257–264.
23. Peterson SJ, Cappola AR, Castro MR, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid*. 2018;28(6):707–721.
24. Peterson SJ, McAninch EA, Bianco AC. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? *J Clin Endocrinol Metab*. 2016;101(12):4964–4973.
25. Gorman CA, Jiang NS, Ellefson RD, Elveback LR. Comparative effectiveness of dextrothyroxine and levothyroxine in correcting hypothyroidism and lowering blood lipid levels in hypothyroid patients. *J Clin Endocrinol Metab*. 1979;49(1):1–7.
26. Ridgway EC, Cooper DS, Walker H, et al. Therapy of primary hypothyroidism with L-triiodothyronine: discordant cardiac and pituitary responses. *Clin Endocrinol (Oxf)*. 1980;13(5):479–488.
27. Samuels MH, Kolobova I, Smeraglio A, Peters D, Purnell JQ, Schuff KG. Effects of levothyroxine replacement or suppressive therapy on energy expenditure and body composition. *Thyroid*. 2016;26(3):347–355.
28. Muraca E, Ciardullo S, Oltolini A, et al. Resting energy expenditure in obese women with primary hypothyroidism and appropriate levothyroxine replacement therapy. *J Clin Endocrinol Metab*. 2020;105(4):dgaa097.
29. McAninch EA, Rajan KB, Miller CH, Bianco AC. Systemic thyroid hormone status during levothyroxine therapy in hypothyroidism: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2018;103(12):4533–4542.
30. Bianco AC, Taylor P. Levothyroxine treatment and cholesterol in hypothyroidism. *Nat Rev Endocrinol*. 2020;16(4):193–194.
31. Ito M, Miyauchi A, Hisakado M, et al. Biochemical markers reflecting thyroid function in athyreotic patients on levothyroxine monotherapy. *Thyroid*. 2017;27(4):484–490.
32. Idrees T, Prieto WH, Casula S, et al. Use of statins among patients taking levothyroxine: an observational drug utilization study across sites. *J Endocr Soc*. 2021;5(7):bvab038.
33. Hegedus L, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, Perros P. Primary hypothyroidism and quality of life. *Nat Rev Endocrinol*. 2022;18(4):230–242.
34. Salas-Lucia F, Bianco AC. T3 levels and thyroid hormone signaling. *Front Endocrinol (Lausanne)*. 2022;13, 1044691.
35. McAninch EA, Bianco AC. New insights into the variable effectiveness of levothyroxine monotherapy for hypothyroidism. *Lancet Diabetes Endocrinol*. 2015;3(10):756–758.
36. Gereben B, McAninch EA, Ribeiro MO, Bianco AC. Scope and limitations of iodothyronine deiodinases in hypothyroidism. *Nat Rev Endocrinol*. 2015;11(11):642–652.
37. Salvatore D, Porcelli T, Ettleson MD, Bianco AC. The relevance of T_3 in the management of hypothyroidism. *Lancet Diabetes Endocrinol*. 2022;10(5):366–372.
38. Stock JM, Surks MI, Oppenheimer JH. Replacement dosage of L-thyroxine in hypothyroidism. A re-evaluation. *N Engl J Med*. 1974;290(10):529–533.
39. Ettleson MD, Prieto WH, Russo PST, et al. Serum thyrotropin and triiodothyronine levels in levothyroxine-treated patients. *J Clin Endocrinol Metab*. 2022:dgac725.
40. Werneck de Castro JP, Fonseca TL, Ueta CB, et al. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. *J Clin Invest*. 2015;125(2):769–781.
41. Jo S, Fonseca TL, Bocco BMLC, et al. Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain. *J Clin Invest*. 2019;129(1):230–245.
42. McAninch EA, Jo S, Preite NZ, et al. Prevalent polymorphism in thyroid hormone-activating enzyme leaves a genetic fingerprint that underlies associated clinical syndromes. *J Clin Endocrinol Metab*. 2015;100(3):920–933.
43. Castagna MG, Dentice M, Cantara S, et al. DIO2 Thr92Ala reduces deiodinase-2 activity and serum-T3 levels in thyroid-deficient patients. *J Clin Endocrinol Metab*. 2017;102(5):1623–1630.
44. Bianco AC, Kim BS. Pathophysiological relevance of deiodinase polymorphism. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(5):341–346.
45. Franca MM, German A, Fernandes GW, et al. Human type 1 iodothyronine deiodinase (DIO1) mutations cause abnormal thyroid hormone metabolism. *Thyroid*. 2021;31(2):202–207.
46. Takahashi S, Ito M, Masaki Y, et al. Association between serum thyroid hormone balance and thyroid volume in patients treated with levothyroxine monotherapy for hypothyroidism. *Endocr J*. 2021;68(3):353–360.
47. Ito M, Miyauchi A, Kang S, et al. Effect of the presence of remnant thyroid tissue on the serum thyroid hormone balance in thyroidectomized patients. *Eur J Endocrinol*. 2015;173(3):333–340.

48. DiStefano 3rd J, Jonklaas J. Predicting optimal combination LT4 + LT3 therapy for hypothyroidism based on residual thyroid function. *Front Endocrinol (Lausanne)*. 2019;10:746.
49. Watsky JG, Koeniger MA. Prevalence of iatrogenic hyperthyroidism in a community hospital. *J Am Board Fam Pract*. 1998;11(3):175–179.
50. Lazarus JH. Investigation and treatment of hypothyroidism. *Clin Endocrinol (Oxf)*. 1996;44(2):129–131.
51. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. *Clin Endocrinol (Oxf)*. 1988;28(3):325–333.
52. Monzani ML, Piccinini F, Boselli G, et al. Changes in quality of life after thyroidectomy in subjects with thyroid cancer in relation to the dose of levothyroxine. *J Endocrinol Invest*. 2023;46(2):319–326.
53. Evron JM, Hummel SL, Reyes-Gastelum D, Haymart MR, Banerjee M, Papaleontiou M. Association of thyroid hormone treatment intensity with cardiovascular mortality among US veterans. *JAMA Netw Open*. 2022;5(5), e2211863.
54. Thayakaran R, Adderley NJ, Sainsbury C, et al. Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study. *BMJ*. 2019;366:l4892.
55. Lillevang-Johansen M, Abrahamsen B, Jorgensen HL, Brix TH, Hegedus L. Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. *Thyroid*. 2018;28(5):566–574.
56. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab*. 2010;95(1):186–193.
57. Lan H, Wen J, Mao Y, Huang H, Chen G, Lin W. Combined T4 + T3 therapy versus T4 monotherapy effect on psychological health in hypothyroidism: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2022;97(1):13–25.
58. Millan-Alanis JM, Gonzalez-Gonzalez JG, Flores-Rodríguez A, et al. Benefits and harms of Levothyroxine/L-triiodothyronine versus levothyroxine monotherapy for adult patients with hypothyroidism: systematic review and meta-analysis. *Thyroid*. 2021;31(11):1613–1625.
59. Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. *Thyroid*. 2021;31(2):156–182.
60. Van Tassell B, Wohlford 4th GF, Linderman JD, et al. Pharmacokinetics of L-triiodothyronine in patients undergoing thyroid hormone therapy withdrawal. *Thyroid*. 2019;29(10):1371–1379.
61. Leese GP, Soto-Pedre E, Donnelly LA. Liothyronine use in a 17 year observational population-based study - the tears study. *Clin Endocrinol (Oxf)*. 2016;85(6):918–925.
62. Planck T, Hedberg F, Calissendorff J, Nilsson A. Liothyronine use in hypothyroidism and its effects on cancer and mortality. *Thyroid*. 2021;31(5):732–739.
63. Shakir MKM, Brooks DI, McAninch EA, et al. Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+liothyronine in hypothyroidism. *J Clin Endocrinol Metab*. 2021;106(11):e4400–e4413.
64. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2013;98(5):1982–1990.
65. Tariq A, Wert Y, Cheriyath P, Joshi R. Effects of long-term combination LT4 and LT3 therapy for improving hypothyroidism and overall quality of life. *South Med J*. 2018;111(6):363–369.
66. Yi W, Kim BH, Kim M, et al. Heart failure and stroke risks in users of liothyronine with or without levothyroxine compared with levothyroxine alone: a propensity score-matched analysis. *Thyroid*. 2022;32(7):764–771.
67. Idrees T, Palmer S, Maciel RMB, Bianco AC. Liothyronine and desiccated thyroid extract in the treatment of hypothyroidism. *Thyroid*. 2020;30(10):1399–1413.
68. Dumitrescu AM, Hanlon EC, Arosemena M, et al. Extended absorption of liothyronine from poly-zinc-liothyronine: results from a phase 1, double-blind, randomized, and controlled study in humans. *Thyroid*. 2022;32(2):196–205.
69. Santini F, Ceccarini G, Pelosini C, et al. Treatment of hypothyroid patients with L-thyroxine (L-T4) plus triiodothyronine sulfate (T3S). A phase II, open-label, single center, parallel groups study on therapeutic efficacy and tolerability. *Front Endocrinol (Lausanne)*. 2019;10:826.
70. Heald AH, Premawardhana L, Taylor P, et al. Is there a role for natural desiccated thyroid in the treatment of levothyroxine unresponsive hypothyroidism? Results from a consecutive case series. *Int J Clin Pract*. 2021;75(12), e14967.
71. O'Sullivan A, Brazg R, Horowitz B, et al. Dose-conversion from LT4 to Armour thryroid. *Thyroid*. 2022;32:A17.
72. Brazg R, O'Sullivan A, Horowitz B, et al. Primary results from a phase 2 study of Armour thyroid in patients with hypothyroidism: the Arch Study. *Thyroid*. 2022;32:A54.
73. Horowitz B, O'Sullivan A, Pepper G, et al. Thypro symptom outcomes in a subpopulation of patients with hypothyroidism from the Arch Study. *Thyroid*. 2022;2022:A17.
74. Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. *Clin Endocrinol (Oxf)*. 2015;82(3):313–326.
75. Unuane D, Velkeniers B. Impact of thyroid disease on fertility and assisted conception. *Best Pract Res Clin Endocrinol Metab*. 2020;34(4), 101378.
76. Groenewegen KL, Mooij CF, van Trotsenburg ASP. Persisting symptoms in patients with Hashimoto's disease despite normal thyroid hormone levels: does thyroid autoimmunity play a role? A systematic review. *J Transl Autoimmun*. 2021;4, 100101.
77. Winther KH, Cramon P, Watt T, 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*. 2016;11(6), e0156925.
78. Ott J, Promberger R, Kober F, et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. *Thyroid*. 2011;21(2):161–167.
79. Bianchi GP, Zaccheroni V, Solaroli E, et al. Health-related quality of life in patients with thyroid disorders. *Qual Life Res*. 2004;13(1):45–54.
80. Guldvog I, Reitsma LC, Johnsen L, et al. Thyroidectomy versus medical management for euthyroid patients with Hashimoto disease and persisting symptoms: a randomized trial. *Ann Intern Med*. 2019;170(7):453–464.
81. Ettleson MD, Bianco AC. Individualized therapy for hypothyroidism: is T4 enough for everyone? *J Clin Endocrinol Metab*. 2020;105(9):e3090–e3104.
82. McManus C, Luo J, Sippel R, Chen H. Is thyroidectomy in patients with Hashimoto thyroiditis more risky? *J Surg Res*. 2012;178(2):529–532.
83. Nordio M, Basciani S. Treatment with myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. *Int J Endocrinol*. 2017;2017, 2549491.
84. Toulis KA, Anastasilakis AD, Tzellos TG, Goulis DG, Kouvelas D. Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. *Thyroid*. 2010;20(10):1163–1173.
85. Gartner R, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab*. 2002;87(4):1687–1691.
86. Benvenga S, Nordio M, Laganà AS, Unfer V. The role of inositol in thyroid physiology and in subclinical hypothyroidism management. *Front Endocrinol (Lausanne)*. 2021;12, 662582.
87. Burgos N, Toloza FJK, Singh Ospina NM, et al. Clinical outcomes after discontinuation of thyroid hormone replacement: a systematic review and meta-analysis. *Thyroid*. 2021;31(5):740–751.
88. Brito JP, Ross JS, El Kawkgi OM, et al. Levothyroxine use in the United States, 2008-2018. *JAMA Intern Med*. 2021;181(10):1402–1405.
89. Ross JS, Rohde S, Sangaralingham L, et al. Generic and brand-name thyroid hormone drug use among commercially insured and Medicare beneficiaries, 2007 through 2016. *J Clin Endocrinol Metab*. 2019;104(6):2305–2314.
90. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. *Br J Gen Pract*. 1993;43(368):107–109.
91. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160(4):526–534.
92. Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. 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*. 2009;94(4):1342–1345.
93. Balendran S, Forsyth C. Non-anaemic iron deficiency. *Aust Prescr*. 2021;44(6):193–196.
94. Soppi ET. Iron deficiency is the main cause of symptom persistence in patients treated for hypothyroidism. *Thyroid*. 2015;25:A-74.
95. Tangney CC, Tang Y, Evans DA, Morris MC. Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. *Neurology*. 2009;72(4):361–367.
96. Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L. Menopause and cognitive impairment: a narrative review of current knowledge. *World J Psychiatry*. 2021;11(8):412–428.
97. Krysta K, Bratek A, Zawada K, Stepańczak R. Cognitive deficits in adults with obstructive sleep apnea compared to children and adolescents. *J Neural Transm (Vienna)*. 2017;124(Suppl 1):187–201.
98. Dayan C, Panicker V. Management of hypothyroidism with combination thyroxine (T4) and triiodothyronine (T3) hormone replacement in clinical practice: a review of suggested guidance. *Thyroid Res*. 2018;11:1.